

# Is the skin an excitable medium? Pattern formation in erythema gyratum repens

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Erythema gyratum repens (EGR) is a rare, inflammatory dermatosis of unknown aetiology. The morphology of the eruption is striking and displays rapidly evolving circinate and gyrate bands of erythematous and scaly skin. Although the aetiology of the pattern is unknown, it has previously been noted that the eruption shares morphologic features with the patterns of spatio-temporal chemical concentration profiles observed in the Belusov-Zhabotinski (BZ) reaction. Yet this morphologic correspondence has not been investigated further. Here we apply a simple non-linear reaction–diffusion model, previously used to describe the BZ reaction, as a template for pattern formation in EGR, and show how the mechanism may provide a biochemical basis for many of the dynamic and morphologic features of the rash. These results are supported by the results of a cellular automaton simulation approximating the dynamics of oscillatory chemical systems—the Hodgepodge machine—where the spatio-temporal patterns developed show astonishing similarities to the morphology of EGR.

*Keywords:* Erythema gyratum repens; Pattern formation; Reaction diffusion; Spatio-temporal patterns

## 1. Introduction

Erythema gyratum repens (EGR) is a rare, non-infectious inflammatory dermatosis of unknown aetiology first described by Gammel [1] (figure 1). The morphology of the eruption is often described as serpiginous [2] or gyrate with bands of inflammation moving across the skin surface. It has been likened to ‘wood-grain’ and the clinical appearance, which may affect the whole integument with the exception of palms and soles, is distinctive. It has been reported as paraneoplastic in 82% of cases where the commonest association is carcinoma of the bronchus [2]. Despite its strong association with underlying malignancy, the pathogenesis remains unknown. However, it is thought by most investigators that the eruption is a manifestation of an immune response in the skin [2,3]. Holt and Davies suggested the rash may be a consequence of either tumour antigens cross reacting with skin antigens, tumour induced hapten production in the skin, or tumour antigen–antibody complexes depositing in the skin [3]. In support of these ideas Caux found positive direct immunofluorescence in both the skin and tumour (bronchial) basement membrane [4]. Although the histology is non-specific, Langerhans cells have been found in an abnormal suprabasal position

suggesting the presence of antigen at that site [5]. Direct immunofluorescence in affected tissue has been reported as both negative [5,6] and positive; the latter has revealed granular C3 and IgG deposition along the basement membrane [4]. It is unknown why EGR is sometimes not paraneoplastic, however, it has been postulated that similar mechanisms to those noted above may occur if non-tumour antigens were involved in the generation of antibody [7].

Despite the distinctive and remarkable clinical appearance of EGR, there is a paucity of discussion in the literature regarding the aetiology of its morphology and rapid evolution. Stone, writing on the causes of annular eruptions, has suggested that cutaneous inflammation may lead to changes in the physico-chemical properties of the ground substance such that the diffusion of pro-inflammatory mediators may be augmented [8]. Hence, it was suggested ring-like structures may be a consequence of outward diffusion. It was noted by Wakeel that the migratory nature of the rash in EGR is difficult to explain [5]. However, Moore, in a letter to the *British Journal of Dermatology* in 1982, noted the similarity of the eruption to the travelling wavefronts of the BZ reaction and in the patterns of growth in agar of the slime

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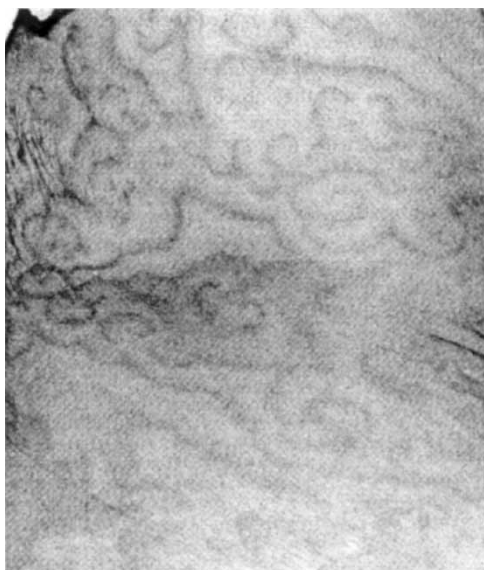


Figure 1. Erythema gyratum repens. Reproduced from Wakeel *et al.* [5] with permission from Blackwell Publishing.

mould *D. Discoideum* [9]. Yet this remarkable morphologic correspondence has not been investigated further.

In 1952, Belusov discovered a chemical reaction in the laboratory in which the concentration of certain chemicals varied periodically in time [10]. It is now known that chemical concentrations can vary periodically in time and space, and if the chemical reactions are of sufficient complexity, their long term behaviour may exhibit chaotic spatio-temporal dynamics [11]. A mixture of malonic acid, potassium bromate, cerous sulphate and sulphuric acid can exhibit target-like patterns of expanding and colliding rings in a thin layer if the differences in chemical concentration are linked to an indicator, such as one that changes color with variations in  $pH$  (figure 2). Rotating spiral forms are also easily produced. The chemistry of such a process is reasonably well understood and involves auto-catalysis and inhibition [12]. Mathematical modeling in one spatial dimension of these reaction sequences leads to equations such that their solutions may exhibit spatio-temporal oscillation in chemical concentration [13]. These one-dimensional plane wave solutions can in fact model the target patterns and the shock-like structures present in the two-dimensional case [14]. In the following, a specific reaction–diffusion model, previously described by Kopell and Howard [13] to explain the concentric ring-like appearance of the BZ reaction, will be used to describe some of the morphologic and dynamic features of EGR. How, then, is this model justified?

First, the morphology of EGR, the BZ reaction and *cAMP* waves in slime mould culture show striking similarities. All display concentric rings of expanding fronts and appear to have distinct “bulls-eyes” developing randomly in the domain on which the patterns arise. In the

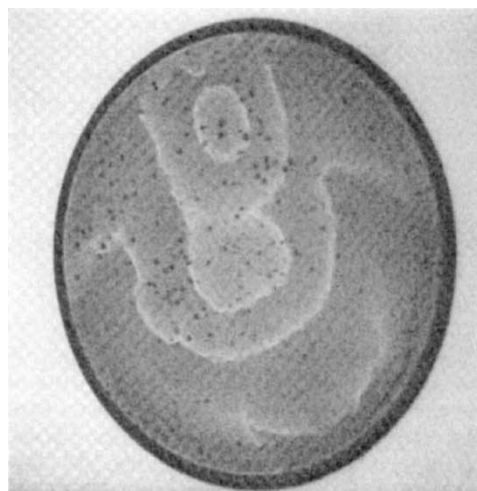


Figure 2. Morphology of the Belusov-Zhabotinski reaction. Reproduced from Ball [17] with permission from Oxford University Press.

BZ reaction individual concentric ring patterns exhibit their own characteristic wavelength [11], and this feature is sometimes observed in EGR. In addition, the morphology of the shock fronts<sup>†</sup> are similar. Spiral forms are present in EGR (see figure 1) and such patterns are easy to produce in the BZ reaction [11]. These morphologic considerations suggest the patterns of cutaneous disease in EGR, by analogy with the BZ reaction and *cAMP* waves in slime mould culture, are due to a wave-like phenomenon.

Second, consider the dynamic properties of EGR. The bands of inflammatory skin move with velocities up to 1 cm per day [2]. Hitherto, there has been no adequate explanation for this observation. As noted above, Stone suggested ring-like phenomena in the skin may be due to simple Fickian diffusion [8]. However, it is impossible for biological molecules to diffuse as quickly as the reported rates of ring expansion in EGR. Small ionic species such as the bromide ion, with a diffusion coefficient of the order  $10^{-5} \text{ cm}^2 \text{ s}^{-1}$  [15], require tens of hours to be transported 1 cm. *In vivo*, the transport of biological molecules of larger molecular weights will, over longer distances, lead to transport times incompatible with the rates of ring expansion reported in EGR.<sup>‡</sup> For example, sucrose, with a diffusion coefficient of  $5 \times 10^{-6} \text{ cm}^2 \text{ s}^{-1}$  [16], requires approximately one month to be transported 5 cm. Mathematical models of the BZ reaction reveal solutions in which the bromide ion concentration waveform achieves velocities of propagation far greater than can be expected by diffusion alone [15]. In the following a similar process is proposed to account for the speed of propagation of the bands of inflammation in EGR.

Third, by analogy with the BZ reaction, EGR appears to undergo a process of *self-organisation*. Hence, it may be

<sup>†</sup>A shock is a discontinuity in a chemical concentration gradient and is produced when different expanding rings collide.

<sup>‡</sup>The characteristic time for diffusive transport is of the order  $x^2/D$ , where  $x$  is the distance and  $D$  is the diffusion coefficient.

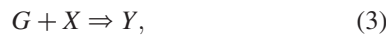
possible to think of the nature of the eruption as an example of a *dissipative structure*, a term used by Prigigone to describe physical systems held far from thermodynamic equilibrium [18]. The organisation of spatio-temporal pattern in the skin is reflected by a reduction in the Shannon entropy of the system. It is a measure of the probability distribution of finding a given molecule in a small volume of skin. Clearly this measure is not maximal in EGR, since the inflammation is spatio-temporally ordered and not smoothly distributed. On the other hand, if the skin eruption in EGR did not represent an example of a dissipative structure, with the passage of time it would be expected that the appearance of the rash would lose coherence, a feature not observed in EGR. Dissipative structures depend on non-linear feedback between the production and destruction of molecular species, and such behaviour is likely to be an important part of immune regulation.

Finally, it appears reasonable to suggest chemical concentration waves can propagate in the skin microenvironment since the existence of chemical concentration waves in biological settings is now well established. For example, macromolecules such as RNA have been shown to exhibit wave-like properties in capillary tubes *in vitro* [19], *cAMP* waves have been observed in slime mould cultures, and calcium waves are thought to play an important role in some aspects of embryogenesis [20]. Significantly, the most successful explanation for the migratory nature of the pigmentary patterns over the skin of the angelfish *Pomacanthus* invokes a reaction–diffusion wave [21].

## 2. Methods

### 2.1 A reaction–diffusion model

Consider the following set of chemical transformations:



Here, the spatio-temporal evolution of  $X$  and  $Y$  is to be determined. By the law of mass action, the above reaction sequence is equivalent to the following coupled partial differential equations, where it is assumed  $D$ ,  $E$  and  $F$  have no biologic role and the diffusion of  $X$  and  $Y$

(with common diffusion coefficient  $d$ ) is included:

$$\frac{\partial A}{\partial t} = k_1 \tilde{C} + k_2 A^2 B - k_3 \tilde{G} A - k_4 A + d \frac{\partial^2 A}{\partial x^2}, \quad (5)$$

$$\frac{\partial B}{\partial t} = -k_2 A^2 B + k_3 \tilde{G} A + d \frac{\partial^2 B}{\partial x^2}, \quad (6)$$

where  $A$ ,  $B$ ,  $\tilde{C}$  and  $\tilde{G}$  denote the concentrations of  $X$ ,  $Y$ ,  $C$  and  $G$ , respectively ( $\tilde{C}$  and  $\tilde{G}$  are assumed constant), the  $k_1$ – $k_4$  are rate constants, and  $t$  is time. With the following substitutions:

$$u = \frac{A}{\tilde{G}}, \quad v = \frac{B}{\tilde{G}}, \quad \tilde{t} = k_1 t, \quad L = \sqrt{\frac{d}{k_1}}, \quad \tilde{x} = \frac{x}{L}, \quad (7)$$

$$a = \frac{\tilde{C}}{\tilde{G}}, \quad b = \frac{k_3}{k_1} \tilde{G}, \quad c = \frac{k_2}{k_1} \tilde{G}^2, \quad e = \frac{k_4}{k_1}, \quad (8)$$

the non-dimensional equations are obtained:

$$\frac{\partial u}{\partial \tilde{t}} = a - eu - u(b - cuv) + \frac{\partial^2 u}{\partial \tilde{x}^2}, \quad (9)$$

$$\frac{\partial v}{\partial \tilde{t}} = u(b - cuv) + \frac{\partial^2 v}{\partial \tilde{x}^2}, \quad (10)$$

where the tildes are dropped for convenience. For simplicity parameters  $a$ ,  $c$  and  $e$  are set to equal unity. Equations (9) and (10) have been studied by Prigigone and Lefever [22]. Wave train solutions will be found if the substitution

$$z = \tilde{t} - (\alpha/\omega)x \quad (11)$$

(where  $\alpha$  and  $\omega$  are the non-dimensional wavenumber and frequency, respectively) yield values of  $\alpha$  and  $\omega$  such that  $2\pi$ -periodic solutions for  $u$  and  $v$  in  $z$  exist. The existence of plane wave solutions for a more general class of reaction–diffusion equations has been discussed in detail by Kopell and Howard [13]. For the purposes of this analysis, it suffices to show that a one-parameter family of plane waves as solutions to equations (9) and (10) will exist if the reaction kinetics, in the absence of diffusion, exhibit stable limit cycle solutions. To demonstrate the existence of a stable limit cycle it is necessary to construct a trapping region in the phase plane which contains an unstable spiral at the critical point<sup>†</sup> (*Poincare-Bendixon theorem*<sup>‡</sup>). The Jacobian for the reaction kinetics of equations (9) and (10) at the

<sup>†</sup>The nullclines are curves in phase space given by (9) and (10) where the space and time derivatives are set to zero. The critical point is found at the intersection of the nullclines.

<sup>‡</sup>The Poincare-Bendixon theorem states that if a trajectory is confined to a closed, bounded region and there are no fixed points in the region, then the trajectory must eventually approach a closed orbit.

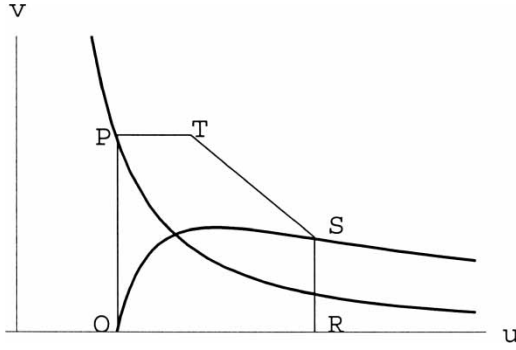


Figure 3. Schematic representation of the existence of a confined set  $PQRST$  for the kinetics (9) and (10) without diffusion for  $b = 3.6$ . Since the critical point is an unstable spiral and all trajectories cross  $PQRST$  pointing inward, a limit cycle solution exists within this bound.

critical point ( $u = 1$ ,  $v = b$ ) is given by

$$\begin{bmatrix} b - 1, & 1 \\ -b, & -1 \end{bmatrix}.$$

For the critical point to be an unstable spiral the eigenvalues must be complex with positive real part. This is only satisfied for  $2 < b < 4$ . Figure 3 shows the construction of a trapping region  $PQRST$  in the  $u, v$  phase plane for  $b = 3.6$ . Along the boundaries  $TP, PQ, QR$  and  $RS$   $dv/dt < 0$ ,  $du/dt > 0$ ,  $dv/dt > 0$  and  $du/dt < 0$ , respectively, hence these trajectories point inward. Since

$$\frac{du}{dt} - \left( -\frac{dv}{dt} \right) = 1 - u \quad (12)$$

it follows that, for  $u > 1$

$$\frac{du}{dt} < -\frac{dv}{dt}. \quad (13)$$

But the line segment  $ST$  has slope  $-1$ , hence, there are no trajectories that can cross this line pointing outward. This completes the trapping region  $PQRST$ , thus satisfying the requirements of the Poincare-Bendixon theorem. Since the intersection of the nullclines is an unstable critical point with growing oscillations, a limit cycle solution exists within this confined set. A stable limit cycle then exists as a solution to the reaction kinetics of equations (5) and (6). Thus a one-parameter family of plane waves will exist as solutions to the reaction-diffusion equations (9) and (10). For other choices of  $b$ , the existence of plane wave solutions depends, as above, on the presence of the corresponding confined set.

Substitute  $z = t - (\alpha/\omega)x$  into equations (9) and (10) and define

$$\frac{du}{dz} = q, \quad (14)$$

$$\frac{dv}{dz} = r. \quad (15)$$

Then

$$\frac{dq}{dz} = \frac{\omega^2}{\alpha^2} (q - 1 + u + 3.6u - u^2v), \quad (16)$$

$$\frac{dr}{dz} = \frac{\omega^2}{\alpha^2} (r - 3.6u + u^2v). \quad (17)$$

The coupled ordinary differential equations (14)–(17) will yield a family of plane wave solutions for differing values of  $\omega^2/\alpha^2$ . Kopell and Howard have solved these equations numerically giving specific values of  $\omega^2/\alpha^2$  and initial conditions that correspond to  $2\pi$ -periodic orbits in  $u, v, du/dz$  and  $dv/dz$  phase space [13]. Since  $z = t - (\alpha/\omega)x$ , it is clear that in the limiting case when the wavenumber approaches zero (i.e. spatial homogeneity) the system (14)–(17) reduces to the differential equations (9) and (10) without diffusion which has a stable spatially homogeneous limit cycle solution. Hence, as  $\alpha^2/\omega^2$  approach zero, a family of plane waves will exist as orbits in  $u, v, du/dz$  and  $dv/dz$  phase space that will approach the stable limit cycle in  $(u, v)$  space. Plane wave solutions for  $u$  and  $v$  are shown in figure 4 plotted using initial conditions supplied by Kopell and Howard [13]. Figure 4(a) shows a representative sample of the family of plane waves that exist for  $b = 3.6$ . Since  $z = t - (\alpha/\omega)x$  figures 4(b) and 4(c) can be interpreted as wave trains moving to the left with wavelength  $\alpha^{-1}$ , frequency  $\omega$  and speed  $\alpha^{-1}\omega$ . Figure 5 shows the limiting case where  $\alpha/\omega = 0$  which corresponds to the stable spatially homogeneous limit cycle.

## 2.2 The Hodgepodge machine

The Hodgepodge machine, introduced by Gerhardt and Schuster [23] is a cellular automaton originally developed in order to model the oxidation of CO on a palladium catalyst. However, as recognised by the authors, the Hodgepodge machine is a simple one-variable model capable of approximating the dynamics of many oscillatory and auto-catalytic chemical processes. In particular, the *excited-refractory-receptive* cycle characteristic of excitable media is approximated by this simple model, such as the oxidation of malonic acid by potassium bromate in the presence of iron or cerium.

The Hodgepodge machine is a discrete model, implemented on a regular lattice, where each lattice site can take on any integer value from zero to  $N$  inclusive. The sites are updated as follows:

$$\sigma_{ij}(t+1) = \left[ \frac{K_{ij}(t)}{\mu} \right] + \left[ \frac{I_{ij}(t)}{\omega} \right] \quad \text{for } \sigma_{ij}(t) = 0,$$

$$\sigma_{ij}(t+1) = \min(S_{ij}(t) + \nu, N) \quad \text{for } 0 < \sigma_{ij}(t) < N,$$

$$\text{where } S_{ij}(t) = \frac{1}{I_{ij}(t)} \sum \sigma_{ij}(t),$$

$$\sigma_{ij}(t+1) = 0 \quad \text{for } \sigma_{ij}(t) = N.$$

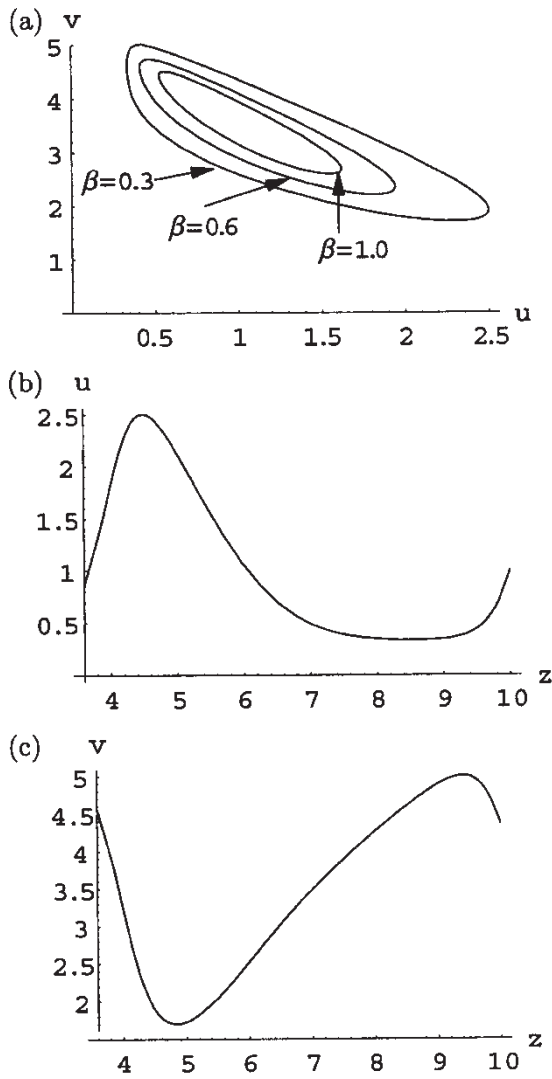


Figure 4. (a) Phase portrait of the oscillating solution to the system (14)–(17) where  $\beta = \alpha^2/\omega^2$  and  $z = t - (\alpha/\omega)x$ . The solution for three values of  $\beta$  are shown, each an example of the family of plane waves with differing periods and wavelengths associated with a particular value of  $b$ . In this example,  $b = 3.6$ . The chemical concentration waveform (b) is shown as  $u$  as a function of  $z$ , and in (c) as  $v$  as a function of  $z$ . The examples shown in (b) and (c) correspond to  $\beta = 0.3$ . These waveforms propagate to the left with speed  $\alpha^{-1}\omega$ .

Here  $\sigma_{ij}(t)$  is the value of the cell at site  $(i, j)$  at time  $t$ , the  $K_{ij}$  are the number of cells in the defined neighbourhood of site  $(i, j)$  with value  $\sigma = N$ , the  $I_{ij}$  are the number of cells in the neighbourhood of site  $(i, j)$  with value  $0 < \sigma < N$ ,  $S_{ij}(t)$  is an average value of the  $\sigma$  sampled over the neighbourhood of  $\sigma_{ij}$  (excluding  $\sigma = N$ ), and  $\mu$ ,  $\omega$  and  $\nu$  are positive constants. The square brackets define the nearest minimal integer value.

Thus the Hodgepodge machine represents an approximation to the reaction kinetics of equations (5) and (6) where the cellular automaton variable may be associated with  $X$ . The autocatalytic reaction (2) approximates the Hodgepodge terms  $K$  and  $I$ , whereas  $k_1$  in equation (5) may be approximated by  $\nu$ . Indeed, examination of figure 4(b) shows the solution waveform for

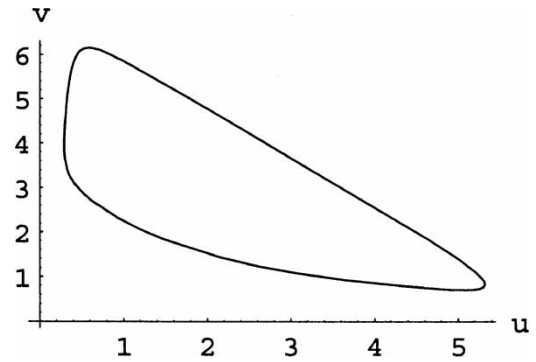


Figure 5. The limit cycle solution without diffusion ( $\beta = 0$ ) for  $b = 3.6$ .

the concentration of  $X$  demonstrating a rapid rise in concentration followed by a gradual fall and a relatively long refractory period. The advantages of the cellular automaton implementation are clear—in contrast to the difficulties associated with finding two-dimensional solutions to non-linear partial differential equations—qualitative results in terms of some of the spatial patterns that may form in excitable media are easily obtained.

### 3. Results

Various investigators have modelled the BZ reaction using reaction–diffusion equations and in many examples quantitative results can be obtained. With a reasonable knowledge of the important chemical reactions and the values of rate constants and diffusion coefficients it is possible to make predictions regarding the expected wave front velocities. In the case of the bromide ion, predictions have proven reasonably accurate [15]. The reaction–diffusion model above has been used by Kopell and Howard [13] to describe plane waves in one spatial dimension in the BZ reaction; these are parallel waves far from the centre or boundary of the pattern. Equations (5) and (6) with their particular non-dimensionalisation as described can be used to account for some aspects of the dynamic behaviour of the BZ reaction—for example setting the wavespeed to  $\sim 10^{-3} \text{ cm s}^{-1}$  and the wavelength to  $\sim 0.1 \text{ cm}$  (where  $\alpha^2/\omega^2 = 0.3$ ) yields  $d = 2.5 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$  and  $k_1 = 10^{-2} \text{ s}^{-1}$ —in this case matching the physical properties of the bromide ion and its experimentally measured rate of production.

Consider the dynamic properties of EGR. The speed of propagation of the inflammatory bands is approximately 1 cm per day while the wavelength (i.e. distance between the midpoints of the successive bands) is of the order 1 cm. With  $\alpha = 0.5447$  and  $\omega = 0.9945$  [13], the preceding constraints determine unique values of the diffusion coefficient  $d$  and the rate constant  $k_1$ . Here,  $d \sim 2.5 \times 10^{-6} \text{ cm}^2 \text{ s}^{-1}$  and  $k_1 \sim 10^{-5} \text{ s}^{-1}$ . With the specific non-dimensionalisation used, the values of the other rate constants are not explicitly defined. Thus, the model and its particular non-dimensionalisation can account for

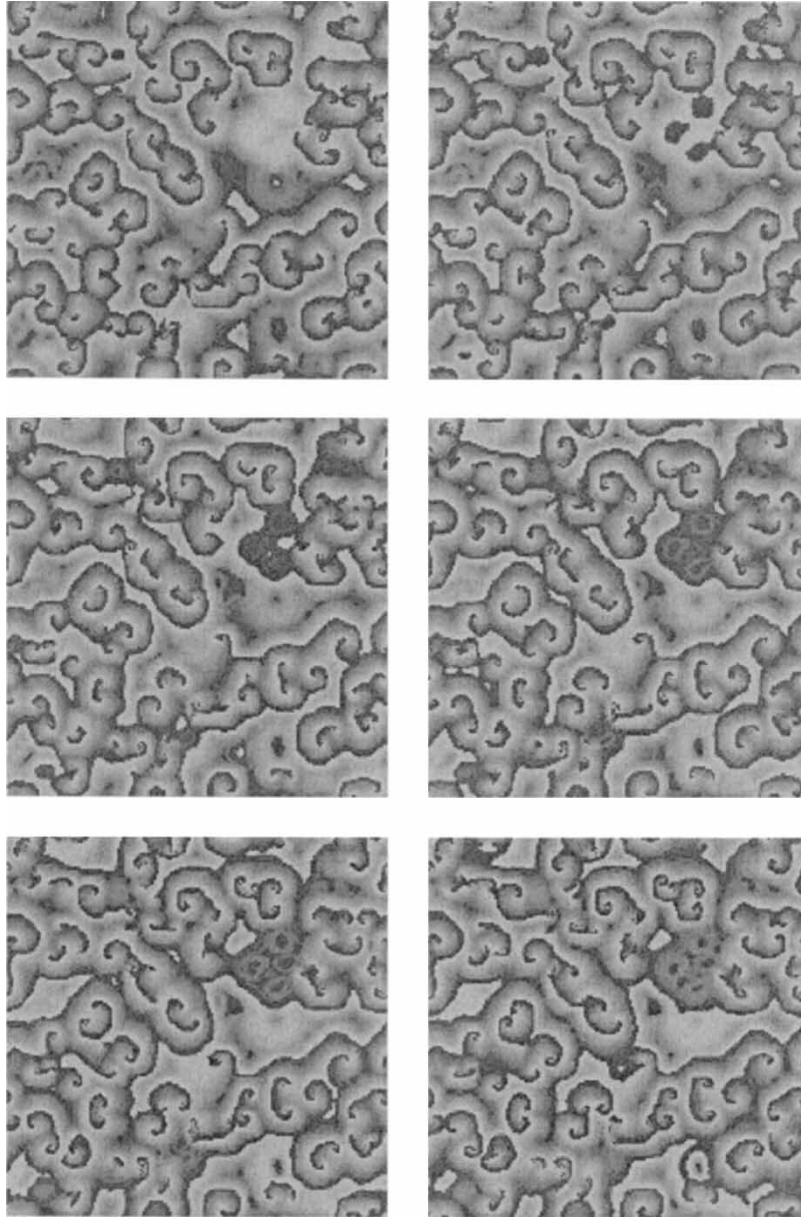


Figure 6. Simulation of the hodgepodge machine on a  $200 \times 200$  grid, with  $N = 100$ , showing the evolution of a Type 4 pattern (with random initial conditions) from  $t = 100$  (left to right, then top to bottom) to 105. Model parameters are defined in the text.

the wavelength and wavespeed of the inflammatory bands; in addition it imposes constraints on the numerical values of physical constants. It suggests  $X$  is a relatively small diffusible molecule (with molecular weight of the order  $\sim 1\text{--}10$  kDa) [24] and that its rate of production plays a critical role in the generation and maintenance of the pattern. The application of the mathematical model to the physical system in the skin—as for the BZ reaction in a petri dish—demands that the solutions are stable to perturbation; this in general is a difficult issue mathematically and will be addressed in the discussion.

What global morphologies can these solutions exhibit? Howard and Kopell have shown that equations (9) and (10) can account for some aspects of

the two-dimensional morphology of the BZ reaction [14], suggesting it may be possible to use the model to explain the patterning in EGR. Here we approximate the typical excitable kinetics described above by the implementation of the Hodgepodge machine. In the example presented, a 12 neighbourhood lattice is used to increase spatial resolution, while the parameters  $\mu$  and  $\omega$  are generalised to non-integer values. Figure 6 shows the typical morphology of Type 4 behaviour from  $t = 100$  to  $t = 106$ , with random initial conditions and where  $\mu = 0.5$ ,  $\omega = 5$ ,  $\nu = 15$  and  $N = 100$ . The patterns display a remarkable correspondence to those observed in both the BZ reaction and EGR. A striking feature observed in both the Hodgepodge simulation and EGR is the presence of

shock-like structures, parallel-like plane waves, concentric rings and “C” shaped double spirals.

#### 4. Discussion

Motivation for considering EGR as a dynamical system stems from Moore [9] where it was noted that the BZ reaction and EGR look similar, hence suggesting a common physical cause. Moreover, he suggested that it may be possible to perform a quantitative analysis by analogy with the BZ reaction and thus obtain insight into the pathogenesis of disease. The aforementioned, then, is an attempt at providing a mathematical and quantitative framework that can account for some aspects of the morphology and dynamics of EGR.

The major features of the model that may be of relevance to the pathogenesis of EGR are twofold. First, it suggests that wave-train like phenomena, if existing in the skin, are due to oscillating concentrations of immunoregulatory mediators. This in turn is dependent on the presence of autocatalysis and inhibition of molecular species. It is known that the immune response in general is characterized by both exponential increases in concentrations of chemical mediators and the subsequent damping of such responses. Chronic inflammation is likely to reflect a balance between both the production and destruction of immunoregulatory mediators and the relative concentrations of agonist and antagonist. The current model embodies these concepts of molecular regulation. Furthermore, systems where there are periodic fluctuations in the concentrations of chemical species—biochemical oscillators—are well known to biochemists; for example, the intracellular glycolytic pathway reveals periodic fluctuations in the concentration of various intermediates [25]. The ideas presented here suggest it may be of value to investigate the skin in EGR looking for spatio-temporal oscillations in the concentrations of various inflammatory mediators. Second, matching the wavelength and wavespeed of EGR to the model yields unique values of  $d$  and  $k_1$ , the diffusion coefficient of  $X$  and the rate constant for its production. The values determined for these constants are reasonable biologically. Additional experimental data are required in EGR so that potential future models are not strictly hypothetical but take into account known cutaneous biochemistry. As a first step, the model suggests investigators should look for immunoregulatory mediators in the skin with molecular weights of the order 1–10 kDa. The rate constant  $k_1$  plays an important role in the generation of the pattern. Hence, the rate at which  $X$  is produced in the skin is critical to the maintenance of the rash. The wave-train pattern would cease not only if the rate of production of  $X$  decreased—as one would expect intuitively, particularly if  $X$  were a pro-inflammatory mediator—but also if its rate of production increased. It may then be possible to switch off an eruption such as EGR by administering a drug that

augments the production in the skin of a pro-inflammatory mediator!

The concentration gradients in the skin are hypothesised to directly lead to the generation of pattern in EGR. The concentration profiles of chemical species will not coincide in space with the rash; rather, there will exist a phase shift (which is not necessarily an integer multiple of the wavelength) that will be determined by the time required for the peak (or trough) concentration of  $X$  to lead to maximal skin inflammation. A constraint on the system, however, is that the inflammation must possess identical spatio-temporal behaviour as the chemical wave-train. Thus the inflammation must resolve in a given location before the next band arrives. The coupled reaction sequence inherent in the model described has the advantage that  $X$  and  $Y$  are out of phase, hence, when  $X$  is at maximal concentration  $Y$  is at a minimum and vice-versa. This means that the damping of the inflammation (which clinically correlates with the reversal of the skin to normal) may be augmented by not only a reduction in the concentration of  $X$  but, if  $Y$  were an antagonist of  $X$ , an increase in the concentration of  $Y$ . Coupled agonist and antagonist activity may be necessary in order to render inflamed skin normal in relatively short time frames.

Chronic immune stimulation (such as antigen–antibody deposition in the skin as proposed by various investigators) may lead to the continual production of  $X$ . This is a non-spatially dependent phenomena and may occur widely over the integument. What is  $X$ ? As a first guess, consider the primary cytokine Interleukin-1 (IL-1). Many of the biological properties of IL-1 are captured in principle by the simple reaction kinetics and the predictions of the model. What are these features? First, one of its active forms is a relatively small extracellular diffusible protein with molecular weight 17 kDa [26]. Second, it is produced constitutively in the skin [27] hence, the reaction sequence in the model may be augmented—with the subsequent development of the rash—by its increased production (still at a constant rate) reflected quantitatively by a change in the value of  $k_1$ . Third, IL-1 may be produced by leukocytes and keratinocytes in the presence of antibody [27] (in EGR the skin is thought to be rendered antigenic by cross reactivity with tumour antigens). Fourth, IL-1 can augment its own production (auto-catalysis) [27] and will be degraded at a rate proportional to its concentration by non-specific proteases. In addition, IL-1 will be transformed either by binding to its membrane-bound receptor (with subsequent cellular internalisation and destruction), or by reacting with its extracellular soluble receptor [26]. Finally, IL-1, as a primary cytokine, is capable of producing skin inflammation when injected into the skin *in vivo* [28]. The typical histology resulting from the administration of IL-1 shows a non-specific perivascular inflammatory infiltrate which shares many morphologic features with the histopathology of EGR. Thus, although IL-1 at minimum is likely to play

a non-specific role in the generation of inflammation in EGR, only further investigation can determine whether IL-1 is of primary importance in the aetiology of both the pattern and pathology of the rash.

There are a number of problems with the mathematical model in attempting to explain a physical phenomenon existing in the skin. First, the model does not take into consideration boundary conditions [13]. Although, this may be reasonable for the region the wave is expanding into (since the skin is a closed two-dimensional surface without bound), the analysis does not account for the centre or bulls-eye of the pattern. Second, a major consideration is the issue of stability of solutions. The mathematical demonstration of stability in wave-like solutions to reaction–diffusion equations is in general an intractable problem; indeed only the simplest of examples will yield to analysis [29]. Kopell and Howard [13] have discussed the issue of stability in regard to plane wave solutions of general reaction–diffusion equations; in the model above it is conjectured that the solution is stable. Mathematical criteria are set forth which are required for stability and the above model possesses properties in which these conditions are met. As the chemistry underpinning the BZ reaction is reasonably well understood it is likely the solutions to the foregoing mathematical model are in fact stable since they correlate well with the phenomena, which, by direct observation, must be stable [13]. If no solutions were stable then no patterns in the BZ reaction could exist. This argument, however, cannot be carried over to EGR since the underlying mechanisms of rash production are unknown.

There are other differences between the use of the current model in EGR and in the BZ reaction. It is assumed that wave-front velocities in EGR are slow in comparison with the BZ reaction. This is likely to have a profound affect on stability. Solutions must exist in a coherent manner for significant time periods. In EGR the wave is required to maintain its form over periods of time that may be measured in weeks—granted this is a significant difficulty—yet the model suggests it is possible at least in principle. Despite the uncertainty of the latter, a remarkable feature of dissipative structures in general is the fact that such systems can maintain themselves for long periods of time [18]. Simple patterns in the BZ reaction have been maintained for days in the laboratory (thus avoiding the degradation expected as a consequence of the second law of thermodynamics) by the continual supply of raw materials and energy and the drainage of products [30]. In the skin (which is an open system) there is a continual supply of matter and energy and drainage of products, directly from the dermis if the reaction–diffusion mechanism occurs in the epidermis or, alternatively, from the blood supply if the reactions are primarily located in the dermis. Only further analysis and experiment can determine whether such slow waves exist in the skin for prolonged periods of time.

Finally, the remarkable similarities of the spatio-temporal patterns observed in the Hodgepodge machine and in EGR add considerable weight to the above hypothesis. It suggests excitable kinetics may be an integral part of some examples of immune regulation. The idea that the morphology and dynamics of EGR may be due to successive waves of chemical concentration propagating in the skin is both novel and without direct experimental support. The lack of convincing alternative hypotheses, however, has provided a major impetus for the current proposal.

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