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Mechanisms of Pattern Formation, Morphogenesis and Evolution

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Abstract:

This chapter briefly introduces the diversity of ways in which developmental mechanisms lead to pattern formation and morphogenesis. Developmental mechanisms are described as gene networks in which at least one of the genes affect some cell behavior (cell division, cell adhesion, apoptosis, cell contraction, cell growth, signal and extra-cellular matrix secretion, etc...). These mediate one of the most important processes in development: the transformation of specific distributions of cell types in space (starting with the zygote) into other, often more complex, spatial distributions of cells types (such as in later developmental stages and ending up in the adult). This chapter explains in detail why genes alone are unable to do that and why they require cell behaviors and some other epigenetic factors. This chapter exposes also why understanding the mechanisms of development is crucial to have a more complete evolutionary theory in which one can explain extant phenotypes based not only on natural selection but also on which phenotypic variation can be produced by development in each generation.

Three main types of developmental mechanisms are described in this respect: Autonomous, inductive and morphogenetic. In inductive mechanisms the spatial distribution of cell types changes due to signaling between cells. In morphogenetic mechanisms these distributions change because cells change their spatial location. This chapter also explains how these three types of mechanisms are combined in animal development and how these different combinations lead to different kinds of phenotypic variation and morphological evolution.

Keywords: Evolution, development, developmental mechanisms, pattern formation, morphogenesis

Introduction:

Evolution can be understood as change over generations on a lineage of reproducing organisms. Development, on the other hand, can be understood as the process of change over an organism's life.

Although in common speech it is often said that one has inherited that or that other phenotypic trait (e.g. eye colors) from some relative, the phenotype is not inherited as such, only the gametes are. Thus any organism's phenotype, and any difference between organisms in successive generations, has to be built de novo from those gametes in each generation. The building of the organism is the process of development. In that sense the range of phenotypic changes that can arise through the process of development determines the range of changes possible in evolution (Alberch 1982). This chapter gives a general overview of the repertoire of mechanisms that operate in development to build the phenotype and its variation.

The changes in development that lead to changes in the phenotype arise, ultimately, from changes in the environment (what is usually called phenotypic plasticity) and changes in the DNA. The identification of these ultimate causes was central to 20th century biology. This identification, although very important, does not by itself allows us to understand or predict how the phenotype will change. In that respect genetics tells us that the inheritance of phenotypic characters is largely due to the inheritance of the DNA and that the changes in these characters imply changes at the level of the DNA (if those changes are heritable). It is currently not understood, however, why or how some specific genetic changes lead to some phenotypic changes, and not to others, and which is the range of phenotypic changes that can arise by genetic changes (in a given generation and population). In a large number of cases there is a description of which genetic changes are associated with which phenotypic changes but this, by itself, does not entail an understanding of why these genetic changes lead to those specific phenotypic changes.

Understanding the relationship between genetic variation and phenotypic variation, also called the genotype-phenotype map, is probably one of the greatest challenges in 21th century biology. This is currently the main limiting factor for the advancement of evolutionary biology, medicine and biology in general. In fact, the rise of evo-devo in late 20th century and early 21th century is largely related to the realization of the importance of the genotype-phenotype map and of its developmental bases in evolution (Alberch 1982; Muller 2007).

It is generally acknowledged that the genotype-phenotype map is quite complex. Usually, this complexity is understood to arise from the fact that the phenotype arises through the interaction between a large number of genes and between those genes and epigenetic factors of several kinds. This is specially the case when the phenotype considered is morphology. Morphology, understood in here as the 3D spatial distribution of cells and cell types in an organism, arises through the process of development. It is important to understand, however, that it is not the case that without these genetic and epigenetic interactions it would be possible to produce realistic phenotypes with a simple genotype-phenotype map (Salazar-Ciudad 2006b, 2007). Without those interactions the phenotype would simply not exist beyond single isolated cells. It is precisely because in development cells interact through extracellular signaling and mechanical interactions that a phenotype made of something more than a single cell or small blob of disorganized cells can be built.

This fact has not always been evident to everybody. This probably has to do with the way in which genetics was formulated in the 19th and early 20th century. Genetics developed before the discovery of DNA, its structure and its role in inheritance. Genetics is the study of inheritance and as such experimental genetics was at first based on crossing organisms with different phenotypes and observing the phenotypes of their offspring. Since phenotypes are complex, those studies predominantly focused on easily identifiable and mostly discrete phenotypic characters (e.g. yellow versus green peas). At some point it was discovered that the patterns of inheritance of some of these characters could be explained by the transmission of some discrete physical particles in the cell's nucleus. Even later it was discovered that these particles are made of DNA and that some DNA sequences code for different sorts of RNA and proteins. From that it may seem possible to say that genes are “coding” for discrete phenotypic characters, such as the greenness or the yellowness of peas, or more in general for characters of all sorts. It is currently known, however, that the information

necessary for the color of the pea, or the information for any phenotypic character for that matter, is rarely contained within the gene "coding" for that character (especially when morphological characters are considered). It is normally impossible to guess the phenotypic effect of a change in a gene product from its DNA sequence, or even from its protein structure. This is not because of a limitation in our knowledge, it is simply because the information is not there. Single genes do not build phenotypic characters or its variation on their own. Genes affect the phenotype because they are embedded in networks of genetic and epigenetic interactions. Due to these networks of interactions, variation in these genes leads to variation in some phenotypes. In a way the information for greenness and yellowness is contained, and distributed, in the whole network of genetic and epigenetic interactions involved in each trait development. How those networks work and how they lead to phenotypes, and their variation, are the aim questions of this chapter. To understand that in more detail it is informative to consider in some more detail what gene products and cells can do.

What gene products and cells can do

What gene products can do:

Sequence variation in a gene can have multiple and complex effects on the phenotype. Gene products, however, can only do a limited number of things:

First, they can bind to each other or to other molecules. Binding refers to non-chemical bonding, the close apposition of molecules due to hydrogen bridges, van der Waals forces and other weak interactions. The specificity of that binding largely depends on the structure of the gene product, this is their constituent atoms, their spatial distribution and their chemical covalent bonds. Non-covalent binding to other molecules can alter the spatial distribution of the atoms in a gene product, a conformational change, and affect then to which other molecules a gene product can bind. Binding can occur with stable molecules or with molecules that are the transitional unstable state between two other molecules and, as a result, catalyze different chemical reactions (as in enzymes).

Second, gene products can move passively, by the physical process of diffusion, or actively, through conformational changes mediated by cycles of bonding, for example to ATP and ADP molecules as in the case of myosin. Gene products, as other molecules, can be moved passively due to binding to a structure that moves, like to an organelle being moved by the gene product kinesin.

Third, gene products can undergo changes of state. This is simply a change in what a gene product is "doing" (among those things described above). These are changes in either the conformation or composition of a gene product (for example as a result of binding or chemical reaction) that change its binding specificity, and possibly, how it moves. Usually this does not occur at random. A given gene product can have a relatively small number of possible conformational states and react to a small number of modified forms (for example by phosphorylation or proteolysis). In that respect many gene products are like small computational devices. They undergo a number of transitions between states, or outputs, depending on the set of molecules that interact with it in each moment (or input). These computations tend to be relatively simple. Many transcriptional factors, for example, can only bind to the DNA if phosphorylated. In these cases the gene product has only two states, the non-phosphorylated one and the phosphorylated one. In other, more complex cases a given conformational change only occurs if a gene product binds to (or is modified by) two different molecules (thus implementing an "AND" logic gate), if it binds to either of them (an "OR" logic gate) or it binds to only one of them (an "XOR" logic gate). What determines the outputs a gene product gives to each set of inputs is basically its structure. In general, however, it is quite difficult to predict the structure, possible conformational changes and binding specificity of a gene product from its sequence. Both questions have been under intense research and it is nowadays widely acknowledged that already at this molecular level there is a rather complex genotype-phenotype map (in here the phenotype would be the

protein structure; Fontana and Schuster 1998). The above discussion applies also to the cis-regulatory elements in the DNA.

If gene products can do only this limited number of things, how come that they can build complex multicellular organisms such as us? It seems they can not do it on their own. To be involved in the building of the body, gene products need to affect what cells do. Again cells can do a small number of things but it is important to realize that those things are not reducible to what gene products can do. Many of the things cells can do (dividing, binding, etc...) are not determined by gene products as such but are intrinsic to cells. In fact, lipid micelles and liposomes are, under some conditions, able to divide, fuse, "die" and bind to each other (Schrum et al. 2010). Environmental factors, noise and some properties of those (like size) determine when these would divide, fuse, adhere or disintegrate. There are a theories suggesting that cells may have originated before and independently from gene products and DNA (Segré et al., 2001).

Since organisms are mostly made of cells (and some extra-cellular matrix; ECM) it is clear that development involves the regulation of what cells do (dividing, binding, moving, etc...) over time and space in the embryo. In that sense, development could be reduced to the description of what cells do in each moment and place. Thus, irrespective of how complex gene products are, gene products influence development to the extent that they affect, directly or indirectly, these things cells do.

What cells can do:

Cells can also do a limited number of things. In here, each of those is called a cell behavior. They can divide. If the mother cell has some internal spatial polarization the two daughter cells can be of different size and inherit a different set of molecules from the mother. Cells can also fuse with each other and they routinely do it in the development of some organs (such as muscle). Cells can grow or shrink in size. They can bind to each other or to the ECM. This is often mediated by adhesion gene products expressed in the membrane that show some binding specificity for molecules present in the membrane of other cells or in the ECM. In spatially polarized cells different parts of the membrane may express different adhesion proteins and, thus, bind to different types of cells. Cells can also die. Cell death may be elicited by signals from other cells as part of the healthy normal development of an organism. Cells can contract part of their body. As a result of contraction and adhesion, cells can change their shape. Cells can move in a passive or active way. Passive movement occurs as a result of cells being bound to cells that move actively or contract actively. Active cell movement is a result of coordinated adhesion and contraction. Cells can also secrete ECM and extracellular diffusible molecular signals than may then bind to specific receptors in other cells.

Cells can also change of state. These are changes in what a cell is doing, this is which cell behaviors are active in each moment and how much. As in the case of molecules, cells can be considered as computational devices that elicit a different response or output, the cell behaviors activated and how much, depending on the inputs received. The inputs are the extracellular signals a cell is receiving (typically diffusible gene products), the concentration of those, the intensity of the mechanical forces it is receiving, the direction of those and whether they are stretching or compressing the cell. In each cell, which output arises from which specific set of inputs is determined by the network of gene products and other molecules expressed in the cell and by some cell-level properties such as the metabolic state, cell size and cell shape. It is important to realize that, although this cell-level computation seems complex, the outputs themselves are relatively simple, the activation of one or several of these cell behaviors with different intensity. In addition, in most organisms' development, cells give relatively fast and short-lived responses to inputs. Development proceeds further simply because these responses often involve the secretion of signals and mechanical forces that are themselves inputs for other cells. In that sense cells are constantly receiving signals and changing their behaviors. Thus, the complexity development does not arise from how cells respond to signals, or from

the signals themselves, but from the emergent spatio-temporal pattern of signals and responses in whole cell collectives.

Developmental mechanisms:

If gene products and cells can do a limited number of things the question is then how are those things organized during development to build the body. In here, as described before Salazar-Ciudad et al., 2003, a *Developmental Mechanism* is any network of interacting gene products in which at least some gene regulates some cell behavior so as to lead to pattern formation. In that sense each developmental mechanism is a different way to arrange what cells and gene products can do, this is, in other terms, a different network topology. This definition pays special attention to the gene network topology and not to the network of which cells are interacting with which. This is mostly for convenience and it could be done in some other way. This definition has the advantage that there is much more empirical information about gene network topologies than about which cells interact with which.

This definition of developmental mechanism considers only gene networks involved in pattern formation. Pattern formation is understood, in here, as the transformation of one spatial distribution of cell types, called in here a developmental pattern, into another one. The process of development can then be described as a sequence of pattern transformations, starting from the zygote, between different developmental patterns over time. Note that from this definition mere changes in morphology (such as in morphogenesis) are also considered pattern formation (see Figure 1). Note also that from the definition of developmental mechanisms gene networks with the same topology and affecting the same cell behaviors but in which genes bind to, or regulate, each other with different intensity would be considered to belong to the same developmental mechanism.

There are two things to stress in here about pattern formation in relationship to developmental mechanisms. First, all pattern formation events start from an initial pattern. It is totally arbitrary and up to the researcher from which initial developmental pattern to which later pattern to focus attention but there is always an initial developmental pattern, at least the zygote, and this one is almost always spatially non-homogeneous. Thus, in the same way that there is not such a thing as a gene to make a leg (or green and yellow peas) there is neither a developmental mechanism to make a leg. There are, instead, developmental mechanisms that can build a leg from some specific initial condition (see Fig.1). The set of different final patterns arising by a developmental mechanism from different initial patterns, different environments or different genetic mutations (as long as those do not change gene network topology) are what is called, in here, the variational properties of such a developmental mechanism.

Second, the process of development implies the creation of new spatial information that is neither present in the genome nor in the structure of the gametes. Historically it has sometimes been suggested that there is no creation of information but simply the transformation or unfolding of it, that in some way the information to build the body would be present in the genome. The concept of information in biology is complex and elusive but in the case of development there is a change in the spatial information over time: cells get into different places within the embryo with a specific pattern. This information can not be said to be present in the genes but it arises from the interaction between those genes and the previously existing developmental patterns (starting from the spatial structure of the oocyte). In that sense new epigenetic information (the developmental patterns themselves) gets generated from previous epigenetic (previous developmental patterns), genetic information (the gene networks) and some other epigenetic information (such as the mechanical properties of cells, the cell behaviors and some other biophysical processes).

Types of developmental mechanisms:

Autonomous:

These are developmental mechanisms in which pattern transformation occurs without cells interacting with each other. Simply the non-homogeneous spatial structure of a cell, typically a zygote, is translated into a multicellular context by cell division. Thus, zygotes, that as mentioned above inherit an spatial structure, can lead, by mere cell division such as in cleavage, to a new pattern in which the different spatial regions of the zygote end up within different cells but with the same spatial relative arrangement between them.

Inductive:

These are developmental mechanisms in which pattern formation is attained by making cells in different places to express different genes because of molecular signaling between cells. These are by far the most studied and best understood developmental mechanisms. The inductive developmental mechanisms that have been proposed in the literature can be classified into two main types:

Hierarchic inductive mechanisms:

In these a group of cells secretes a diffusible signal (or expresses a membrane-bound signal) that then diffuses in the extra-cellular space (or binds to a receptor on a cell in close contact to it) and binds to extra-cellular receptors on other cells. That binding activates a signal transduction pathway which leads to gene expression changes in the receiving cells. The receiving cells may respond by secreting some other extra-cellular signals that may reach the original group of cells sending the first signal. In hierarchic mechanisms, by definition, the response of cells to incoming signals does not affect how these incoming signals are being secreted at the source (this is at the cells that originally send the signal). This makes the dynamics of these mechanisms simpler to understand (see Figure 1). As a result of this signaling a new pattern arises that in the simplest case contains two groups of cells or territories: the original group of cells sending the signal and the set of cells that receive that signal at a concentration high enough for the activation of its receptor. The latter group has a distribution in space, or territory shape, that resembles that of the former with some variation in width, depending on how much the signal diffuses, and some blurring due to the averaging nature of the diffusion process itself (Salazar-Ciudad 2006a).

In more complicated cases different concentrations of the original signal can lead to the differentiation of different types of cells, as in the French flag model, but even in this case the shape of the new induced groups of cells would resemble that of the group of cells sending the signal. This is concentric rings around the cells sending the signal (see Figure 1). In even more complicated examples, signals coming from different sources (see Figure 2) can combine, e.g. using logical operations, in space to lead to slightly more complex patterns. In a 2D lattice of cells maximal complexity patterns (where each cell has a different gene expression pattern) can be attained from two signals producing perpendicular gradients (see Figure 3). This, however, requires a rather complicated network in which very small differences in each signal concentration can activate completely different gene expression patterns downstream.

Emergent hierarchic networks:

In these the response of cells to incomings signals involves the secretion of secondary signals that affect the rate at which the first signals are being secreted. As a result of that, patterns arise that have groups of cells whose spatial distribution does not usually resemble that of the cells sending the first signals. In the simplest cases the secondary signals activate the secretion of the first and then these

make a positive loop by which all cells end up expressing both signals. The most interesting case is, however, when one signal, usually called an activator, promotes its own secretion and that of another signal, the inhibitor, that when received by cells inhibits the secretion of the activator. Depending on the diffusibility of these signals and on how much they affect each other, rather complex patterns can arise from these networks. These mostly consist of stripes or spots of high activator concentration. In some cases very similar patterns arise from different initial conditions while in others, depending on the exact network, these stripes and spots arise as concentric rings around the signals in which the activator was expressed in the initial conditions. This type of mechanisms is usually called "reaction-diffusion" or "Turing-like" mechanism (Meinhardt 1982).

Morphogenetic mechanisms:

From the above discussion it seems clear that not many developmental patterns can be achieved from autonomous and inductive mechanisms alone. The former only translate spatial asymmetries within the zygote into groups of cells while the latter only produces stripes, spots and distorted copies of the shapes of the groups of cells sending a signal. By combining signals coming from groups of cells in different spatial locations more complex patterns can be attained. The location and shape of the groups of cells sending a signal is, however, not free to change in any imaginable way. Irremediably, if these territories are themselves produced by inductive mechanisms, their shapes are modifications of those of other previous territories and, ultimately, only of those spatial regions present in the zygote. In the zygote there are normally only two or three more or less perpendicular axes along which two or three spatial regions are present: the animal-vegetal axis, an anterio-posterior axis and in some species a left-right axis. In addition none of those mechanisms can change the location of cells in space (they only change the location of cell types or gene expression within groups of cells).

It is by the use of morphogenetic developmental mechanisms that the spatial distribution of cells, and not only cell types, can be changed. Changes in cell spatial location are due to mechanical interactions between cells. There is a quite large diversity of those (see Salazar-Ciudad et al. 2003 for a review) but in general, in here, the gene network involved is not so important as the diversity of cell behaviors used.

Mechanical forces are generated by cells and transmitted through cells and ECM. There are four cell behaviors that can generate forces: cell contraction, cell growth, cell division and ECM secretion (Lecuit et al. 2011). Cell division probably generates forces in a secondary way since it involves contraction and growth of the membrane. Adhesion by itself may not actively generate forces but it mechanically couples cells so that the forces in one cell pulls others.

From simple initial conditions morphogenetic mechanisms can lead to rods, tubes, invaginations, cavities and extensions in one dimension while others contract (Newman 1994; Newman et al. 2006; Salazar-Ciudad, 2006a). From more complex initial conditions much more complex morphologies can arise, up to the ones observed in animals.

Composite developmental mechanisms:

Morphogenetic mechanisms can do more than change cells spatial location. If inductive and morphogenetic mechanisms act interspersed in time or at around the same time, then the locations and shapes of the territories sending signals are not reducible to the spatial regions within the zygote and their combinations by logical operations (as with inductive mechanisms). Morphogenetic mechanisms can act on the groups of cells sending signals and then signals can diffuse from a larger repertoire of territory shapes. This is not so much the case if inductive mechanisms act first in development to establish different cell types in a field of cells and then different morphogenetic mechanisms act in each cell type or combination (those are called morphostatic combined mechanisms and the former

morphodynamic combined mechanisms).

By combining inductive and morphogenetic mechanisms in a morphostatic way one can produce all the territory shapes possible by inductive mechanisms (mostly concentric rings) and the ones possible from the deformation of those by morphogenetic mechanisms. Combining inductive and morphogenetic mechanisms in a morphodynamic way allows, in addition, the territory shapes arising from the secretion of diffusible signals from the territory shapes possible by morphogenetic mechanisms. This clearly allows many more of those shapes and a higher complexity in those. This difference is supported by computational models of development and it has been suggested to have wide implications for the evolution of morphology and development (Salazar-Ciudad and Jernvall 2004; Salazar-Ciudad 2005) (see Marín-Riera and Salazar-Ciudad 2016 in this same book).

Evolution by morphostatic and morphodynamic mechanisms:

From the above discussion and simulation studies it has been proposed that when combining the same set of inductive and morphogenetic mechanisms (or for the set of all possible combinations of inductive and morphogenetic mechanisms), morphodynamic combinations would generally lead to more complex genotype-phenotype maps and to more complex and disparate morphological variation than morphostatic combinations (see Figure 4). By more disparate it is meant that the different patterns arising from a given composite developmental mechanism (e.g. from changes in the initial patterns or mutations in the mechanisms not affecting its topology) would be more different between each other in the case of morphodynamic composite developmental mechanisms than for the case of morphostatic composite developmental mechanisms. This has lead to propose that when major changes in morphology are observed in evolution (e.g. in novelty) these are more likely to arise from morphodynamic mechanisms than from morphostatic mechanisms. This is simply due to the larger disparity of morphologies or patterns possible by those mechanisms. This would be specially the case for complex morphologies since morphodynamic mechanisms are much more likely produce complex patterns than morphostatic mechanisms.

The relatively high non-linearity imposed by the interdependent interactions between inductive and morphogenetic mechanisms makes that morphodynamic mechanisms are less likely to produce gradual variation. This is, a higher proportion of genetic mutations in a morphodynamic mechanisms will lead to qualitatively different new final patterns or to no change in the produced pattern at all. In those situations in evolution when a very optimal morphology has been reached, either globally or for a specific organ, it may be more advantageous to not to change that morphology or to change it only slightly in a gradual way. This is more likely to be possible if this morphology is produced by a morphostatic mechanism. Thus, while in many cases morphodynamic mechanisms would be the mechanisms that would first arise in evolution to produce a specific morphology, there may often be a selective pressure to replace these morphodynamic mechanisms by morphostatic mechanisms to produce the same phenotypes or small variations from those. This replacement, however, would be less likely for complex morphologies since morphostatic mechanisms are less likely to produce complex pattern transformations (for the reasons exposed in the previous section).

Note that the distinction between morphostatic and morphodynamic mechanisms does not imply a difference in the number of genes involved or in genetic complexity. This genetic complexity comes from the specific mechanisms being combined not from whether these are combined in a morphostatic or mophodynamic way. In that respect a mechanisms can change from being morphostatic to being morphodynamic, or vice versa, by a mere change in the relative timing of activation of its different composing mechanisms (in most cases these changes would lead to dramatic changes on the pattern transformations produced). From these simulation studies and from the previous section one can expect that, given the higher capacity to produce complex pattern transformations of morphodynamic mechanisms, morphostatic mechanisms would require, in general, more genetic interactions, and the

combination of more inductive and morphogenetic mechanisms, to produce a complex pattern than morphodynamic mechanisms (although that would depend on the specific pattern being produced too). In that respect it is perhaps interesting to comment that there seems to be substantial differences between animal groups at the level of how morphostatic or morphodynamic their whole development is (Salazar-Ciudad 2010). Vertebrates are found to be the most morphodynamic and are also generally perceived as the most complex, although this may be just a mere perception.

Although mechanisms can change to be morphostatic to morphodynamic by mutations affecting the relative timing of their composing mechanisms, having morphostatic or morphodynamic mechanisms in the development of morphology, either of the whole body or a body part, can have major consequences on evolution. Thus, lineages making extensive use of morphodynamic mechanisms, such as vertebrates, should be expected to have variation that is more complex and less gradual compared to the variation expectable in lineages using a comparatively more morphostatic development, such as diptera for example. These differences should be expected also between organs in the same organism that are morphodynamic to different extents and should lead to evolve in different ways (i.e. more gradual simple changes versus more complex and more disparate changes).

In summary, this chapter exemplifies how considering a bit more in detail the nature and dynamics of developmental mechanisms allows to make predictions on how development evolves and on how development affects morphological evolution. These predictions are not possible from classical evolutionary approaches centered on genomes, genes, alleles and their replacement over time.

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Figure Captions:

Figure 1: Simple example of pattern formation. The initial developmental pattern in A gives rise to the developmental pattern in E. B shows a possible developmental mechanism, inductive hierarchic, able to produce this pattern formation. In A and E the square represents a lattice of epithelial cells seen from above. In A the area in dark grey marks the spatial distribution of the cells expressing a transcriptional factor TF1. The same dark grey territory is present in E but in addition there is a new territory, in medium grey, expressing a transcriptional factor, TF2. In B GF1 stands for a growth factor 1, whose expression gets activated by TF1, while GF2 stands for growth factor 2, whose expression is also activated by TF1. R1 stands for the membrane receptor of GF1 and R2 of that of GF2. These are assumed to be expressed in the whole epithelium. STP1 stands for the signal transduction pathway of GF1 and STP2 for that of GF2. For simplicity molecules are not represented in those. The pattern represented in E arises from the diffusion of GF1 and GF2. These are expressed in the same cells than TF1, since their expression is activated by it, but are secreted in the extracellular space and diffuse. Both GF1 and GF2 get degraded over time but GF2 is smaller and then effectively diffuses at larger distances than GF1. C shows the spatial distribution of GF1 and D that of GF2 (for simplicity the different concentrations of these molecules are not represented, simply where the molecules are present in the extracellular space). It is in those two regions marked in C and D that the concentration of those molecules is large enough to activate their receptors and the signal transduction pathways. STP1

inhibits the expression of TF2 while STP1 activates it. As a result TF2 is expressed there where GF2 is present but GF1 is not. This is a ring at certain distance from GF1. Notice that the territory of expression of TF2 resembles a ring with a shape similar to that of territory TF1 centered around it. The broken line indicates transcriptional inhibition. G shows the developmental pattern resulting from the same developmental mechanism in B acting on the initial developmental pattern in F.

Figure 2: As in figure 1 but in here the developmental pattern in E has a new territory where transcriptional factor TF3 is expressed. This gene is expressed where both GF1 and GF2 are present at enough concentration to activate their respective receptors. The discontinuous lines in E mark where the two growth factors are present (as also shown in C and D).

Figure 3: Initial pattern in which two territories express each a different growth factor (GF1 and GF2). These are secreted in the extra-cellular space and produce two perpendicular gradients along a lattice of epithelial cells. As a result each cell is receiving a unique combination of concentrations of those two growth factors. Then each cell can be said to receive a distinct unique epigenetic information. For that to translate into a real developmental pattern in which each cell expresses a unique combination of genes a very complex gene network is required (too complex to be shown in here). In addition, this network would be different for lattices with different number of cells.

Figure 4: This figure exemplifies that the relationship between genotype and phenotype (parameter space and morphospace) is more complex in morphodynamic than in morphostatic mechanisms. The figure shows in different shadows of grey the genetic variation or developmental parameter variation in a given population and time (left) and the resulting morphological variation by morphostatic (upper right) and morphodynamic mechanisms (bottom right). Each shadow of grey represents the distribution of produced phenotypes by a different developmental mechanisms. Notice the wider spread of produced morphologies in the case of morphodynamic mechanisms.