The Influence of Receptor-Mediated Interactions on Reaction-Diffusion Mechanisms of Cellular Self-organisation

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Abstract Understanding the mechanisms governing and regulating self-organisation in the developing embryo is a key challenge that has puzzled and fascinated scientists for decades. Since its conception in 1952 the Turing model has been a paradigm for pattern formation, motivating numerous theoretical and experimental studies, though its verification at the molecular level in biological systems has remained elusive. In this work, we consider the influence of receptor-mediated dynamics within the framework of Turing models, showing how non-diffusing species impact the conditions for the emergence of self-organisation. We illustrate our results within the framework of hair follicle pre-patterning, showing how receptor interaction structures can be constrained by the requirement for patterning, without the need for detailed knowledge of the network dynamics. Finally, in the light of our results, we discuss the ability of such systems to pattern outside the classical limits of the Turing model, and the inherent dangers involved in model reduction.

Keywords Reaction-diffusion · Self-organisation · Receptor-mediated patterning · Turing models

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1 Introduction

Ever since the rejection of the preformationist idea that minute animacules lay essentially fully formed within germ cells, the self-organisation of biological structure during development has puzzled and fascinated scientists. For instance, recent high throughput sequencing studies have emphasised that phenotypic diversity emerges from relatively similar genomes and proteomes, while cross-species genetic rescue studies (Leuzinger et al. 1998) have highlighted a universality of developmental processes via homologous pathways, suggesting that diversity instead arises from differences in regulatory DNA rather than protein coding sequence evolution (Alberts et al. 2002; Carroll 2005). This biological economy ensures that many aspects of metazoan development can be analysed from studies of fruit flies and nematode worms and, at the same time, motivates theoretical modelling to test and explore the detailed consequences of hypothesised universal developmental mechanisms.

One such common theme in developmental processes is the crucial role of cell–cell communication, in particular long-range range signalling, for orchestrating differential gene expression and biological morphogenesis over scales which are much larger than that of a cell. Numerous diffusing biochemical signals, known as morphogens, have been demonstrated as instigating cell fates in a spatially heterogeneous manner via a differential cellular response to concentration levels, durations, and gradients (Wolpert 2002; Gilbert 2006). While the characteristic lengthscale of morphogen signalling typically ranges from tens of microns to millimetres (Alberts et al. 2002; Gregor et al. 2005; Kicheva et al. 2007), and thus is insufficient at organ scales, complex structures can form via sequential induction, with a cascade of repeated cell fate differentiation at the morphogen scale inducing ever finer detail (Alberts et al. 2002; Wolpert 1994).

One of the best examples of a developing organism in which the mechanisms of spatial organisation have been defined is the Drosophila embryo. In this system a morphogen called bicoid is produced at the future anterior pole of the embryo and diffuses from this source to form a concentration gradient across much of the embryo. Bicoid protein acts in a concentration-dependent manner to control expression of gap genes, which refine the bicoid morphogen gradient and regulate the expression of pair rule genes. In this way, a concentration gradient of bicoid ultimately serves as a positional guide, instructing nuclei of their position relative to the anterior pole and, via differential interpretation, ultimately defines the 14 parasegments which emerge in the initially unsegmented embryo. However, in the Drosophila embryo no true symmetry ever exists to be broken as bicoid localisation to the future anterior pole is achieved during the formation of the egg by maternal inputs (Wolpert 2002; Gilbert 2006). Thus, by this morphogen gradient system positional information is elaborated, but importantly in the context of this work, it is not generated de novo.

A fundamentally different mode of pattern formation, and one which is capable of breaking symmetry without pre-existing positional information, has been known to be theoretically possible since Turing’s (1952) seminal study. In particular, periodic patterns with a defined size and spacing can spontaneously emerge by the amplification of random molecular noise via a crucial combination of diffusion and biochemical reactions, in distinct contrast to elaboration of existing het-