Competitive reaction diffusion systems with spatial cues: homeoprotein and the stability of compartments in developing nervous system

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Context: The specification of territories in the nervous system relies on the precise positioning of boundaries between different functional areas. Each territory is characterized by the expression of a specific combination of molecular marks, including transcription factors (TFs), before developing into areas endowed with specific functions. The emergence of compartments in the cerebral cortex or in the spinal cord is a paradigmatic example of this process. From a theoretical perspective, the specification of territories in the nervous system represents a particular case of the general phenomenon of patterning. We owe to Alan Turing the first theoretical model of how patterns form. In his 1952 seminal article The chemical basis of morphogenesis, Turing explains how reaction-diffusion properties of two morphogens, in the presence of a catalyst, can lead to the emergence of heterogeneities even if the tissue is initially homogeneous [1]. This is a universal pattern formation mechanism: the interaction of molecular species can create regular spatial patterns, provided that they exhibit different diffusion constants and have auto-activating and reciprocal inhibitory properties. Turing-like mechanisms alone do not lead to the emergence of predictable shapes. Another popular patterning mechanism has been proposed in 1969 by Lewis Wolpert [2] with the concept of Positional Information (PI). This model, also known as the French Flag Model (FFM), requires a continuous morphogen gradient and the existence of thresholds. A typical abstract example is the differentiation of cells into blue, white and red populations when exposed to high, intermediate or low morphogen levels (thus the FFM), each territory corresponding to the expression of specific genes, in many cases transcription factors (TFs) defining specific areas within the neuroepithelium.

If one compares the two models, Turing's model allows the formation of precise and neat boundaries that lack of reproducibility in their positioning, while the PI model provides a pre-pattern that constrains the boundary positioning, but suffers from fuzziness due to an uncertainty in the morphogen concentration at which a threshold appears.

Model: It might thus be useful to verify if recent findings in developmental biology may permit to reconcile the advantages of the two models. In vertebrates the most popular illustration of the PI theory is provided by the compartmentalization of the neural tube in response to the diffusion of the ventral and dorsal morphogens Sonic Hedgehog (Shh) and Bone Morphogenetic Protein (BMP), respectively. A continuous gradient activates ventral and dorsal genes and territories are formed that express distinct TF subsets. In this model, differentiation is based on the almost general rule that within a developing neuroepithelium, each side of a boundary expresses a TF, in most cases a Homeoprotein (HP) transcription factor, which amplifies its own expression and represses that of its counterpart (on the other side). An important novelty of this study is to introduce in the calculations the intercellular transfer of HPs allowed by two short peptidic sequences present in their DNA-binding domain [3].

Mathematical contribution The problem therefore falls in a more general setting of species in competition within a non-homogeneous medium (related to the orientation of morphogen gradients). We investigate these systems and show that in the limit of arbitrarily small diffusion, there exists a unique monotonic stationary solution, which splits the neural tissue into two winner-take-all parts at a precise boundary point: on both sides of the boundary, different neuronal types are present. In order to further characterize the location of this boundary, we use a blow-up of the system and define a traveling wave problem parametrized by the position within the monotonic gradient: the precise boundary location is given by the unique point in space at which the speed of the wave vanishes [4].

In conclusion, it is demonstrated that the addition of the simple property of HP transfer integrates a local Turing's mechanism within the PI model first proposed by Wolpert and provides a very parsimonious model for the formation of precise and stable boundaries.

References

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