

## SECTION 11

## A MATHEMATICAL MODEL OF TWO CELLS

## VIA TURING'S EQUATION

BY

S. SMALE

(11.1) Here we describe a mathematical model in the field of cellular biology. It is a model for two similar cells which interact via diffusion past a membrane. Each cell by itself is inert or dead in the sense that the concentrations of its enzymes achieve a constant equilibrium. In interaction however, the cellular system pulses (or expressed perhaps over dramatically, becomes alive!) in the sense that the concentrations of the enzymes in each cell will oscillate indefinitely. Of course we are using an extremely simplified picture of actual cells.

The model is an example of Turing's equations of cellular biology [1] which are described in the next section. I would like to thank H. Hartman for bringing to my attention

---

Reprinted with permission of the publisher, American Mathematical Society, from Lectures in Applied Mathematics. Copyright © 1974, Volume 6, pp. 15-26.

the importance of these equations and for showing me Turing's paper.

The general idea of our model is to first give abstractly an example of a dynamical system for the chemical kinetics of four chemicals (or enzymes). This dynamics represents the reaction of these chemicals with each other and has the property that every solution tends to one unique stationary point or equilibrium in the space of concentrations as time goes to  $\infty$ . This is the sense in which the cell is dead, where the cell consists of these four chemicals. After a period of transition, the chemical system stays at equilibrium. We emphasize that our reaction process is an abstract mathematical one and that we have not tried to find four chemicals with this kind of chemical kinetics.

The next step is to give four positive diffusion constants for the membrane which could describe the diffusion of the four chemicals past the membrane. The cellular system consisting of the two cells separated by the membrane will be described by differential equations according to Turing. With our choice of the chemical kinetics and diffusion constants this new dynamical system will have a nontrivial periodic solution and essentially every solution will tend to this periodic solution. Thus no matter what the initial conditions, the interacting system will tend toward an oscillation (with fixed period). After an interval of transition, it will oscillate.

Both the equilibrium of the isolated cell and the oscillating solution of the interacting system described above are stable (or are attractors) and even stable in a global

way. But more than this, the equations themselves are stable so that any equations near ours have the same properties. Our dynamical systems are "structurally stable." This gives them at least a physical possibility of occurring.

In Turing's original paper some examples of Turing's equations are given with oscillation. However, these are linear and it is impossible to have an oscillation in any structurally stable linear dynamical system. Linear analysis can be used primarily to understand the neighborhood of an equilibrium solution. Development of linear Turing theory has been carried very far in the very pretty paper of Othmer and Scriven [1].

Our example has reasonable boundary conditions, as one or more of the concentrations goes to 0 or to  $\infty$ . Also, a complete phase portrait of the differential equation in eight dimensions for the cellular system is obtained.

This example and Turing's equations as well go beyond biology. The model here shows how the linear coupling of two different kinds of processes, each process in itself stationary, can produce an oscillation. This is the coupling of transport processes (in this case diffusion across a membrane) and transformation processes (in this case chemical reactions). In ecology, Turing's equations have another interpretation; see, e.g., Levin [1]. Also S. Boorman's Harvard Thesis has a related interpretation and analysis.

We finally remark that our results could equally well be interpreted as putting a single cell into an environment which could start it pulsating.

(11.2) We give a brief description of Turing's equations [1]. These are sometimes called Rashevsky-Turing equations because of earlier work of Rashevsky on this subject.

One starts from a cell-complex, in either the biological or mathematical sense of the word, e.g., as given in Figure 11.1.

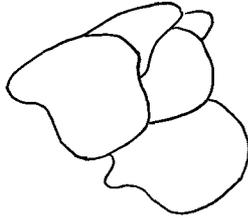


Figure 11.1

From the mathematical point of view this system is a cell-complex structure on a two- or three-dimensional manifold (e.g., an open set of  $R^2$  or  $R^3$ ). Suppose there are  $N$  cells and they are numbered  $1, \dots, N$ .

It is supposed that the cells contain enzymes (or chemicals, or "morphogens" in the terminology of Turing) which react with each other. Suppose there are  $m$  of these chemicals. Then the state space for each cell is the space

$$P = \{x \in R^m \mid x = (x^1, \dots, x^m), x^i \geq 0, \text{ each } i\},$$

where  $x^i$  denotes the concentration of the  $i^{\text{th}}$  chemical.

The state space for the system under discussion is the Cartesian product  $P \times \dots \times P$  ( $N$  times) or  $(P)^N$ . Thus a state for this cellular system is a point,  $x \in (P)^N$ ,

$x = (x_1, \dots, x_n)$  with each  $x_i \in P$  giving all the concentrations for the  $i^{\text{th}}$  cell,  $i = 1, \dots, N$ . The dynamics for the typical cell by itself is given by an ordinary differential equation on  $P$ ; this can be described by a map  $R: P \rightarrow R^m$  and  $dx/dt = R(x)$ . This  $R$  describes how the chemicals react with each other in that cell; the subject of chemical kinetics deals with the nature of  $R$ . Most typically, the dynamics of  $dx/dt = R(x)$  on  $P$  is described by the existence of a single equilibrium  $\bar{x} \in P$  such that every solution tends to  $\bar{x}$ ; at least this will be the case if conservation laws have been taken into account one way or another (as in the situation in Turing [1] or Othmer and Scriven [1]).

A natural boundary condition on this equation is that if  $x \in P$ ,  $x = (x^1, \dots, x^m)$ , with  $x^k = 0$ , then the  $k^{\text{th}}$  component  $R^k(x)$  of  $R(x)$  is positive.

So far we have discussed each cell in some kind of hypothetical isolation. The cells are separated from each other by a membrane which allows for diffusion from one cell to adjoining cells. In the simplest case of diffusion, if a certain chemical has a bigger concentration in the  $r^{\text{th}}$  cell than an adjoining well, then the concentration of that chemical decreases in the  $r^{\text{th}}$  cell, at a rate proportional to the difference. This gives some motivation to Turing's equations which add this diffusion term to give an interaction between the cells.

$$(T) \quad \frac{dx_k}{dt} = R(x_k) + \sum_{\substack{i \in \text{set of cells} \\ \text{adjoining } k\text{th cell}}} \mu_{ik} (x_i - x_k), \quad k = 1, \dots, N.$$

Let us explain (T) in detail. The first term above,

$R(x_k)$  gives the chemical kinetics in the  $k^{\text{th}}$  cell. The 2nd term above describes the diffusion processes between cells. Thus  $x_i - x_k \in \mathbb{R}^m$  represents the difference of the concentrations of all the chemicals between the  $i^{\text{th}}$  and  $k^{\text{th}}$  cells. Here  $\mu_{ik}$  is a linear transformation from  $\mathbb{R}^m$  to  $\mathbb{R}^m$  or an  $m \times m$  matrix. In the most natural simple case, and the case we develop here,  $\mu_{ik}$  is a positive diagonal matrix. Also the chemical kinetics for each cell is considered the same. (T) is a 1st order system of ordinary differential equations on the state space  $(P)^N$  of the biological system, and will tell how a state moves in time.

We specialize to a case of 2 cells adjoined along a membrane which is the example pursued in the rest of the paper.

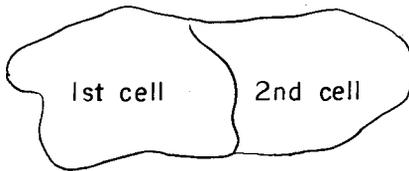


Figure 11.2

$$(T_2) \quad \begin{aligned} dz_1/dt &= R(z_1) + \mu(z_2 - z_1), \\ dz_2/dt &= R(z_2) + \mu(z_1 - z_2). \end{aligned}$$

This is an equation on  $P \times P$  with  $(z_1, z_2) \in P \times P$ . Here  $\mu$  will be of the form

$$\begin{pmatrix} \mu_1 & 0 \\ & \ddots \\ 0 & \mu_m \end{pmatrix}$$

with each  $\mu_i > 0$ . This is the most simple case. We may also write  $(T_2)$  as given by a vector field  $X$  on  $P \times P$  where

$$X(z_1, z_2) = (R(z_1) + \mu(z_2 - z_1), R(z_2) + \mu(z_1 - z_2)).$$

(11.3) Here we state our results.

Main Theorem. Let  $P = \{z \in \mathbb{R}^4, z = (z^1, z^2, z^3, z^4), z^i \geq 0\}$ . There exists a smooth  $(C^\infty)$  map  $R: P \rightarrow \mathbb{R}^4$ , and  $\mu_1, \dots, \mu_4 > 0$  with the following properties (1), (2), (3) below:

(1) The differential equation  $dz/dt = R(z)$  on  $P$  is globally asymptotically stable and is structurally stable.

In other words there is a unique equilibrium  $\bar{z} \in P$  of the differential equation and every solution tends to  $\bar{z}$  as  $t \rightarrow \infty$ . That  $R$  is structurally stable means that the equation  $dz/dt = R_0(z)$  has the same structural properties as  $dz/dt = R(z)$  if  $R_0$  is a  $C^1$  perturbation of  $R$ . (See [1] for details on these kinds of stability and background on ordering differential equations.)

(2) On  $P \times P$  with  $z = (z_1, z_2) \in P \times P$  the differential system,

$$(T) \quad \begin{aligned} dz_1/dt &= R(z_1) + \mu(z_2 - z_1), \\ dz_2/dt &= R(z_2) + \mu(z_1 - z_2), \end{aligned} \quad \mu = \begin{pmatrix} \mu_1 & 0 \\ & \ddots \\ 0 & \mu_4 \end{pmatrix},$$

is a "global oscillator" and is structurally stable.

More precisely, a global oscillator on  $P \times P$  is a dynamical system which has a nontrivial attracting periodic solution  $\gamma$  and except for a closed set  $\Sigma$  of measure 0,

every solution tends to  $\gamma$ , as  $t \rightarrow \infty$ . In fact, here  $\gamma$  is a six-dimensional smoothly imbedded cell and on  $\gamma$  every solution tends to the unique equilibrium  $(\bar{z}, \bar{z})$  of (T).

(3) The boundary conditions are reasonable in the following way. Let  $z_0 = (z_0^1, z_0^2, z_0^3, z_0^4) \in P$  satisfy  $z^k = 0$  for some  $k$  between one and four. Then the  $k^{\text{th}}$  component  $R^k(z_0)$  of  $R(z_0)$  is positive.

The above theorem gives mathematical precision to the statements made in Section 1 via the interpretation of (T) as in Section 2.

The example is related to the phenomena of Hopf bifurcation; see Section 3. Our analysis is more global however, and we have a complete description of the phase portrait.

(11.4) In this section we show how to construct the differential equations of the previous section.

Towards obtaining the vector field  $Q: P \rightarrow R^4$  of the main theorem of Section 3 we will find a  $C^\infty$  vector field  $Q: R^4 \rightarrow R^4$  on  $R^4$  and

$$\mu = \begin{pmatrix} \mu_1 & & & 0 \\ & \ddots & & \\ 0 & & & \mu_4 \end{pmatrix}$$

with these properties:

(1)  $Q$  has the origin, 0, as a global attractor for the equation  $dz/dt = Q(x)$  on  $R^4$ .

(2) There is a  $K > 0$  such that if  $z \in R^4$ ,  $\|z\| \geq K$ , then  $Q(z) = -z$ .

(3) On  $R^4 \times R^4$  the vector field

$$(z_1, z_2) \rightarrow (2Q(z_1) + \mu(z_2 - z_1), 2Q(z_2) + \mu(z_1 - z_2))$$

is a global oscillator.

Once such a  $Q$  has been found we finish as follows: Choose some  $\bar{z} \in P$  so that  $z - \bar{z} \in P$  for all  $z$  with  $\|z\| \leq K$ . Let  $R(z) = 2Q(z - \bar{z})$ . Then  $R$  will have the properties of Section 3.

This changes the question from  $P$  to  $R^4$  where we can use the linear structure systematically (even though our equations are not linear).

To find a  $Q$  as needed above we first ignore property (2), or behaviour of  $Q$  at  $\infty$  and concentrate on (1) and (3). In fact we shall find  $S: R^4 \rightarrow R^4$  satisfying (1) and (3) with  $S$  replacing  $Q$  and after that  $S$  is modified to satisfy (2).

Toward constructing this  $S$ , observe that the set  $\Delta = \{(z_1, z_2) \in R^4 \times R^4 \mid z_1 = z_2\}$  has the property that the vector field

$$(*) \quad (2S(z_1) + \mu(z_2 - z_1), 2S(z_2) + \mu(z_1 - z_2))$$

is tangent to  $\Delta$ . That is,  $\Delta$  is invariant under the flow and on  $\Delta$  the flow is contracting to the origin.

Now suppose  $S$  satisfies  $S(-z) = -S(z)$  or that  $S$  is odd. Then on

$$\Delta^\perp = \{(z_1, z_2) \in R^4 \times R^4 \mid z_1 = -z_2\}$$

the vector field (\*) is invariant and has the form

$$z \rightarrow S(z) - \mu(z)$$

(up to a factor of 2). From these considerations we are motivated to seek an odd map  $S: \mathbb{R}^4 \rightarrow \mathbb{R}^4$  which satisfies the following:

(S1)  $S$  has 0 as a global attractor and  $S - \mu$  is a global oscillator on  $\mathbb{R}^4$ .

(S2)  $\Delta^1$  is an attractor for (\*) on  $\mathbb{R}^4 \times \mathbb{R}^4$ .

(S3) Boundary conditions can be made good.

The heart of the matter lies in (1); we consider that next. First consider the matrix

$$\bar{\mu} = \begin{pmatrix} a & 0 & \gamma a & 0 \\ 0 & a & 0 & \gamma a \\ -\gamma a & 0 & -2a & 0 \\ 0 & -\gamma a & 0 & -2a \end{pmatrix}$$

where  $a < -1$  and  $\sqrt{2} < \gamma < 3/2$ , in linear coordinates  $y = (y^1, \dots, y^4)$  on  $\mathbb{R}^4$ .

Note that  $\bar{\mu}$  has real positive eigenvalues say  $\mu_1, \mu_2, \mu_3, \mu_4$ . This can be checked easily since  $\bar{\mu}$  resembles a  $2 \times 2$  matrix. Also there is a linear change of coordinates which changes the matrix

$$\mu = \begin{pmatrix} \mu_1 & & & 0 \\ & \ddots & & \\ 0 & & & \mu_4 \end{pmatrix} \text{ into } \bar{\mu}.$$

The coordinates of chemical concentrations are those in which  $\bar{\mu}$  has the diagonal form. Thus the  $y_i$  do not represent concentrations. However the  $y$  coordinates are much easier to work with.

We give now  $S$  as the sum of a linear map  $S_1: \mathbb{R}^4 \rightarrow \mathbb{R}^4$  and a cubic map  $S_3$  in terms of the  $y$ -coordinates.

Thus let  $S = S_1 + S_3$  with

$$S_1 = \begin{pmatrix} 1+a & 1 & \gamma a & 0 \\ -1 & a & 0 & \gamma a \\ -\gamma a & 0 & 2a & 0 \\ 0 & -\gamma a & 0 & 2a \end{pmatrix}$$

$$S_3(y) = (-(y^1)^3, 0, 0, 0).$$

One notes now that  $S$  is odd and since the inner product  $\langle Sy, y \rangle < 0$  if  $y \neq 0$  (an easy check) it follows that the origin of  $R^4$  is a global attractor for  $S$ .

The next step is to check that  $S - \mu$  takes the form

$$\left[ \begin{pmatrix} 1 & 1 \\ -1 & 0 \end{pmatrix} \quad 0 \\ 0 \quad \begin{pmatrix} 4a & 0 \\ 0 & 4a \end{pmatrix} \right] + S_3.$$

Thus the  $(y^1, y^2)$  2-dimensional subspace is a contracting invariant subspace in  $R^4$  for  $S - \mu$ , since  $a < 0$ ; on this subspace, the equations for  $S - \mu$  take the form

$$dy'/dt = y^2 - ((y')^3 - y^1), \quad dy^2/dt = -y^1.$$

This is Van der Pol's equation (see Hirsch-Smale [1]), which we know is a global oscillator.

Thus  $S - \mu$  is a global oscillator on  $R^4$ .

The next step is to show that (S2) is true. This can be proved along the following lines.

The vector field  $X$  on  $R^4 \times R^4$  given by

$$X(z) = (2S(z_1) + \mu(z_2 - z_1), 2S(z_2) + \mu(z_1 - z_2))$$

can be written in the form  $Y_1(z) + Y_2(z)$  where  $Y_1(z) \in \Delta$ ,  $Y_2(z) \in \Delta^\perp$ . Then

$$Y_1(z) = (S(z_1) + S(z_2), S(z_1) + S(z_2)),$$

$$Y_2(z) = (S(z_1) - S(z_2) + \mu(z_2 - z_1), \\ -(S(z_1) - S(z_2) + \mu(z_2 - z_1))).$$

That  $X$  points toward  $\Delta^\perp$  follows from the lemma.

Lemma.  $\langle S(z_1) + S(z_2), z_1 + z_2 \rangle \leq 0$ .

Proof of Lemma. Write  $S = S_1 + S_2$ . We already know

$$\langle S_1(z_1) + S_1(z_2), z_1 + z_2 \rangle = \langle S_1(z_1 + z_2), z_1 + z_2 \rangle \leq 0.$$

But

$$\langle S_3(z_1) + S_3(z_2), z_1 + z_2 \rangle = [-(y_1^1)^3 - (y_2^1)^3] \cdot (y_1^1 + y_2^1)$$

and that is  $\leq 0$  since, for any real numbers  $a$  and  $b$ ,  $(a^3 + b^3)(a + b) \geq 0$ .

Finally one "straightens out" the flow of  $S$  outside some large ball. One uses a smooth function  $\phi: \mathbb{R}^+ \rightarrow \mathbb{R}^+$ ,  $0 \leq \phi \leq 1$ ,  $\phi \equiv 0$  in a neighborhood of  $0$ , and  $\phi(r) \equiv 1$  for large enough  $r$ ; then

$$Q(z) \equiv (1 - \phi(\|z\|))S(z) - \phi(\|z\|)z.$$

It can be shown that  $Q$  satisfies (1), (2), (3) with suitable constants in the definition of  $\phi$ .

(11.5) We end this note with some discussion of our results.

Various forms of Turing's equations, or reaction-

diffusion equations have appeared in one form or another in many works and fields. However, any sort of systematic understanding or analysis seems far away. Before one can expect any general understanding, many examples will have to be thought through, both on the mathematical side and on the experimental side. This is one reason why I have worked out this model.

Moreover, the work here poses a sharp problem, namely to "axiomatize" the properties necessary to bring about oscillation via diffusion. In the 2-cell case, just what properties does the pair  $(R, \mu)$  need to possess (where  $R$  is "dead") to make the Turing interacting system oscillate? In the many-cell case, how does the topology contribute?

We have not hesitated to make simplifying assumptions here, because we were not making an analysis, but producing an example. Because of the structural stability properties of this example, one can use it to obtain more complicated examples, e.g., with as many cells (more than one) as one wants, as many chemicals (more than three) as one wants and complicated diffusion matrices. But it is more difficult to reduce the number of chemicals to two or even three. Also it is a problem to construct a model with three cells and two or three chemicals.

There is a paradoxical aspect to the example. One has two dead (mathematically dead) cells interacting by a diffusion process which has a tendency in itself to equalize the concentrations. Yet in interaction, a state continues to pulse indefinitely.

Several chemists have pointed out to me that interpreting the reaction R to be an "open system" makes the model more acceptable.

There is quite a history of numerical work on related systems which I will not try to cover here.

Finally, there is a partial differential equation analogue to the version of Turing's equations studied here. This can be found in Turing's paper [1]. In this P.D.E. context the recent work of L. Howard and N. Kopell on the Zhabotinsky oscillation bears strong analogies to the present work.