Submitted to *Chaos*, 25 February 1992.

Cellular Dynamata and Morphogenesis

by

Ralph H. Abraham
Mathematics Department
University of California
Santa Cruz, CA 95064

Dedicated to: Alan Turing

Abstract. A reaction-diffusion system (such as the models of Fick, Fisher, Kolmogorov-Petrovsky-Piskunov, Rashevsky and Turing) is discretized by Southwell's relaxation method, to obtain a cellular dynamaton, a complex dynamical system similar to a cellular automaton. This is then coupled to a spatial array of identical dynamical schemes, in the style of Thom and Zeeman, to provide pedagogic examples of complex dynamical systems of coupled cellular dynamata, which are capable of morphogenesis. Some practical problems of numerical simulation are discussed.

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CHRONOLOGY

1728 Bernoulli
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1977 Zeeman

1. Introduction. The concepts of complex dynamical systems and of cellular dynamata have evolved from modeling efforts in mathematical biology, one of the most exciting current frontiers of the applied mathematical art. Here, we trace this historical evolution, in relation particularly to the fascinating problem of biological morphogenesis. We are interested primarily in *mathematical morphogenesis:* an study of space-time patterns in mathematical objects constructed from dynamical systems theory. Any implications for the biological sciences remain for the future. We will describe exemplary dynamical models, complex systems of cellular dynamata, in which experimental work might reveal pattern-formation behavior suggestive of natural phenomena.

2. Historical survey. Reaction-diffusion equations were introduced relatively recently into the mathematical literature, in attempts to make models for morphogenesis, that Mount Everest of theoretical biology. This is the story, as far as we know it. The simple (linear) diffusion equation was created by Fourier for his theory of heat (1807). Perhaps this was partly inspired by the wave equations of Euler and d'Alembert (1752) and Sophie Germain (1807). Soon it was used by Fick (1860), a physiologist and colleague of Helmholtz in Berlin, for the diffusion of blood through tissue. Later it was adapted by Heavyside (1899), the telegrapher, for his cable equation. This is particularly significant, as Heavyside was interested in the capability of the diffusion equation to support traveling waves, and thus pulses of Morse code. This property led to the first applications to morphogenesis, of (Fisher, 1930/1958) and Kolmogorov, Petrovsky, and Piskunov (Kolmogorov, 1937) . An excellent numerical method for the integration of these equations was developed by (Southwell, 1940) using spatial discretization to reduce the partial differential equation to a system of ordinary differential equations. Further applications were envisioned in (Rashevsky, 1938) and (Turing, 1952) . The latter has been particularly influential, and is noteworthy for the use of spatial discretization. This was not just a technique of numerical analysis, as in Southwell's method, but an attempt to model plant tissue more faithfully. This, together with the metabolic models of (Thom, 1975) and (Zeeman, 1977) led to the development of cellular dynamata (or CDs, or cellular dynamical systems.)

The equations written by these people, transcribed to a common notation, are as follows. Let $D \subset R^n$ be the closure of an open set, the *domain*, with $n = 1, 2,$ or 3. Assume the boundary satisfies some conditions of regularity if necessary. Let $\boldsymbol{F}$ be an appropriate space of real-valued functions on D, incorporating fixed boundary conditions. Let $I \subset R$ be an interval, and $u : I \to \boldsymbol{F}$ a smooth curve. We are concerned with equations of evolution for u,

$$u' = V(u) \tag{2.1}$$

where the vectorfield or operator, V, is defined almost everywhere in $\boldsymbol{F}$. The *Fourier heat equation* is the well-known

$$u' = c\,\Delta u + \rho \tag{2.2}$$

where u represents the distribution of heat in D, $u \geq 0$, $c \in R$ is a positive constant, Δ is the Laplacian ($n = 1, 2,$ or 3), and $\rho \in F$ is a fixed function describing the heat sources and sinks. Special cases are named for Laplace, Poisson, and Heavyside.

The *Fick equation*, also called the *porous medium equation* (Aronson, 1984) , is a simple, nonlinear modification,

$$u' = c\,\Delta(u^m) + \rho \tag{2.3}$$

where m is a positive integer. As this has been found to be a good model for the isentropic flow of an ideal gas in a homogeneous porous medium (u representing the density), it may be appropriate for biological models as well. Written in the traditional Fickian form ($m > 1$)

$$u' = c\ \mathrm{div}\,(mu^{m-1}\ \mathrm{grad}\,u) + \rho \tag{2.4}$$

The function cmu^{m-1} may be regarded as the diffusion rate (diffusivity), which increases with density. Thus the equation is useful for modeling the population (that is, migration) dynamics of a species which dislikes crowds, and is sometimes called the density-dependent diffusion equation. All of these are *diffusion systems*. The first *reaction-diffusion systems* were introduced independently in (Fisher, 1937) and in (Kolmogorov, 1937) .

First we will describe the *Fisher equation*. Applications of the diffusion concept (and the heat equation) to the diffusion of populations of species (fish, birds, mammals) had already been made. Fisher applied this idea to populations of species of genes within a single animal species (allelomorphs) in Ch. VI of his classic text on natural selection (Fisher, 1930/1958) . But this depends not only on diffusion (migration) but also on reaction (sexual union). After seven years, there appears in (Fisher, 1937) the Fisher equation

$$u' = c\,\Delta u + u(1-u) \tag{2.5}$$

which models the diploid case. Thus, there are two alleles, of frequency u and $(1-u)$, respectively. The reaction term, $u(1-u)$, is of logistic form; this is the simplest model (mass action law) for sexual interaction. Fisher established the traveling wave property for this equation and determined the wave speed. See (Murray, 1980) , (Brown, 1984) , (Weinberger, 1984) , (Ludwig, 1979) , and (Fife, 1979) for details. The paper of Kolmogorov, Petrovsky and Piskunov (Kolmogorov, 1937) established analogous results for the *KPP equation*, with a more general reaction term,

$$u' = c\,\Delta u + \Omega_g(u) \tag{2.6}$$

where $g : [0, 1] \to R$, and $\Omega_g(u) = g \circ u$, usually written $g(u)$. They assumed that $g(0) = g(1)$ and g is concave. Further generalizations of Fisher's results have been made. See (Brown, 1984) and refererces therein, especially (Kametake, 1976) ; (Rashevsky, 1938) discusses a similar idea.

A further step in the evolution of the diffusion equation was its application to two or more diffusing species, with mutual interactions. This occurred in the context of chemical kinetics (reactions of the linear catalytic type) in (Turing, 1952) and later with mass action kinetics, and in the context of population dynamics (interactions of predator-prey, cooperation, or other types of reaction dynamics). These fields remain active, and closely related, even today, see (Nicolis, 1977) and (Fitzgibbon, 1984) . We turn now to the *Turing equations*,

$$\begin{aligned} u' &= c\,\Delta u + \alpha u - \beta v \\ v' &= d\,\Delta v + \gamma u + \delta v \end{aligned} \tag{2.7}$$

where $u, v : I \to F$. Turing showed the existence of a symmetry-breaking pitchfork bifurcation, hence called the *Turing bifurcation*, in which a standing-wave pattern emerges from a uniform distribution of the morphogens, u and v. This result assumes: $\alpha, \beta, \gamma > 0$. The bifurcation parameter is d. When $d > c$, standing waves develop. This is well-described in (Maynard-Smith, 1968) and (Conway, 1984) . Turing applied his result to phylotaxis, see Part I of (Abraham, 1982-88) .

The replacement of the linear reaction terms with first order reaction kinetics for a reaction $A + B \rightleftarrows AB$ (u and v denoting the concentrations of A and B, resp.) leads to the equations

$$\begin{cases} u' = c\,\Delta v - K_A uv - K_D u + \alpha \\ v' = d\,\Delta v - K_B uv - K_D v + \beta \end{cases} \tag{2.8}$$

while in another much studied case, the *Brusselator* of (Nicolis, 1977) , Ch. 7

$$\begin{cases} u' = c\,\Delta u + A + u^2 v - Bu - u \\ v' = d\,\Delta v + Bu - u^2 v \end{cases} \tag{2.9}$$

Today, standing and rotating waves have been established in general reaction-diffusion systems of the form

$$\begin{aligned} u'_1 &= D_1 \Delta u_1 + f_1(u_1, \ldots, u_m) \\ &\vdots \\ u'_m &= D_m \Delta u_m + f_m(u_1, \ldots, u_m) \end{aligned} \tag{2.10}$$

by, for example, (Auchmuty, 1984) ; see also (Erneux, 1975) , (Winfree, 1980) , (Fife, 1976) , and (Kopell, 1973) .

In this unbroken line of development, beginning apparently with Pearson and Blakeman around the turn of the century (see p. 436 in (Edelstein-Keshet, 1988)) and revived in (Fisher, 1930/1958) , an important bifurcation took place in (Turing, 1952) . Perhaps stimulated by his problem of phylotaxis (growth bud formation in the apical meristem of the branches of plants), or by the earlier work of (Rashevsky, 1938) , or through contact with the master numerical analyst Southwell, his colleague in the British war effort (Southwell, 1940) , he discretized spatial variables into mathematical cells corresponding to physiological cells (or clusters of them). The system (1.7) is then reduced to a linear dynamical system, in case $n = 1$,

$$\begin{cases} u'_i = c(u_{i+1} + u_{i-1} - 2u_i)/2 + \alpha u_i - \beta v_i \\ v'_i = d(v_{i+1} + v_{i-1} - 2v_i)/2 + \gamma u_i + \delta v_i \end{cases} \tag{2.11}$$

in which Turing established a periodic attractor. This result was later extended in (Smale, 1976) .

A model for a biological organ as an array of identical cells defined as a standard dynamical system with controls, appearing in (Rashevsky, 1938) , and (Turing, 1952) , has been the inspiration for the CD systems described in this paper. Our goals here are to describe these CD models in general (Section 3), to describe two specific examples — one the discretization a la Turing of a reaction-diffusion system (Section 4), the other an array of identical dynamical schemes such as the well-known Duffing system (discretization of a nonlinear wave equation, Section 5) — and to then couple these two exemplary CD's together, creating some simple pedagogic models somewhat like biological organs (Section 6).

These models may be regarded as spatial discretizations of the morphogenetic fields of (Thom, 1975) and Zeeman, (Zeeman, 1977) and this work has been much influenced by them (esp. Zeeman's heart and memory models). But the CD models could be made in closer fidelity to the observed dynamics of the target organ, whether it be cell membrane, enzymatic membrane, apical meristem, pituitary, cerebral cortex, distributed computer network, slime mold or world populations. We end with some comments on numerical techniques for the simulation of CD models (Section 7).

The important role of morphogenesis in the field of mathematical biology is described in great detail in the recent texts of the subject. See especially (Edelstein-Keshet, 1988) and

(Murray, 1989) . The distinction between mathematical models of morphogenesis and the science of biological morphogenesis must be kept in mind.

3. Cellular dynamata. We begin by recalling briefly the concepts of complex dynamical systems. A *dynamical scheme* is a dynamical system depending upon control parameters. Thus if S is a manifold (the *state space*), $X(S)$ a suitable space of dynamical systems (vectorfields) on S, and C another manifold (the *control space*), a dynamical scheme is a map, $\mu: C \to X(S)$. In Thom's language, this is called a *morphogenetic field.* Given two of these

$$\mu_1: C_1 \to X(S_1)$$

$$\mu_2: C_2 \to X(S_2)$$

a *serial coupling* is a function, $\sigma: S_1 \to C_2$. Details and numerous examples may be found elsewhere (Abraham, 1990) . The canonical examples are the forced pendulum and the forced Van der Pol oscillator. From these fundamentals we may construct elaborate networks of serially coupled dynamical schemes, suitable for designing dynamical models of biological and social systems, which we call *complex dynamical systems.*

By a *cellular dynamical system* we mean a spatial array of dynamical schemes, each identical to one called the *standard cell,* which are serially coupled among themselves. A typical arrangement might be a cubical lattice, with mutual coupling between nearest neighbors. Any control parameters not determined by coupling within the cellular dynamical system are regarded as free controls of the entire scheme, and may be coupled to an external system, or set to fixed values.

A cellular dynamical (CD) system is much like the cellular automaton (CA) of (Neumann, 1966) The analogy may be made by identifying the attractors of the standard cell as (roughly) the set of finite states, and integration of the coupled system for a fixed interval of time as the successor function. Next we consider some examples from the spatial discretization of reaction-diffusion systems.

4. Reaction-diffusion systems. In a sequence of examples, we now show how the reaction-diffusion systems of Turing and KPP may be transformed into cellular dynamical systems.

Example 4.1. We start with a single Fickian diffusion equation, Fisher's equation

$$u' = c\,\Delta u + u(1-u) \tag{4.1}$$

where $D \subset R^n$ is a regular domain with boundary, $u_t: D \subset R^n \to R^n$ is a smooth function ($t \in I \subset R$, $n = 1, 2,$ or 3) and $u: t \to u_t$ is a smooth curve in an appropriate

function space, F, such as $F = C^3(D, R)$. Let $F_0 \subset F$ denote the closed affine subspace defined by the given boundary conditions. The right-hand-side may be regarded as a vectorfield on F_0, V, defined almost everywhere, and the evolution equation (3.1) describes the tangency of u to V. We proceed in two steps. For simplicity, we will describe these steps only in the case of one spatial variable: $n = 1, D = [a, b]$.

In the first step, we discretize the spatial domain, $D = [a, b] \subset R$, into N intervals $\{[x_i, x_{i+1}]: i = 0, \ldots, N-1\}$ of equal width. By evaluating a function $u \in F$ at the endpoints, we obtain a projection

$$\pi: F \to R^{N+1}; u \to (u(x_0), \ldots, u_i(x_N))$$

and let $F_o = \pi(F_0)$, which is an affine subspace of R^{N+1} of codimension 2,

$$F_0 = \{(u_0, \ldots, u_N) \in R^{N+1} \mid u_0 = A, u_N = B\}$$

for boundary conditions (A, B). The vectorfield V on F_0 projects (approximately) onto the vectorfield V on F_0 defined, with central difference approximation, by

$$V(A, u_1, \ldots, u_{N-1}, B) = (0, V_1, \ldots, V_{N-1}, 0) \tag{4.2}$$

where

$$V_i = \frac{c}{2(\Delta x)^2}[u_{i+1} - 2u_i + u_{i-1}] + \varepsilon u_i(1 - u_i), \quad i = 2,.., n-1.$$

This is the starting step in the numerical interaction scheme known as the method of lines, or Southwell's relaxation method.

Step 2. We now factor this dynamical system of dimension $N-1$ (3.2) into a cellular dynamical system having $N-1$ standard cells, each with one state variable and one control parameter. Note that

$$V_i = \left[-\frac{2c}{(\Delta x)^2} u_i + \varepsilon u_i^3\right] + \frac{c}{2(\Delta x)^2}(u_{i+1} + u_i)$$

So we consider the scheme

$$u' = V_C(u) = -\frac{2c}{(\Delta x)^2} u + \varepsilon u^3 + C \tag{4.3}$$

as the standard cell of a cellular dynamical system, with spatial array $(x_1, \ldots, x_{N-1})$.

Serial couplings exist between nearest neighbors only, as shown in Fig. 4.1.

Fig. 4.1 about here.

with coupling functions, $C_i = \frac{c}{2(\Delta x)^2}(u_{i+1} + u_{i-1})$. Note that if $i = 1$, $u_{i-1} = A$ and for $i = N - 1$, $u_{i+1} = B$.

Example 4.2. We now consider a 2-component reaction-diffusion system

$$\begin{cases} u' = c\,\Delta u + \varepsilon u^3 + f(u, v) \\ v' = d\,\Delta v + \mu v^3 - f(u, v) \end{cases} \tag{4.4}$$

where $f(u, v) = \alpha uv - \beta(u + v)$, representing first-order chemical kinetics with constants $\alpha, \beta \in R$, or any other function. Transforming each of these equations as in Example 4.1, we obtain a CD system having a standard cell (2 state variables, 2 controls) with schematic diagram, again, as in Fig. 4.1,

$$u' = -\frac{2c}{(\Delta x)^2} u + \varepsilon u^3 + f(u, v) + C$$

$$v' = -\frac{2d}{(\Delta x)^2} v + \mu v^3 - f(u, v) + D$$

with coupling functions

$$C_i = \frac{2c}{(\Delta x)^2}(u_{i+1} + u_{i-1})$$

$$D_i = \frac{2d}{(\Delta x)^2}(v_{i+1} + v_{i-1})$$

By now it is clear how to transform an arbitrary reaction-diffusion system into a CD system.

5. Reaction-wave systems. Besides the heat equation of Fourier and its progeny, the wave equation of d'Alembert also yields interesting CD systems, through spatial discretization. In the notation of Section 3, the *linear wave equation*,

$$u'' = c^2 \Delta u \tag{5.1}$$

may be rewritten as the system

$$\begin{cases} u' = v \\ v' = c^2 \Delta u \end{cases} \tag{5.2}$$

on the domain $F_0 \times F_1$ defined by boundary conditions,

$$F_0 = \{u \in F \mid u(a) = A, u(b) = B\}$$

$$F_1 = \{v \in F \mid v(a) = A', v(b) = B'\}$$

Discretizing, we obtain a vectorfield (V, W) on $F_o \times F_1$, where $F_o = \pi(F_0)$ as in Section 4, $F = \pi(F_1)$ similarly, and the components of the vectorfields are

$$\begin{cases} V_i(u, v) = v_i \\ W_i(u, v) = \dfrac{c^2}{2(\Delta x)^2} [u_{i+1} - 2u_i + u_{i-1}] \end{cases} \tag{5.3}$$

This may then be factored into a CD system, with standard cell,

$$\begin{cases} V(u, v) = v \\ W(u, v) = -\dfrac{c^2}{(\Delta x)^2} u + C \end{cases} \tag{5.4}$$

representing a linear spring. The coupling is by nearest neighbors,

$$C_i = \frac{c^2}{2(\Delta x)^2} [u_{i+1} + u_{i-1}] \tag{5.5}$$

as in Fig. 4.1. This is actually the discretization used by Johann I Bernoulli (1728) and d'Alembert (1749) to create the original wave equation (Cannon, 1981) . If instead of the linear wave equation (4.1) we had chosen a nonlinear one with friction, such as

$$u'' = c^2 \Delta u - \varepsilon \Delta(u^3) + \gamma u' \tag{5.6}$$

then the same process yields a CD system with standard cell,

$$\begin{cases} V(u,v) = v \\ W(u,v) = -\dfrac{c^2}{(\Delta x)^2}\,u - \dfrac{\varepsilon}{(\Delta x)^2}\,u^3 + \gamma v + C \end{cases} \tag{5.7}$$

representing a nonlinear damped spring. In this case, the serial coupling functions are

$$C_i = \frac{c^2}{2(\Delta x)^2}\,[u_{i+1} + u_{i-1}] - \frac{\varepsilon}{2(\Delta x)^2}\,[u_{i+1}^3 + u_{i-1}^3] + \frac{\gamma}{\Delta x}\,v_{i+1} \tag{5.8}$$

Note that if periodic forces are applied, we obtain a coupled array of Duffing systems.

6. Abstract memory models. To create biological organ models in the next section, we are going to couple together two different CD systems—one modeling the diffusion of morphogens (control metabolites or hormones) in the extracellular space, the other modeling the dynamics of the cells, and their near-neighbor interactions (if any). To exercise the concepts and demonstrate the capacity of such a system for morphogenesis, we are going to develop here an example of a coupled system of two CD systems, inspired by Zeeman's model for the transfer from short-term to long-term memory (Zeeman, 1977).

Example 6.1. The first CD system will be Example 4.1 from Section 4, representing the Fickian diffusion equation, with no sources or sinks. The discretization is done on the scale of the biological cells of a fictitious membrane, through which the hormone is supposed to be diffusing. All the cells of this membrane (which we shall take to be one-dimensional, to simplify the drawings) are identical, and the standard cell model will be the hysteretic *toggle switch*,

$$x' = x^3 - x - A \tag{6.1}$$

which is the simple bistable device of catastrophe theory. Its response diagram, the *double fold catastrophe*, is shown in Fig. 6.1.

Fig. 6.1 about here.

We suppose that the neighbor interactions in this membrane are nil, but that each cell is controlled by the average of the hormone concentration over its surface. This is approximately the value of u at the center of the cell, or u_i for the i-th cell. The coupling between the two CD systems is from the state of the first in a given cell (say u_i) to the control of the second *in the same cell.* Thus we have:

x: the spatial variable (continuum version)

$x_1, \ldots, x_{N-1}$: the locations of the centers of the equally-spaced identical cells (switches)

u: the concentration of hormone in the extracellular space (continuum version)

$u_1, \ldots, u_{N-1}$: the average hormone concentrations perceived by the separate cells

$\alpha_1, \ldots, \alpha_{N-1}$: the states of the cells (switches)

subject to the dynamical equations,

$$u'_i = -\frac{2c}{(\Delta x)^2}u_i + \varepsilon u_i^3 + C_i \tag{6.2}$$

with nearest neighbor coupling

$$C_i = \frac{c}{2(\Delta x)^2}(u_{i+1} + u_{i-1})$$

from (3.3), with intracell dynamics,

$$\alpha_i' = \alpha_i^3 - \alpha_i - A_i$$

from (5.1), and with

$$A_i = bu_i$$

to control the i-th cell (toggle switch) by the morphogen concentration around it. This is shown in Fig. 6.2. With initial conditions for the u_i's and α_i's chosen, let the dynamic begin. We suppose that the diffusion rate is small with respect to the relaxation rate of the switches. Thus, the α_i's go quickly to the (one or two) point attractors (ON and OFF) of the switches. As the hormone continues to diffuse to a (moderate) constant, the trajectories of the α_i's follow these attractors. While the software pattern of the initial u_i's (the short-term memory) is forgotten, the pattern (of ON's and OFF's) of the α_i's (the long-term memory) is latched into hardware. If this constant value of hormone (determined by the boundary conditions outside the cortex) is lowered, all of the switches are reset to OFF because the ON state has disappeared by a fold catastrophe. If the hormone level is now raised to the middle (again by external action at the boundary), the switches stay off (because of hysteresis). This is the *toggle memory model.*

Fig. 6.2 about here.

Example 6.2. This system is very much like a computer memory. In Zeeman's original model, inspired by neurophysiological networks, the standard cell was the Duffing system. This is a nonlinear spring (compare 4.7) with periodic forcing,

$$\begin{cases} x' = y \\ y' = -kx + hx^3 - cv + A\sin\theta \\ \theta' = 2\pi f \end{cases} \tag{6.3}$$

where the coefficients k (Hooke's spring constant), h (hardness of the spring), c (Coulomb friction constant) and A (coupling constant of the forcing oscillator) are *fixed*, and f (the frequency of the forcing oscillator) is a *control parameter*. The response diagram of this scheme (locus of attractors and separatrices) is the famous hysteresis curve, discovered by (Duffing, 1918) , see Fig. 6.1. Its behavior, in this abstract system of two coupled CD systems, is the same as the toggle switch, except that the states (ON and OFF) are oscillations (periodic attractors) rather than static equilibria (point attractors). We call it the *vibrating memory model.* Playing with this model will reveal several different mechanisms for the production of a single pattern (zebra stripes, for example) in long-term memory.

7. Membrane models. We specialize to two spatial dimensions, $n = 2$, and consider a homogeneous biological membrane from the physical point of view. We regard the cells as a uniform distribution of identical dynamical systems, say a square array. Among them, a carrier liquid, or serum, percolates. This was called a *morphogen* in (Turing, 1952) . The existence of morphogens in living systems is still controversial. This biochemical metabolite, H, diffuses within the membrane, interacting with H-receptors on the surface of the standard cell. Here we develop a few specific examples of this scheme, to illustrate the type of model proposed here. In all cases we will discretize the partial differential equations at the centers of the cells.

Example 7.1. For the percolation of H, take the linear heat equation with no sources (1.2, $\rho = 0$). For the standard cell, take the Duffing scheme (5.3), with no secretion. This is a two-dimensional version of the *vibratory memory model*, described at the end of the preceding section. It is able to latch patterns which occur briefly in the distribution of H-concentration, perhaps due to external forces.

Example 7.2. Among the behaviors of the cells might be the release of another metabolite, R, into the extracellular space, which also diffuses within the carrier liquid. We now add to the previous example an additional morphogen, R, which is secreted by the standard cells (as a response to the stimulus of the hormone, H) into the extracellular serum. Thus, it also diffuses. Taking identical (linear heat) models for each diffusion

(but with different diffusivity) we have the equations,

$$u' = \Delta u, \tag{7.2A}$$

for diffusion of H, and

$$\begin{cases} \alpha' = \beta \\ \beta' = -A_1\alpha + A_3\alpha^3 - B\beta + F\sin\theta \\ \theta' = 2\pi\mu \end{cases} \tag{7.2B}$$

for the standard cell, with coupling

$$\mu_i = Gu_i, \tag{7.2C}$$

that is, the forcing frequency within the i-th cell is proportional to the H concentration around it (frequency modulation by metabolite H), and

$$v' = d\Delta u + \rho \tag{7.2D}$$

for the diffusion of R, with the source term

$$\rho_i = E\alpha_i, \tag{7.2E}$$

so that the secretion rate of R around the i-th cell is proportional to its displacement, α_i. This system produces, from a transient (short-term, software) pattern of H, a latched (long-term, hardware) copy, which maintains a latched (long-term, software) pattern in the concentration of the response metabolite, R. See Fig. 7.1.

Fig. 7.1 about here.

Example 7.3. This is identical to the preceding, except we suppose that H and R are the same substance. The governing equations are

$$u' = c\Delta u + \rho \tag{7.3A}$$

$$\begin{cases} \alpha' = \beta \\ \beta' = -A_1\alpha + A_3\alpha^3 - B\beta + F\sin\theta \\ \theta' = 2\pi\mu \end{cases} \tag{7.3B}$$

$$\mu_i = Gu_i \tag{7.3C}$$

$$\rho_i = E\alpha_i \tag{7.3D}$$

This system is able to latch a long-term memory in the stimulus hormone level, and maintain it. Probably some dynamic patterns, such as rotating waves, can also be self-sustained.

Example 7.4. We now consider an inhomogeneous organ (or membrane) consisting of two kinds of cells, A and B, each uniformly distributed. We imagine that one cell of each type shares approximately the same location, in a uniform square lattice. Through this lattice, again, circulates serum containing a single diffusing hormone. We may represent this system by coupling together *three* CD systems. If the standard model for cells of type A is the uniform oscillator,

$$\theta' = 2\pi\mu \tag{7.4A}$$

and for B, the nonlinear damped spring scheme,

$$\begin{cases} \alpha' = \beta \\ \beta' = -A_1\alpha + A_3\alpha^3 - B\beta + C \end{cases} \tag{7.4B}$$

with serial coupling between them defined by

$$C_i = F\sin\theta_i \tag{7.4C}$$

and interaction with H defined by

$$\mu_i = Gu_i \tag{7.4D}$$

as in (6.2B), then we regain Example 7.2. This example indicates how inhomogeneous organs fit into our scheme. Again, morphogenetic behavior occurs. We see here a

similarity with the models of (Hoffman, 1989) for the visual cortex, in which visual images are transformed by the nonlinear action of a Lie group, infinitesimally generated by distinct distributions of special cells.

Many variations on these examples are possible, and worth considering. The diffusion equation may be replaced by a nonlinear, population-dependent porous medium equation. The number of morphogens may be increased, and biochemical interactions between them allowed. The coupling between hormones and receptors, assumed linear in these examples, may be replaced with more realistic (even empirical) laws. More importantly, we may add near neighbor interactions to the standard cell models of each homogeneous distribution, as well as interactions between closest neighbors of distinct populations (as in Example 7.4). The standard cell model may be a more realistic one from the literature of physiology, such as (Dempsher, 1984) or (King, 1984) . The frontier at this time is the exploration of examples like these in numerical simulation on massively parallel machines, using interactive computer graphics to observe the results (at least, for $n = 1$ or 2), as in (Abraham, 1991) . For a stimulating review of experiments with CD systems, see (Crutchfield, 1987) .

8. Numerical simulation techniques. In case a model were made according to this strategy of coupled CD systems, its utility would certainly depend primarily on its numerical simulation by digital computer. As it is simply a dynamical system with special structure, the numerical simulation could be carried out by direct application of traditional methods for dynamical systems, such as a Runge-Kutta autostep method. However, if the spatial resolution of a two-dimensional membrane is taken as 100 by 100 (a modest choice), then each array has 10,000 points. In the case of Example 7.2 (suitable for an organ such as the adrenal cortex) the overall dynamical system has dimension 40,000. Obviously, some acceleration techniques are in order. Let us, first of all, decompose the coupled CD complex into its separate CD components. In Example 7.2, these are three: the H diffusion system, the array of (uncoupled) identical cells, and the R diffusion system. (Introducing weak coupling in the second subsystem does not change this decomposition.)

For a single subsystem derived from a partial differential equation (PDE), the direct application of an ordinary differential equation (ODE) solver — such as Euler or Runge-Kutta — is rather slow. In case the algorithm is Euler, this method is identical to the *relaxation method* of Southwell for the PDE. But as Southwell's method was originally applied (during World War II) by hand, the motivation for acceleration tricks was strong. And Southwell did indeed invent some excellent ones, see (Southwell, 1940) . For example, his strategy called *advance to a finer net* is extremely effective for the relaxation of nonlinear heat and wave equations. Furthermore, as the coupling terms of CD systems obtained by discretization (as in Sections 4 and 5 above) are between nearest neighbors only, the domain may be divided into subsets, each to be integrated (in parallel) by a *separate processor.* This division into subsets may be compatible with that of Southwell's advance to a finer net. In addition, both of these techniques may also be applied to the CD subsystems corresponding to spatial arrays of identical cells (there are two of these in Example 7.4) provided that their couplings are sufficiently local—for example, among nearest neighbors only. Thus, CD subsystems of reasonable models

(comprising coupled CD systems) may be accelerated considerably.

What then, of the integration (numerical simulation) of the complex model *in toto*? Let us assume that each CD subsystem is managed adequately by its own parallel processor, by an autostep method such as RKS4/5 the Runge-Kutta-Butcher algorithm of fifth order, with embedded Sarafyan of fourth order for step size adjustments, see (Lapidus, 1977) , p. 173. As step-size is being varied independently in all of the simultaneous and parallel subsystem simulations, the coupling between them must be effected at periodic rendezvous times. Thus, we may use (in each subsystem simulation) the technique of *periodic reportage*. This means that at agreed intervals called *giant steps* (of pseudo-real time), each subsystem simulator is to round off its integration (with a *special baby*step, or small time step, if necessary) and report its *current state* to registers readable by the others, and perhaps recorded for posterity. The faster siblings must then wait for the slower ones to finish. Thus is a complete giant step taken. As the current states are available for coupling the siblings only at giant steps, the intervening babysteps (differing in total number for each simulator, as local time step adjustments are made by them) are made as if the other siblings were asleep. Thus, a poorer accuracy is maintained in the control values than in the internal dynamics of the subsystem. (How much poorer, if any, depends on the choices made by the master of the game.) This is appropriate for loosely coupled systems, or when the internal dynamics are much faster than the controls, as in Example 7.1, the vibratory memory model. With this strategy of periodic reportage, the simulation of coupled CD systems may be accomplished in a network of microcomputers, with readily available software. The integration of a sibling by the parallel-processing relaxation method, on the other hand, is more tightly coupled. This could be accomplished in a highly parallel machine.

9. Conclusion. CD complexes, the coupled cellular models proposed here, are not well-known to pure mathematics or to experimental dynamics. There is no great body of existing theory upon which to fall back. CD complexes owe their complexity to the level of fidelity with which they attempt to imitate natural systems. To the extent to which they may succeed as models, then, their behavior may be anticipated through the study of those natural systems, the target systems they aim to simulate. Thus, the best expert of the behavior of coupled CD models, to date, must be experimental scientists, such as neurophysiologists.

The situation is somewhat better for the CD simplex, a singleton CD model, coming from a PDE of evolution type. There is a growing body of literature on the morphogenetic behavior of reaction-diffusion equations (Fitzgibbon, 1984) and a corresponding body of theory for reaction-wave equations (which are closer in behavior to our vibration memory model) cannot be far behind.

The particular strategy described here for the architecture of models of complex systems such as networks of biological organs is now at about the level of mathematical physics two centuries ago. Altogether, it is clear that a further advance in this strategy will be greatly facilitated by a period of extensive experimental work. And miraculously, as described in the last section, the tools required for the rapid execution of the necessary experiments are being provided by the computer revolution at about this time. So we

hope to see some successful models in the near future.

Acknowledgements. It is a pleasure to acknowledge hospitality and financial support from Thinking Machines, Inc., in September, 1984, from the Institute des Hautes Etudes Scientifiques (Bures) in March, 1985, and from NASA Goddard Space Flight Center in August, 1989.

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FIGURE CAPTIONS

Fig. 4.1. A CD system with one-dimensional spatial substrate.

Fig. 6.1. The response diagram of the double fold catastrophe.

Fig. 6.2. The CD memory model with toggle cells and Fickian diffusion.

Fig. 7.1. A CD vibrating memory model with two diffusing metabolites and a two-dimensional spatial substrate.

Fig. 4.1

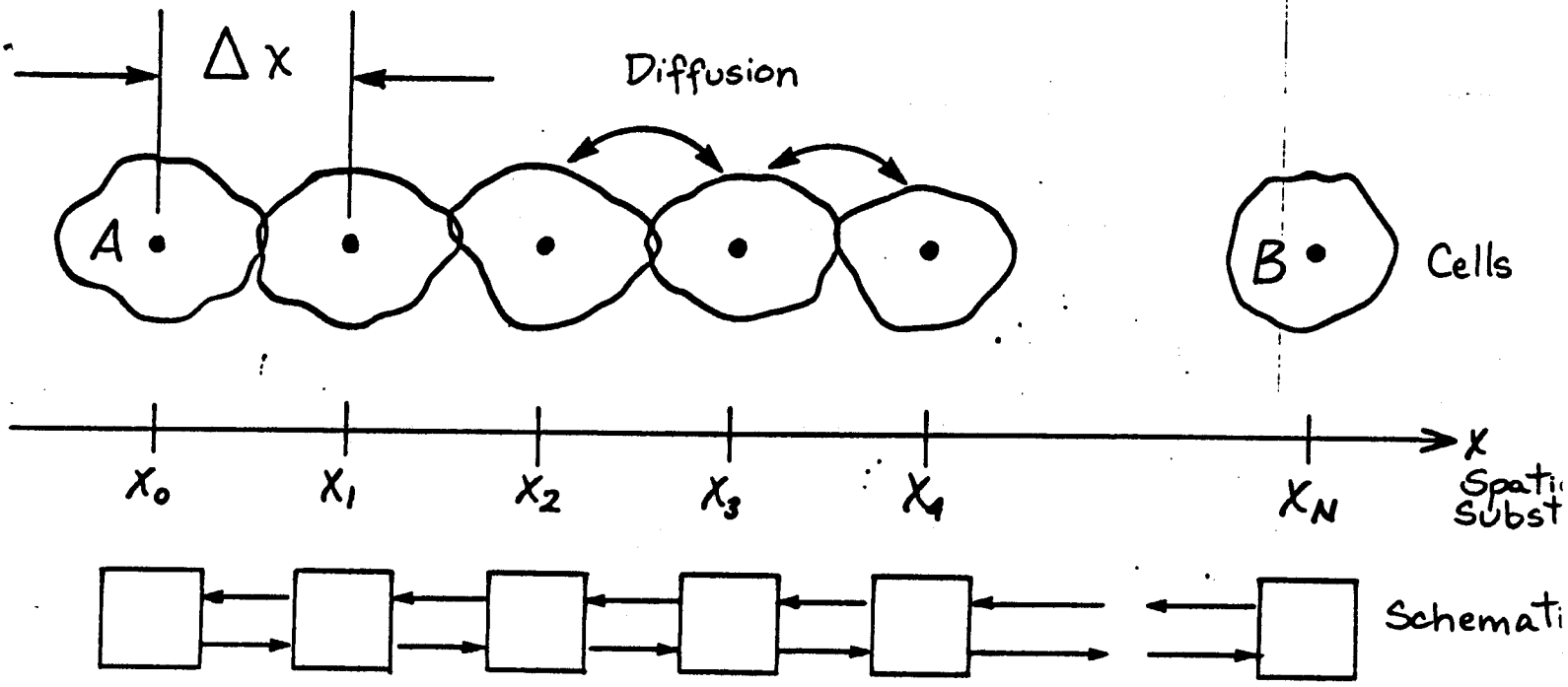
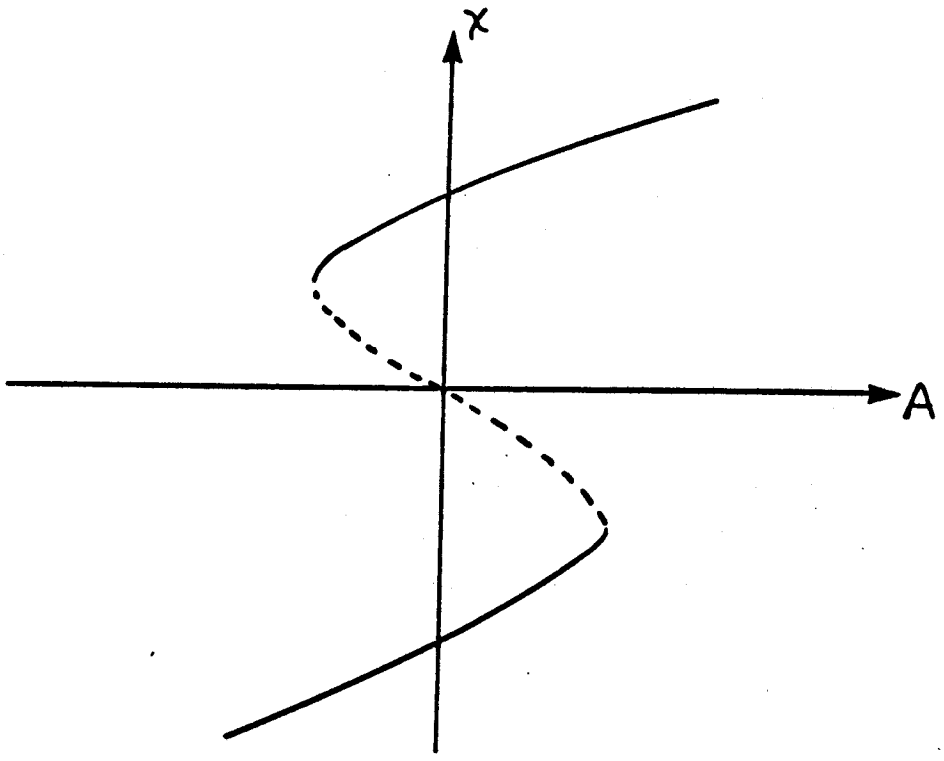

Δx
Diffusion
A
B
Cells
x
x_0
x_1
x_2
x_3
x_4
x_N
Spati
Subst
Schemati

Fig. 5.1


x
A

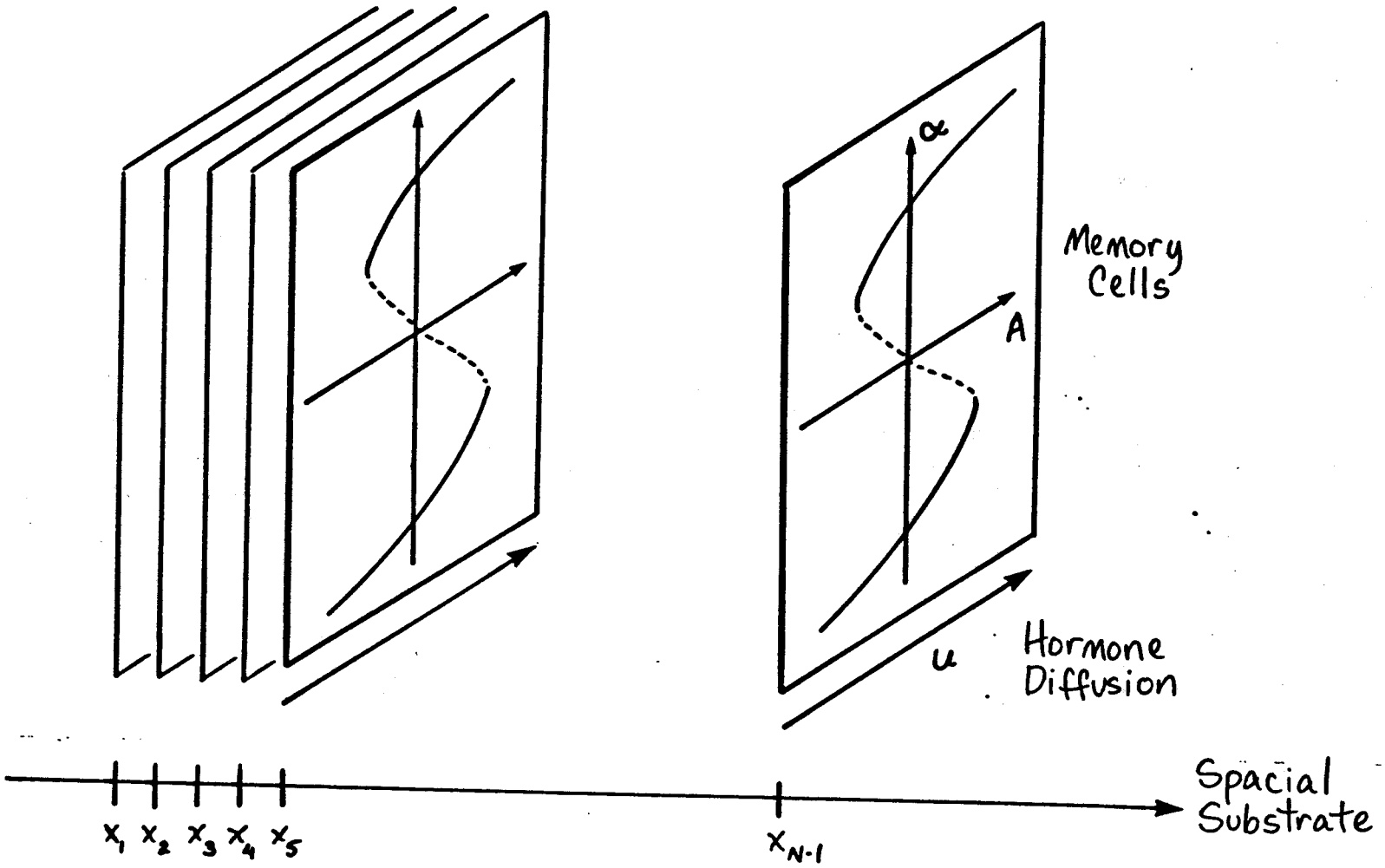

α
A
Memory Cells
u
Hormone Diffusion
x_1 x_2 x_3 x_4 x_5
x_{N-1}
Spacial Substrate

Fig. 1.