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Labyrinthine Turing Pattern Formation in the Cerebral Cortex

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I propose that the labyrinthine patterns of the cortices of mammalian brains may be formed by a Turing instability of interacting axonal guidance species acting together with the mechanical strain imposed by the interconnecting axons.

Introduction

Labyrinthine patterns, of which those displayed on the surface of the mammalian brain are a notable biological example, are some of the most striking encountered in nature. A half-century ago Turing (Turing, 1952), who was studying morphogenesis in biological systems, had the insight that diffusion is not always a homogenizing influence, and that spatial patterns would be formed by a reaction–diffusion system combining local activation with long-range inhibition. Spots and stripes on animal coats (Bard, 1981; Murray, 1989), patterning on sea shells (Meinhardt, 1997), stripes on tropical fish (Kondo & Asai, 1995), and even alligator teeth (Murray & Kulesa, 1996), have all since been put forward as examples of Turing patterns in nature (Koch & Meinhardt, 1994). Here I propose that the morphogenesis of labyrinthine patterns in the mammalian brain may likewise be an instance of biological Turing pattern formation.

The cerebral cortices of the higher mammals, and in particular humans, are made up of a system of convoluted ridges (gyri) and valleys (sulci) (Fig. 1). The pattern of gyri and sulci forms during the development of the foetus: in humans the brain's surface is almost smooth at twenty-four weeks, but between then and birth the cerebral cortex gradually assumes its characteristic wrinkled form. This is not merely buckling, but is the result of a deformation of the initial geometry, so that it would be necessary to introduce cuts to smooth it out. As with the colouring of animal pelts, while the overall morphology for a particular species is fixed, the detailed pattern is unique to each individual, indicating that the specific form is decided during development of the embryo. It is clear that the convolutions increase the surface area of the cortex compared to the smooth brains of lower animals. This allows a large cortical area to fit inside the head, and in addition may minimize wiring volume, and benefit the synchronization of neuronal firings (Griffin, 1994). Whatever may be the functional origin of this pattern, however, there remains the interesting question of its morphogenesis.

During embryonic development, neurons migrate from the thalamic areas within the brain where they are produced to the cortex, where they wire themselves up to other neurons via connecting axons (Rakic, 1988). Over a century ago Ramón y Cajal speculated (Ramón y Cajal, 1893) that axons use chemical signals to find their way. The growth cone at the tip of the axon senses gradients in the concentration of axonal guidance species that may be either fixed to the cellular substrate, or diffusing through it (Goodhill & Urbach, 1999). Many such diffusive axonal guidance molecules have since been identified, some of which are attractive (chemoattractants) or activate axon growth, while others are repulsive (chemorepellants) or inhibit growth (Baier & Bonhoeffer, 1994; Tessier-Lavigne & Goodman, 1996). On the other hand, mechanical models for cortical folding have been put forward (Richman *et al.*, 1975; Todd, 1982; Raghavan *et al.*, 1997).

Figure 1: The labyrinthine patterns of the cerebral cortex of a human brain: (a) dorsal view; (b) lateral view.

It has recently been proposed (van Essen, 1997) that mechanical tension is the driving force for the formation of gyri and sulci; that the surface of the cortex buckles and deforms under the tensile loading imposed by the interconnecting axons. The idea has been shown to be consistent with data on neuronal connectivity in the cat and the macaque (Scannell, 1997), and does a good job of explaining the presence of gyri and sulci as high and low connectivity regions, but leaves open the question of the overall form of the pattern: why is it labyrinthine? Here I marry the mechanical-tension hypothesis to the idea of axonal pathfinding with diffusing chemicals and show that the two together can provide an explanation for the labyrinthine nature of the convolutions.

Reaction–diffusion equations and Turing patterns

To model the pattern formation I propose an interaction between two diffusing biologically active chemical species. One of the species inhibits axon growth, and the other activates it, and moreover they interact to activate and inhibit each other. A process of this form we may describe mathematically by a pair of coupled reaction–diffusion equations

$$\begin{aligned} \dot{u} &= F(u,v) + \nabla^2 u, \\ \dot{v} &= G(u,v) + \delta \nabla^2 v, \end{aligned} \tag{1}$$

where u and v are the scaled concentrations of the two diffusing and reacting chemical species, with u being the activator and v the inhibitor. $F(u,v)$ and $G(u,v)$ represent the interaction kinetics. Turing showed that a spatially homogeneous steady state of Eq. (1) may become unstable via a symmetry-breaking bifurcation if $\delta > 1$, that is when the inhibitor diffuses more rapidly than the activator. Associated with the instability is a critical wave number that determines the wave length of the resulting pattern. Numerical simulations of pattern formation in systems with Turing instabilities have provided examples of the formation of patterns that are periodic in one and two spatial dimensions (spots and stripes) (Judd & Silber, 2000), together latterly with nonperiodic patterns including labyrinths (Muratov & Osipov, 1996). Moreover, a variety of chemical Turing patterns, including stripes, spots, and rhombs, have been obtained in laboratory experiments (Castets *et al.*, 1990; Ouyang & Swinney, 1991; Watzl & Münster, 1995).

Stripes and spots in biological settings have been explained with the Turing bifurcation mechanism. The aim here, given that a Turing instability can produce labyrinthine patterns, is to apply this understanding in a biological context to explain their appearance in the brain. We as yet have no knowledge of the molecular biology involved in the interactions. However, the universality of the Turing bifurcation mechanism allows us to choose a simple model for the activation and inhibition kinetics $F(u,v)$ and $G(u,v)$ of the chemical species involved, knowing that the same qualitative effects can be obtained with a more detailed mechanism faithful to the molecular biology. To illustrate the interaction dynamics, I take the van der Pol–FitzHugh–Nagumo equations (van der Pol & van der Mark, 1928; FitzHugh, 1960, 1961; Nagumo *et al.*, 1962) with diffusive coupling of both variables

$$\begin{aligned} \dot{\psi} &= \gamma(\eta - \psi^3/3 + \psi) + \nabla^2 \psi, \\ \dot{\eta} &= -\gamma^{-1}(\psi + \nu + \beta\eta) + \delta \nabla^2 \eta. \end{aligned} \tag{2}$$

Here ψ represents the concentration of activator, and η the concentration of inhibitor, of an autocatalytic interaction whose kinetics are determined by γ: for $\gamma < 1$ local inhibition dominates, while for $\gamma > 1$, local activation is uppermost. ν and β determine the number and type of equilibrium states of the local dynamics; see Fig. 2. The spatial interaction is determined by δ: for $\delta < 1$ the inhibitor has shorter range than the activator, but for $\delta > 1$ the opposite is true. This van der Pol–FitzHugh–Nagumo model has a homogeneous equilibrium state that is unstable to spatial

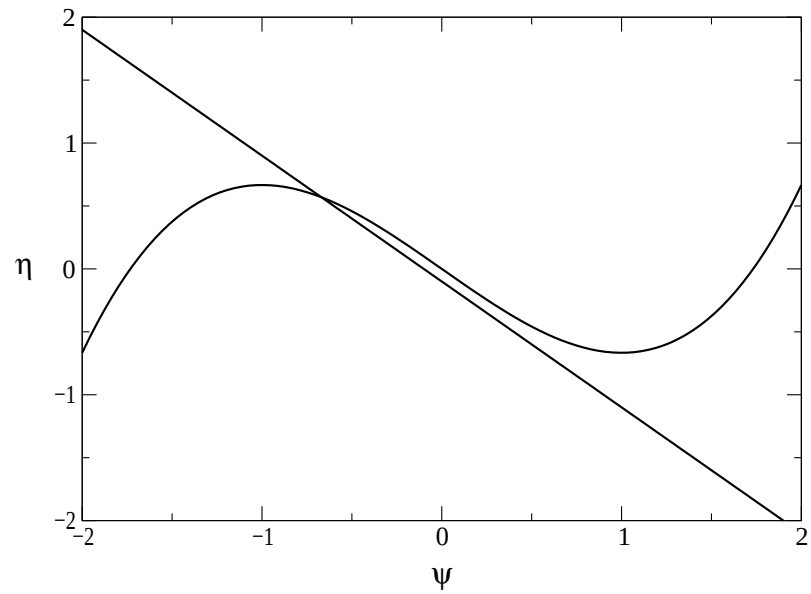

Figure 2: The system without diffusion; nullclines of (2) given by $\dot{\psi} = 0$ and $\dot{\eta} = 0$, that is $\eta = \psi^3/3 - \psi$ and $\eta = -(\psi + \nu)/\beta$, for the parameter values $\beta = 1$, $\nu = 0.1$ used in the simulations presented here. For these parameter values there is a single equilibrium state, where the nullclines cross, which is unstable, leading to pattern formation. In many systems in which patterns form the nullclines have this characteristic N-shape (Cartwright *et al.*, 1997).

oscillations via a Turing bifurcation for $|\nu| < \sqrt{\delta(\delta\gamma^2 - \beta)}\,(3\delta\gamma^2 - 2\delta\gamma^2\beta - \beta^2)/(3\delta^2\gamma^3)$, and in addition is unstable to temporal oscillations via a Hopf bifurcation for $|\nu| < \sqrt{\gamma^2 - \beta}\,(3\gamma^2 - 2\gamma^2\beta - \beta^2)/(3\gamma^3)$. Figure 3 presents the van der Pol–FitzHugh–Nagumo equations integrated on a two-dimensional domain that represents the cerebral cortex. At the parameter values of Fig. 3 a homogeneous initial condition is unstable to both a Turing and a Hopf bifurcation, and a static labyrinthine pattern is formed. The initial conditions contained a small amount of noise, mimicking the variability of individuals, so in each simulation run the details of the labyrinthine pattern were distinct, as the pattern developed following the individual distributions of activator and inhibitor. The vertical axis illustrates with the concentration of activator how mechanical tension decorates the labyrinthine pattern with a three-dimensional structure of convolutions, as axons growing preferentially in the activated regions force these to grow upwards into heavily interconnected gyri, while the nonactivated regions become the more sparcely connected sulci between them.

Biochemical and mechanochemical mechanisms

One can conceive of several possible mechanisms for the interaction of axonal guidance species with each other and with axons to produce the above dynamics. The first possibility is that a direct chemical reaction between the species is involved, as in chemical Turing pattern formation. This seems unlikely. It appears more probable that the interaction between activator and inhibitor species is mediated by the medium, that is by cortical cells or axons. This mechanism implies that cortical cells or axons would not merely passively sample concentration gradients of guidance molecules, but would actively alter them. Such interactions have been postulated as necessary in diffusive axonal guidance (Hentschel & van Ooyen, 1999). Furthermore, secretion of axonal guidance species by axons (Zheng *et al.*, 1994), and interactions between molecules involved in axonal guidance and growth (Ernst *et al.*, 2000) have been observed, so it is plausible that an activating and an inhibiting guidance species may be interacting at a cellular level. In any case, the simple scenario presented above may be a caricature of a more complicated series of interactions between more than two axonal guidance molecules. But the outcome of the process will nevertheless depend on the balance between activation and inhibition at each point, so the Turing bifurcation mechanism mediated by local activation plus long-range inhibition will still apply.

There is then the question of the timing of the laying down of the pattern. Is it concurrent with the axonal growth, so that the pattern appears as it forms, or is it put into place earlier — when the foetus is smaller — as a prepattern that the axons use for guidance later in embryonic development? Both scenarios have been proposed in other biological Turing patterns: prepatterning in animal coat markings (Bard, 1981; Murray, 1989), and concurrent patterning in fish skin patterns (Kondo & Asai, 1995). Here, developmental disorders that are thought to have a predominantly genetic basis and that result in malformation of the cerebral cortex (Dobyns & Truwit, 1995) — all of which lead to severe mental retardation — may give some insight into the mechanism of pattern formation. The best known of these is lissencephaly, in which the surface of the cortex does not have the normal gyri and sulci, and the brain is smooth. Other conditions are pachygyria, in which the convoluted pattern is larger-scaled than normal, with few, large gyri and sulci, and polymicrogyria, which is the opposite case of the pattern being smaller-scaled than is usual, so that there are many small sulci and gyri. Finally, so-called cobblestone lissencephaly has been described, in which the brain has a cobbled or pebbled surface. One can immediately see that these developmental errors are consistent with a Turing instability. In pachygyria and polymicrogyria the wave length of the pattern is respectively greater and less than usual, which could indicate either, with concurrent patterning, that the ratio of diffusion coefficients δ has altered or, in the

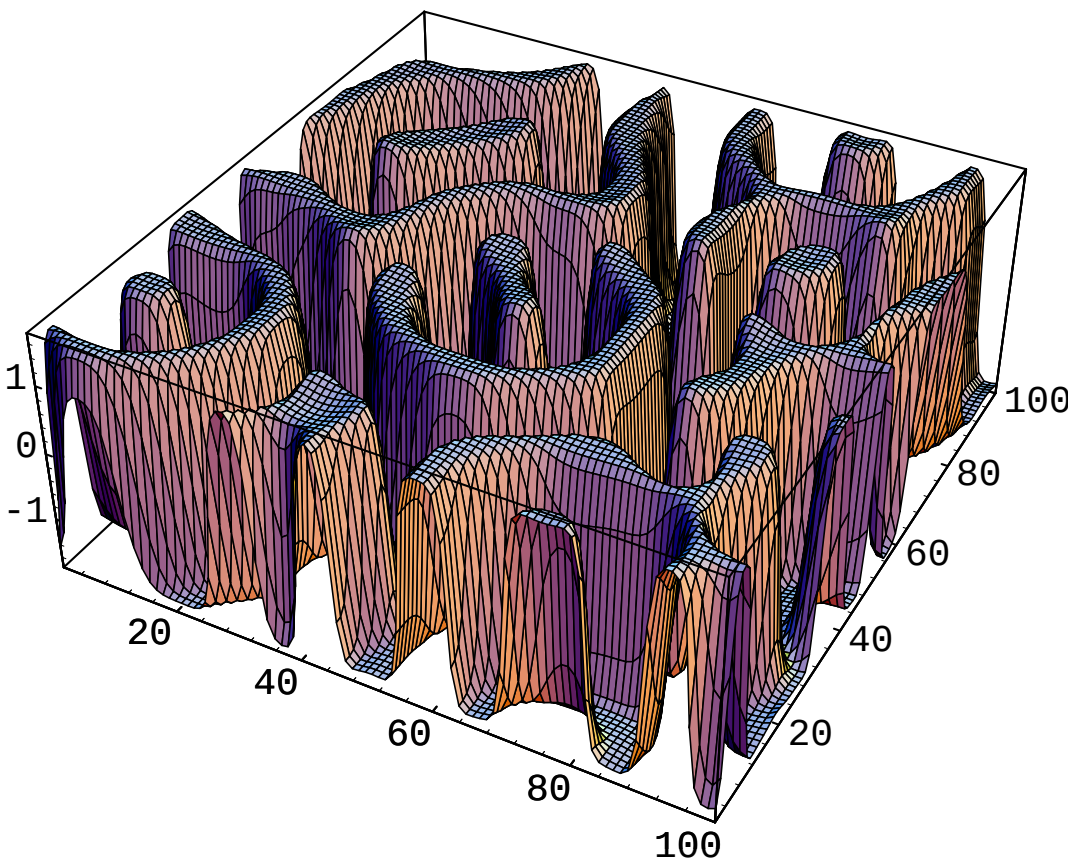

Figure 3: Equations (2) integrated on a two-dimensional periodic domain with parameters $\gamma = 2$, $\beta = 1$, $\nu = 0.1$, and $\delta = 20$. Height represents the concentration of activator. The static labyrinthine pattern is fully formed at the time $t = 40$ shown here and remains stable thereafter. Concentration, time, and distance are in dimensionless units here.

case of the prepatterning scenario, that the prepattern was laid down earlier and later than normal, respectively. On the other hand, the cobblestone pattern may be interpreted as a change in the morphology from a labyrinth to spots. This change can be produced in the van der Pol–FitzHugh–Nagumo model of Eqs (2) if the local kinetics are altered so that the system remains unstable with respect to the Turing instability but is stable to the Hopf instability (Muratov & Osipov, 1996). In the same way, lissencephaly may be caused by a change in the interaction dynamics leading to the homogeneous state becoming stable to both the Hopf and Turing instabilities, or alternatively may simply indicate the absence of the normal axonal guidance species.

A further possible mechanism for the production of the convolutions is that there is just one activating diffusive guidance molecule involved, and the part of the other, inhibiting species is taken by the growing axons themselves. The mechanical strain in the cortical tissue induced by the interconnecting axons may then play the rôle of the long-range inhibitor. The mathematics for this mechanochemical model differ in detail from the reaction–diffusion system presented in Eqs (1) and (2) above. However, this type of model is closely related to the reaction–diffusion type — the key concept of long-range inhibition plus short-range activation being common to both — and is capable of forming similar patterns (Kauffman, 1993). Mechanochemical models have been proposed to model biological morphogenesis in systems such as cellular morphology, in which mechanical strain in the cytoskeleton interacts with the concentration of free calcium (Odell *et al.*, 1981; Oster & Odell, 1984; Goodwin & Trainor, 1985). A more detailed analysis of biologically faithful mechanochemical equations for the formation of sulci and gyri is underway; but I wish to emphasize that the physics of the reaction–diffusion equations, presented above, to a large extent carries over to the mechanochemical case, and allows the formation of similar patterns. To distinguish between the biochemical and mechanochemical hypotheses, and indeed between the prepatterning and concurrent patterning hypotheses, will require extending our understanding of the molecular biology of axonal guidance and growth.

Discussion

Neuroanatomy classifies sulci and gyri as primary, secondary, or tertiary, depending both upon their order of appearance in the developing brain, and upon their variability between individuals. During cortical development, nuclei within the inner thalamic areas of the brain are first wired up to nearby areas of the cortex; visual thalamic areas project to visual cortical areas, auditory thalamic areas project to auditory cortical areas, and so on. These cortical areas are subsequently interconnected during the process of forming the convolutions of the cortex. In humans there are more than fifty functional subdivisions of the cortex, but only in a few instances is there a correlation between these areal boundaries and those of the convolutions (Zilles *et al.*, 1997). This may well be because neighbouring areas may have connections along their mutual boundary comparable to the connectivity within each area alone, as folding *is* correlated with connectivity (Scannell, 1997). If the initial conditions for the cortical pattern formation were completely uniform, perturbed only by noise, as in the simulation of Fig. 3, then the convolutions for each individual would emerge completely uncorrelated. In fact, differences in the folding pattern between individuals increase from primary to secondary to tertiary convolutions; the primary convolutions are more or less fixed in place, while it is at the level of the tertiary convolutions that there is freedom for the pattern to develop in a much more variable manner. An example of this variability is provided by Einstein's brain, examination of which has shown the absence of a sulcus found in other subjects in the inferior parietal area; it has been surmised that the consequent greater neuronal connectivity in that region, which is responsible for mathematical thought, may help to account for his genius (Witelson *et al.*, 1999). Furthermore, abnormal sensory experience can lead to abnormal convolutions (Rakic, 1988); the probable chain of events is that sensory experience influences connectivity, and

thence the folding pattern. All this implies that the initial condition for pattern formation contains information at the level of the primary convolutions. The thalamic input determines the initial conditions for the folding pattern through the pattern of cortical projections. The Turing mechanism takes these initial conditions and moulds from them a labyrinthine pattern of convolutions through connection-density-dependent growth and mechanical tension. The physical Turing mechanism may then be operating at the level of the tertiary convolutions, under genetic control at the level of the thalamic input.

The Turing instability produces a labyrinthine pattern from an initially homogeneous system by symmetry breaking. In physics and chemistry — in excitable chemical reactions, block copolymers, magnetic fluids, and superconductors (Dickstein *et al.*, 1993; Seul & Andelman, 1995) — labyrinthine patterns have been explained as the result of local activation combined with long-range inhibition (Goldstein *et al.*, 1996). In particular, the spontaneous appearance of labyrinths in a chemical reaction has been seen as a Turing instability in a reaction–diffusion system. I have set out here to understand biological labyrinthine patterns in this context. I have shown that labyrinthine patterning in the cerebral cortex is consistent with a Turing instability. This mechanism joins together two familiar ideas in cortical development: the part played by axonal pathfinding chemicals in guiding neuronal connectivity, and the role of mechanical tension in the uplifting of cortical areas into gyri. The hypothesis that diffusing and interacting axonal guidance molecules cause a Turing instability allows one to understand the breakdown of homogeneity during cortical development; at the same time the mechanical tension induced by the high connectivity in activated regions explains why the gyri and sulci form a labyrinth. The idea may provide valuable insight into developmental disorders of the cortex like lissencephaly. There is as yet no molecular-biological evidence for such a Turing mechanism, but I hope that the present article will stimulate such research. The present hypothesis is not meant to suggest that genes have no rôle in the production of the convolutions of the cerebral cortex, but rather to propose that this biological process may take advantage of the physical mechanism of pattern formation induced by the mathematical theory of Turing bifurcation.

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