MODELING APPROACHES IN EMBRYO DEVELOPMENT

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Contents

Summary

In the recent years modeling approaches in Developmental Biology are driving research in this field at an accelerated pace. On the one hand, this has been possible by the

development of experimental techniques that allow the quantification of the molecular and morphogenetic processes that underlie embryo formation. On the other hand, multidisciplinary approaches that combine Mathematics, Physics, and Biology have contributed with novel viewpoints. Herein we review some advances in modeling approaches toward the understanding of embryo development. While a complete coverage of all the developments in this field is beyond the scope of this contribution, we have been as comprehensive as possible in reviewing particular problems that have played a key role to understand fundamental concepts in embryo development from the modeling point of view. The review is divided in five sections that cover different spatiotemporal scales and techniques. In addition we sketch some mathematical formulations that are useful to tackle this sort of problems. The result is an overview that provides a general picture of these processes and approaches that will hopefully help the non-experts to be introduced in this fascinating topic while will serve as a reference to the experts.

1. Introduction

The word embryo refers to any developing organism between fertilization and birth and Developmental Biology is the branch of Science that studies the processes that drive such phenomenon. Thus, in opposition to most branches in Biology that focus on adult structures and functions (being), the questions posed by Developmental Biology try to understand the becoming. E.g., a geneticist may study how genes of a particular cell type are transmitted over generations, a physiologist may ask about the function of those genes, a molecular biologist about their interactions at the molecular level, yet a developmental biologist will ask: how come that those genes were expressed in that particular cell type? Nonetheless, since embryo development is an extremely complex process, a broad viewpoint is required and an overlap between different approaches naturally arises.

As Scott F. Gilbert mentions in his classical book “Developmental Biology”, this discipline has been described as “the last refuge of the mathematically incompetent scientist”. This review will show that this definition not longer applies. Mathematical and physical principles are now applied to understand embryonic development and, when possible, to derive laws. In fact, this is not a recent tendency. W.K. Brooks (1848-1908) and D´Arcy Thomson (1860-1948) were pioneers in the field of Mathematical Biology applied to the growth of organisms. A. Turing (1912-1954) further contributed to these ideas when proposing a simple mechanism by means of which the interactions (reactions) and diffusion of chemical species lead to a patterning process out of a random initial distribution of chemicals. This mechanism was a major breakthrough for the mathematical formulation of Developmental Biology since embryonic development relies on the temporal and spatial induction of different cell fates and in many instances, cell differentiation is related to the existence of a spatiotemporal pattern of gene expression. It is also worth mentioning C.H. Waddington's conceptual proposal on the epigenetic landscape for the developmental choices cells make. This proposal was afterwards formalized through the theory of dynamical systems being an inspiration for subsequent studies on cell fate choices.

Nowadays mathematical approaches are common when studying embryonic development and modeling efforts are pursued to characterize and understand how patterns of gene expression arise and tissue dynamics develops. Herein, we will use the term pattern for any spatial or temporal heterogeneous distribution of gene expression. Importantly, models for pattern formation can be used as conceptual tools to pinpoint and understand key elements of the process and to make predictions. Thus, models should not be used to only reproduce existing data and confirm mechanisms but also to profit for their predictive capabilities and feedback to perform new experiments. In this review we provide an overview of different crucial aspects of modeling approaches in developmental processes. Our objectives are twofold. On the one hand, we go over past and recent research in developmental pattern formation mechanisms and models in order to present a general idea of the current knowledge. Thus, we include different viewpoints: mathematical formalisms, experimental observations, and the mechanical and topological characterization of pattern formation. On the other hand, we would like also to promote further research by identifying open problems of this field.

This review is divided in six sections. Right after this first section of introduction, the second section presents the basic mechanisms that promote spatial interactions (a fundamental component in pattern formation) and reviews mechanisms for molecular pattern generation. The third section is devoted to gradients as a primary driving force in developmental patterning. Gradients are used to provide positional information to cells within a primordium. In that section we review how gradients are formed and interpreted, and their precision is characterized. Section 4 deals with issues in regards of the segmentation and compartmentalization processes in development. We also introduce a tool for deriving mathematical models from network graphical representations using as an example the formation of organizing boundaries. Section 5 focuses on mechanical interactions in development. There we show that energetic and mechanistic considerations are key in some developmental processes and review modeling techniques that use this approach. In addition we reveal how formalisms from foam theory have been used to characterize tissue topologies. Finally, the review concludes with a summary of the main ideas introduced herein. All in all, we show that modeling in Developmental Biology is a promising field of research that has shed light on, and will surely elucidate, fundamental open problems in embryo development.

2. Mechanisms of Pattern Formation in Development

Cell fate specification relies on differential gene expression. Cells read and interpret protein activities driven by gene expression, triggering signals for differentiation. In order to understand how cells become differentiated into an organized and reliable structure we need to answer how the molecular patterns that trigger differentiation signals are generated as well as how cells read and interpret them. While this section is devoted to mechanisms for molecular pattern formation, pattern interpretation is discussed in Section 3 in the context of morphogen gradients and positional information. Note that molecular patterns can be considered as pre-patterns that indicate which fates cells will acquire and in which spatial locations. This has been the prevailing view of pattern formation in development and will be the basis for this section, while discussions on the assumptions of this view can be found at the end of this section as well as in Section 3. Since molecular activity is required for

differentiation, the mechanisms discussed in this section should be understood as mechanisms for gene and protein expression which yield molecular activity. In Section 4, the differences between gene expression and activity will be discussed with a specific example.

There is a wide variety of molecular patterns that drive organized embryonic structures. These patterns range from spatial stationary heterogeneous distributions given by a single molecule that forms a gradient (i.e. its concentration decays over space), dynamical periodic waves of gene expression of different interacting genes sweeping a tissue (e.g. the cyclic genes during somitogenesis in vertebrates), to periodic and branching patterns, to mention a few. In this section, we summarize different mechanisms for the formation of stationary molecular patterns. We review two kinds of patterns that have received special attention in the last decades: non-periodic patterns formed by a single gradient and periodic patterns constituted by one or several molecular components.

From a conceptual point of view, two different ways for the formation of patterns can be envisaged. On the one hand, patterns can be created from an existing asymmetry or polarity (e.g. from another heterogeneous profile). On the other hand, patterns can be created *de novo* when there is no previous consistent asymmetry. In this section we focus mainly on *de novo* pattern formation, while Sections 3 and 4 are devoted to specific examples of patterns arising from a previously settled polar cue.

2.1. Spatial Coupling for Pattern Formation

Independently of the presence or absence of initial polar cues, pattern formation always requires spatial coupling. This coupling enables the transfer of information over space to create an organized structure such as a pattern. Without spatial coupling, the dynamics at each spatial location is independent of the dynamics in any other location, impeding the construction of a spatial non-random structure.

Different processes mediate spatial coupling. One of them is the transport of a molecule. This transport can be non-directed (i.e. towards all directions) or polar (i.e. towards a specific direction). Diffusion is a paradigmatic example of a non-directed transport. In 1952 Alan Turing proposed and demonstrated from theoretical grounds that diffusion of two molecules can create patterns *de novo* which could be potentially relevant for morphogenesis. Nobel Laureate Francis Crick evaluated in 1970 whether diffusion could be a long-range transport mechanism yielding gradients along embryos. He showed that diffusion could transport proteins on realistic time scales of a few hours in tissues about 30-70 cell diameters wide. Since then, diffusion has been considered the major transport mechanism taking place during embryonic pattern formation.

Diffusion arises from the random motion of molecules in all directions. As a result, diffusion *per se* tends to homogenize the concentration of the diffusing molecule over space. In addition, due to the inherent randomness of diffusion which prevents persistent straight motions, it is possible to prove that the root mean square of the displacement of diffusing molecules increases with time as its square root. Hence, diffusion enables to reach very short distances rapidly, while it involves long time

intervals to achieve large distances, when compared to ballistic motion. At present, diffusion is commonly named restricted or effective diffusion. These terms emphasize that diffusion in embryos is not occurring just in an aqueous medium, but in crowded environments with non-uniform matrix geometries and molecular distributions that interact with the diffusing molecule and slow down its dynamics.

There are other non-directed transport mechanisms occurring in cells. This is the case of transport through cells by cycles of endocytosis and exocytosis (named transcytosis; see Section 3 for its relevance in morphogen gradients). Since this transport involves vesicle trafficking and recycling, its dynamics are expected to be slower than those of diffusion alone in an aqueous medium. Note that this transport mechanism can become potentially directed if, for instance, the polarity of cells influences the vesicular transport or ligand externalization. Being a new transport process unveiled in the last decade, it lacked of a mathematical description that could evaluate its main features. Recently, a first mathematical description of this transport has been provided by Bollenbach and colleagues. This description shows that non-directed transcytosis coupled to extracellular diffusion of the ligand can be described for large length scales and small ligand concentrations as an effective passive diffusion.

There are several examples of directed transport mechanisms acting during embryonic development. The transport of a molecule mediated by a fluid flow (advection) is directed in the direction of the fluid flow, while the transport of charged molecules is also directional and its polarity is set up by voltage differences. In plants, the hormone auxin, a key hormone for plant development, is transported polarly. Albeit it is still unknown how this polarity of auxin flow is controlled, the asymmetric localization of protein carriers that enable active auxin efflux and influx transport from cells is crucial. Pattern formation driven by such hormonal polar transport is reviewed in the following subsections.

Importantly, spatial coupling can also be driven by other means than the transport of physical entities. This is the case of the binding of receptor and ligand proteins anchored in different cell membranes. In this case, when the ligand and the receptor bind, a signal is triggered within the cell harboring the receptor. Hence, information from the cell that has the ligand (signaling cell) is transferred to the cell that has the receptor (target cell), setting a spatial coupling. This kind of spatial interaction can also drive molecular patterns as shown below.

More than one mechanism of spatial coupling can be acting at the same time during pattern formation. Mathematical modeling becomes extremely useful in such cases since it can evaluate the contribution of each kind of coupling to the pattern formation process. An exemplifying case can be found when one of the spatial couplings favors homogenization (no pattern), while another one drives patterning. In this case, mathematical modeling can pinpoint under which circumstances (range of parameter values) a pattern is expected to arise. Finally, note that we have only mentioned spatial coupling mechanisms which involve molecular elements. However, as described in section 5, spatial coupling can also occur between cells through physical/mechanical interactions.

2.2. Patterns Formed from Polar Cues

One of the paradigmatic examples of pattern formation though polar cues is gradient formation. A spatial gradient of a molecule corresponds to a non-periodic spatial heterogeneous molecular distribution that decays over space. Molecular spatial gradients have been unveiled in many different contexts of development and in many different species, ranging from vertebrates to plants and have been shown to control morphogenesis. In this section we briefly sketch which elements are required to create gradients in order to emphasize the differences with *de novo* pattern formation mechanisms, which are reviewed in the next subsection. Section 3 extensively studies gradient formation and its implications on morphogenesis.

Spatial gradients can settle down within the extracellular space or inside cells and need to span large enough distances to be relevant for morphogenesis. One of the most studied molecular gradients in Developmental Biology is the graded profile the transcription factor Bicoid forms within the syncytium of the fruit fly, *Drosophila melanogaster*, along the antero-posterior axis. This gradient poses the minimal elements required to create a non-periodic graded distribution. On the one hand, an initial polarity is needed. On the other hand, transport of the molecule over long distances must occur. In the case of Bicoid the polarity is given by transcription, which occurs only at the anterior pole of the embryo. While there is controversy of how Bicoid is transported (see section 3), diffusion across the embryonic cytoplasm of the syncytium is the common transport mechanism being proposed. These two factors (a polar transcription and non-directed transport) can drive Bicoid gradient formation. However, if there are no additional processes being involved, the Bicoid gradient is expected to change significantly over time, since the concentration of the molecule is expected to increase constantly. This is not what is observed experimentally. Indeed Bicoid gradient has been reported to exhibit an exponential profile which is stationary (or nearly stationary). Therefore, additional processes are participating to shape this gradient. Albeit a thorough discussion of this gradient is made in section 3 we indicate herein that degradation of the Bicoid protein across the space accounts for this exponential gradient profile. Therefore, albeit a polar cue and long-range transport are the minimal elements required to create a gradient, additional processes can also participate which also shape the gradient profile and control its properties. A mathematical description of the dynamics of gradient formation, as exemplified in section 3, can evaluate how each process shapes the gradient, which alterations on the gradient profile (at transient and stationary times) are expected to occur when a perturbation is applied, and which properties does the gradient profile exhibit. Conversely, by analyzing how the gradient is modified when changes or perturbations are applied, we can infer how it is created.

Most of the gradients reported during embryonic development are driven by a polar cue arising from local inhomogeneous sources of protein transcription or protein translation (e.g. transcription/ translation is restricted to a small spatial region). However, the polarity required for gradient formation can arise also from directed transport. This is the case of the spatial gradient of the hormone auxin in the root apex of the plant *Arabidopsis thaliana*. Plants develop and form new structures throughout their lives through the dividing activity of meristems. In *Arabidopsis*, auxin flows from apical regions into the root through the vascular tissue and returns to the apical regions

through the epidermis. A maximum of auxin has been found in a domain (columella initial cells) at the root apex. However, no local, polar biosynthesis sources of auxin are known within the root. Importantly, auxin transport involves a non-directed motion, corresponding to diffusion, and a directed active transport mediated by protein carriers at the cell membranes. While auxin diffuses across the extracellular space and can passively enter into cells, diffusing within them as well, the direction of its flow is mainly controlled by the polar localization of protein carriers that facilitate efflux (and influx) transport from cells. Through mathematical and computational analyses of the auxin flow in the root Grieneisen and coworkers have unveiled that efflux polar transport can drive this gradient within the root architecture. Hence, in this case, the polar transport of auxin provides the polar cue and, together with diffusion, the spatial coupling required for gradient formation.

Polar cues can underlie other kinds of patterns, which do not have just a gradient profile. This is the case of periodic patterns that are created within an already patterned tissue. In this case, the primary pattern acts as a source of polarity. As expected, spatial coupling is required also to drive these patterns. Invertebrate embryonic segmentation exemplifies this scenario since it proceeds by the progressive subdivision of the embryo, relying at each step on polar cues given by previously settled down patterns. Sections 3 and 4 review examples of this kind of patterns.

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Biographical Sketches

Javier Buceta. Dr. Buceta graduated in Physics from University Complutense of Madrid (M.Sc. Fundamental Physics). In addition, he also has a M.Sc. degree as Computer Analyst (Madrid Education Council). In his PhD ('Fluctuations in Spatially Extended Systems', summa cum laude and award of

excellence) he researched on pattern formation, molecular motors, interfacial dynamics, and phase transitions. During that period, he collaborated in both national and international research projects and performed research stays in different institutions such as the Institute for Scientific Interchange (Italy) and the University of Limburgs (Belgium).

Afterwards, he moved to the University of California San Diego (UCSD), Dept. of Chem. and Biochem. and the Institute for Nonlinear Science, where he joined Prof. Lindenberg's group and worked on pattern formation, population dynamics, disease spreading, granular matter, stochastic processes, and tumor growth. During that period he was granted by La Jolla Interfaces in Science (LJIS)/Centre for Theoretical Biological Physics programme (Burroughs Wellcome Fund) to conduct research on 'Pattern Formation and Left-Right Symmetry Breaking in Embryo Development' and collaborated with Prof. Izpisúa-Belmonte's team (Salk Institute).

In November 2004, he moves to his current position at the Barcelona Science Park (PCB) as a "Ramón y Cajal" research fellow. Since then, he is the group leader of the so-called TheSiMBioSys Group (Theoretical and In Silico Modeling of Biological Systems Group). In the recent years, he has been funded to conduct research on pattern formation in embryo development and on a Systems Biology approach to the development and compartmentalization of the wing imaginal disc of Drosophila. Dr. Buceta has an extensive publication list that covers different topics from Physics to Biology, peer review several journals, and recently published, as co-author, a graduate Biophysics textbook: Topics in Biophysics (ISBN 84-362-5317-5, Cuadernos de la UNED, Madrid).

Marta Ibañes Miguez. Dr. Ibañes is a physicist focused on nonlinear and stochastic dynamics in the field of Developmental Biology. At the University of Barcelona, she pursued a PhD project under the supervision of Prof. José María Sancho and Prof. Jordi García-Ojalvo devoted to the modeling of noise-induced nonlinear phenomena, such as phase transitions and pattern formation. During this period, she was a visiting research scholar at the Physics department of the University de les Illes Balears (Spain) under the supervision of Raúl Toral and at the Physics department of the University of Crete (Greece) under the supervision of G. P. Tsironis. Under an European research project and in collaboration with the University of Crete, during the second half of her PhD thesis she pursued an additional sided project on the topic of spatially-localized and time-periodic vibrational modes along linear chains with an outlook to energy transfer in biopolymers. After receiving her PhD in Physics (with award) she switched to Developmental Biology by joining in 2003 as a postdoctoral research associate the laboratory lead by Prof. Juan Carlos Izpisúa Belmonte at the Salk Institute for Biological Studies (La Jolla, CA, USA). Her research focused on the dynamics of left-right symmetry axis determination and limb development in vertebrate embryos at different scales, from the molecular (gene networks) to the cellular and tissue (fluid biophysics and cell dynamics) levels, applying her skills on mathematical and computational modeling of these processes. Additionally, she worked in collaboration with Prof. Cliff Tabin (Harvard Medical School, MA, USA) and his group on left-right asymmetric gut morphogenesis.

Dr. Ibañes is now a "Ramon y Cajal" Researcher at the Structure and Condensed Matter Department of the University of Barcelona. After moving to Barcelona, she implemented the European Master in Biophysics from the University of Barcelona and has been its coordinator during three years (2005-2008). She has started a new research line on plant vascular patterning and its hormonal control in collaboration with the group in plant molecular biology lead by Dr. Ana I. Caño-Delgado (CSIC, Spain). She has also expanded her research to models for neurogenesis and for stochastic transcription dynamics.

Johannes Jaeger. Dr. Johannes Jaeger is an evolutionary developmental biologist. He was born in Chur, Switzerland on March 17, 1973. He finished his secondary education in 1992 with a federal degree in modern languages in St. Gallen, Switzerland. After his basic undergraduate training as an arch-reductionist and Drosophila geneticist in the laboratory of Prof. Walter Gehring in Basle, Switzerland in the late 1990s, he completely switched sides and did a Master in Holistic Science with Prof. Brian Goodwin at Schumacher College, Dartington, Devon, U.K, which he finished with distinction in Sep 2000. During his PhD project under the supervision of Prof. John Reinitz at Stony Brook University, Long Island, New York he finally learned to combine experimental and theoretical aspects of his interests by applying gene circuit models to simulate quantitative gene expression patterns in the early Drosophila embryo.

After receiving his PhD in Genetics from Stony Brook University in Dec 2005, Dr. Jaeger worked as a postdoctoral research associate at the Museum of Zoology in Cambridge, U.K. He was recognized researcher on a project grant by the Biotechnology and Biological Sciences Research Council (BBSRC) which was concerned with establishing the molecular and computational tools for a comparative analysis of developmental gene regulatory networks among different species of flies, midges and mosquitoes. He is now a junior group leader (since Oct 2008), in the EMBL-CRG Systems Biology Research Unit at the Centre for Genomic Regulation (CRG) in Barcelona, Spain. His group investigates the evolution of developmental gene regulatory networks, using early development of flies and midges as an example.

Dr. Johannes Jaeger was the organizer of the Cambridge Seminar Series in Evolutionary Developmental Biology from 2006 to 2008, and is an Academic Editor of the open access journal PLoS ONE.