



Of mice and plants: Comparative developmental systems biology



Kirsten Ten Tusscher

Computational Developmental Biology, Department of Biology, Faculty of Science, Utrecht University, the Netherlands

ARTICLE INFO

Keywords:

Comparative systems biology
Antagonistic morphogen gradients
Oscillators
Turing patterns

ABSTRACT

Multicellular animals and plants represent independent evolutionary experiments with complex multicellular bodyplans. Differences in their life history, a mobile versus sessile lifestyle, and predominant embryonic versus postembryonic development, have led to the evolution of highly different body plans. However, also many intriguing parallels exist. Extension of the vertebrate body axis and its segmentation into somites bears striking resemblance to plant root growth and the concomitant pre patterning of lateral root competent sites. Likewise, plant shoot phyllotaxis displays similarities with vertebrate limb and digit patterning. Additionally, both plants and animals use complex signalling systems combining systemic and local signals to fine tune and coordinate organ growth across their body.

Identification of these striking examples of convergent evolution provides support for the existence of general design principles: the idea that for particular patterning demands, evolution is likely to arrive at highly similar developmental patterning mechanisms. Furthermore, focussing on these parallels may aid in identifying core mechanistic principles, often obscured by the highly complex nature of multiscale patterning processes.

1. Introduction

Arguably, animals and plants have evolved the most intricate multicellular body plans on our planet. Still, the animal and plant kingdom shared a last common ancestor some 1.6 billion years ago, far preceding the invention of plant and animal multicellularity. Thus, the body plans of animals and plants represent independent evolutionary trajectories (Meyerowitz, 2002).

At first sight, animal and plant multicellular development appear hugely different. First, plant cells are encased in stiff cell walls that glue them to their immediate neighbors while animal cells are typically more soft and capable of migration. As a consequence the mechanics and morphogenesis of plant and animal development are highly distinct. Furthermore, animals, apart from metamorphosis, undergo most of their intricate patterning embryonically. Instead, most plant development occurs beyond the embryonic stage, forming most organs and body parts over the course of life. Additionally, the fitness of animals with a complex bilaterian body plans critically depends on scaling of body parts with overall body size as well as precise left right symmetry, both necessary for normal mobility. In contrast, the sessile nature of plants necessitates flexible adaptation of the size, number and positioning of plant organs to environmental conditions to optimize the capture of light, water and nutrients, while resisting e.g. mechanical stresses from wind.

However, on closer inspection, also many parallels exist in terms of the type of signalling systems and resulting spatio-temporal patterns

deployed in animal and plant developmental processes. Parallels that must have arisen from convergent evolutionary processes. In some cases, constraints on how gene regulation and cell fate specification work may have channeled plants and animals down similar paths. An example is the combinatorial use of the so-called ABC MADS box genes to specify the distinct organs within plant flowers and the use of the famous Hox homeobox genes to specify distinct regions, along the longitudinal body axis in animals (Meyerowitz, 2002). In other cases, biophysical constraints on transport processes may have guided convergence, for example in the use of branched vascular architectures to transport food sources, waste products and signals, as illustrated by the requirement for vascularization in tumor growth in both animals and plants (Ulrich and Aloni, 2000). In yet other cases, parallelism may indicate that the mechanism plants and animals both evolved, is the most simple, most robust, and/or evolutionary easiest discoverable mechanism. Indeed, an extensive body of modeling work in the field of evo-devo demonstrates that for a particular pattern, only a limited number of generating mechanisms exist (Salazar-Ciudad et al., 2001a, 2001b; François et al., 2007; Fujimoto et al., 2008; Ten Tusscher and Hogeweg, 2011). Additionally, often clear differences in robustness or evolvability within this limited set of alternatives can be demonstrated ((Salazar-Ciudad et al., 2001a, 2001b; Fujimoto et al., 2008; Ten Tusscher and Hogeweg, 2011). These studies thus indicate that, given a certain selective pressure, evolution is likely to repeatedly arrive at similar “solutions”. The resulting re-occurring patterning mechanisms are often referred to as general morphogenetic design principles.

E-mail address: k.h.w.j.tentusscher@uu.nl.

<https://doi.org/10.1016/j.ydbio.2018.10.024>

Received 11 September 2018; Received in revised form 31 October 2018; Accepted 31 October 2018

Available online 03 November 2018

0012-1606/ © 2018 Elsevier Inc. All rights reserved.

Identifying new similarities in developmental patterning mechanisms of evolutionary distant organisms expands our knowledge of the numbers and types of morphogenetic design principles that are repeatedly used by evolution (Mentink and Tsiantis, 2015). In addition, pinpointing these design principles, and linking them to particular types of network organization and tissue level processes, is of critical importance for systems biology approaches of developmental patterning. It will prevent us from ending up with large network descriptions simply incorporating all that is known of the process of interest yet impossible to meaningfully analyze, and instead help us focus on the essential parts of the patterning process.

In this review, I will focus on parallels in animal and plant developmental patterning mechanisms, discussing the shared design principles and elementary core mechanisms that can be gleaned from these resemblances.

2. Axial growth and extension: the vertebrate posterior growth zone and the plant root tip

In plant roots, organ growth is spatially organized into distinct developmental zones (Ishikawa and Evans, 1995; Verbelen et al., 2006). At the tip, protected by a root cap, are the quiescent center and stem cells responsible for fueling the growth process through their slow divisions. These slow divisions give rise to daughter cells that are pushed out of the stem cell niche into the rest of the meristem, where they undergo multiple rounds of more rapid amplification divisions. Next, as cells become displaced shootward even further they enter the elongation zone where cells start taking up water into their vacuoles to drive a spectacular increase in cell size. Finally, cells progress into the differentiation zone, where they obtain the characteristics specific for the different cell types of the root, e.g. root hairs for epidermal cells to increase uptake surface, or sieve plates in vascular cells to reduce the resistance for long distance transport processes. This spatial organization into distinct zones bears resemblance to the way the posterior growth zone driving axial extension in vertebrate embryos is organized (Aulehla and Pourquié, 2010; Oates et al., 2012). Here, at the distal end called the presomitic mesoderm new cells arise due to cell division processes, as well as initially cell migration. As cells through growth move out of this domain they gradually differentiate, changing their motility and adhesive properties and finally reorganize into somites.

Underlying this similar spatial organization into distinct zones is a similar molecular patterning mechanism (Fig. 1). In both vertebrates and plant roots, a signalling gradient emanates from the tip of the growth zone, with gradually declining signal levels dictating the transitions to the distinct zones. In case of plant roots, a combined gradient of the plant hormone auxin and the PLETHORA (PLT)

transcription factors originates from the quiescent center and stem cell niche. High auxin and PLT levels support stemness, intermediate levels support division, and for low levels cell expansion and differentiation occur (Sabatini and Scheres, 1999; Mähönen et al., 2014). Similarly, in vertebrates a posterior gradient of FGF and Wnt signalling maintains cells in an undifferentiated, dividing state and as levels drop differentiation ensues (Aulehla and Pourquié, 2010; Naiche et al., 2011; Kumar and Duester, 2014). At first sight, this spatial patterning of domains resembles the spatial patterning first proposed by Lewis Wolpert (Wolpert, 1969). However, there is a fundamental difference with the vertebrate and plant root systems discussed here. While in the case of Wolpert's original proposal morphogen gradient driven patterning occurs inside a static tissue, here patterning takes place in a polarly growing tissue (Fig. 2). As a consequence, rather than individual cells residing in and contributing to a single domain, cells sequentially traverse the different domains. This dynamic mode of patterning puts additional constraints on the underlying mechanisms. Indeed, interestingly neither the vertebrate nor the plant root system use the classical diffusion driven mechanism for gradient formation. Instead, both systems make use of a highly stable signalling molecule which production is constrained to the tip of the growth zone. As cells leave the production zone due to growth they inherit a high level of the stable signalling molecule, which subsequently in parallel with their further displacement gradually declines. This results in a gradient generating mechanism that automatically enables cells to change zones as they displace. In case of plant roots, PLT protein stability ensures gradient formation (Mähönen et al., 2014), while in case of vertebrate axial growth, stability of the FGF mRNA is key to gradient formation (Dubrulle and Pourquié, 2004).

Left alone, these PLT and FGF signalling centers would eventually collapse due to the continuous growth and division induced dilution of signalling molecules. Both systems therefore deploy positive feedbacks that continuously restore high signal production levels. In plants, auxin engages in a positive feedback with the PLETHORA (PLT) genes (Pinon et al., 2013; Mähönen et al., 2014; Santuari et al., 2016), while in vertebrates FGF and Wnt positively affect one another (Ciruna and Rossant, 2001; Cunningham et al., 2015a). However, in isolation this positive feedback combined with the induction of division by these high signalling levels would lead to unlimited expansion of the growth domain. Thus, additional mechanisms are required to spatially constrain the growth domain (Fig. 1). In the case of plant root tips, a self-organized (Benkova et al., 2003; Xu et al., 2006; Mironova et al., 2012; Du and Scheres, 2017, 2018) intricate pattern of polarly localized auxin exporting PIN proteins, referred to as the reflux loop, is responsible for funneling most auxin towards the QC (Blilou et al., 2005; Grieneisen et al., 2007). This is thought to contribute to constraining the

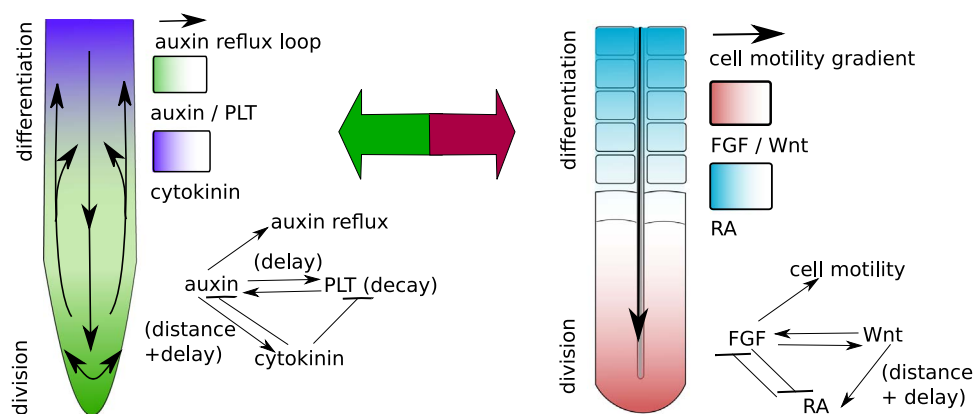


Fig. 1. Comparison of axial extension patterning in plant roots and vertebrates. Left: root tip axial patterning with a focus on interactions between auxin, cytokinin and PLETHORAS (PLT). Right: vertebrate axial patterning, centred on FGF, Wnt, RA and cell motility interactions.

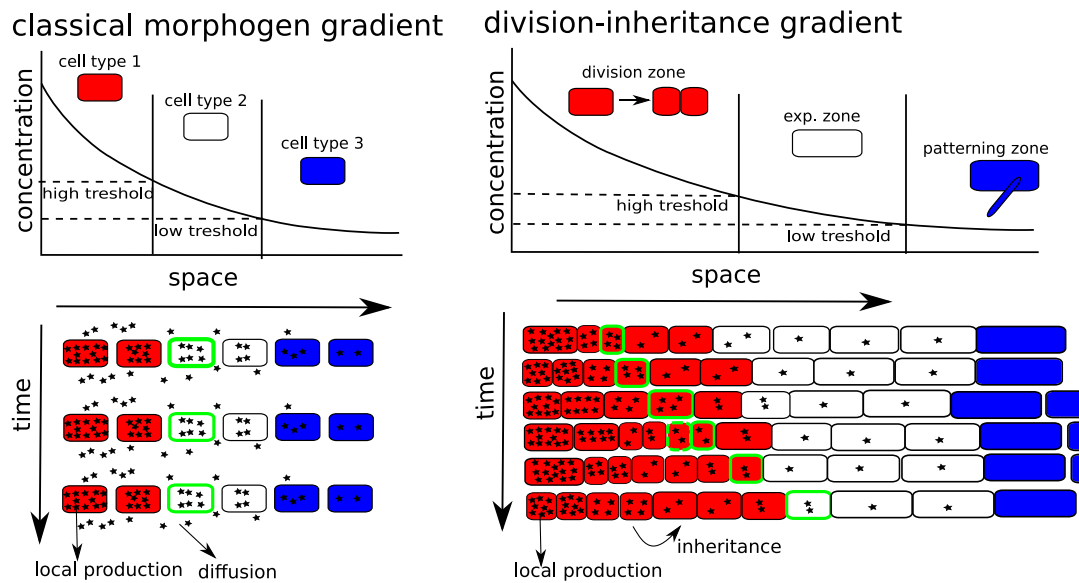


Fig. 2. Comparison of classical diffusion driven and division-inheritance driven gradients. Left: In the classical morphogen gradient proposed by Wolpert (Wolpert, 1969), local production (leftmost red cell) of signal via diffusion leads to a tissue level gradient (illustrated by particle numbers). Different morphogen levels cause cells to differentiate into different cell types (top). Patterning occurs inside a static, non-growing tissue, causing an individual cell (green edge) to maintain a constant position and cell fate. Right: In the division-inheritance gradient, local production (leftmost red cell) of a stable signal is inherited by daughter cells and gradually decreases through further divisions and decay, thereby producing a gradient (particle numbers). Different signal levels dictate different cellular behaviours, here the example of the plant root tip is taken with cells dividing for high levels, expanding for intermediate levels and differentiating into e.g. root hair cells for low levels (top). Patterning occurs inside a tissue growing from one end, causing an individual cell (green edge) to move from left to right through an individual developmental zone and then into the next.

auxin/PLT maximum to the root tip. In the vertebrate posterior growth zone, a MAPK/ERK signalling gradient downstream of FGF has been shown to result in a motility gradient, with highest mobility of cells in the posterior (Delfini et al., 2005; Mara et al., 2007; Bénazéraf et al., 2010). It can be speculated that the observed net movement of cells towards the anterior helps constrain the FGF/Wnt domain by locally reducing cell numbers.

In addition both systems use an opposite, antagonistic gradient to spatially constrain the growth zone (Fig. 1). In case of plant roots, the auxin antagonizing cytokinin gradient is centred at the elongation zone and induces elongation and differentiation (Dello Iorio et al., 2008). In vertebrates, a retinoic acid (RA) gradient emanating from the segmented mesoderm induces cellular differentiation (Aulehla and Pourquié, 2010; Naiche et al., 2011; Kumar and Duester, 2014). Both in the case of auxin and cytokinin (Dello Iorio et al., 2008; Di Mambro et al., 2017) as well as in the case of FGF/Wnt and RA (Diez del Corral et al., 2003; Cunningham et al., 2015a, 2015b) the antagonism consists of a mutual repression between the opposing gradients. Such antagonism is critical to sharply and robustly delineate developmental boundaries (see e.g. (Manu et al., 2009; Sokolowski et al., 2012)), and appears a regular evolutionary invention deployed in many patterning systems. Finally, both in the vertebrate and plant root system the levels and location of production of antagonistic growth repressing signals is controlled via the growth inducing gradients. In plant roots, in addition to antagonizing cytokinin inside the high auxin domain, auxin also induces cytokinin signalling outside of this domain (Moubayidin et al., 2013), although how come it does this only outside the main auxin domain remains to be elucidated. On a similar note, Wnt appears involved in inducing RA synthesis and signalling (Olivera-Martinez and Storey, 2007). Here, it appears that a delayed induction of RA beyond the main domain of FGF and Wnt signalling is achieved due to the fact that the Wnt gradient extends somewhat further than the FGF gradient, and Wnt induces RA signalling only once FGF levels have dropped sufficiently (Fig. 1). By using this regulatory architecture, increases in growth domain will cause increased antagonistic signalling, thus

pushing back the growth domain, while a decrease in growth region will be restored through a reduction in antagonizing signals.

3. Axial segmentation: vertebrate somitogenesis and lateral root priming

In parallel with growing and thereby extending their body axis, both vertebrates and plants subdivide their axis into a repetitive series of segments. In the case of vertebrates, the differentiating mesoderm becomes subdivided into somites that will give rise to the future vertebrae, ribs and skeletal muscles (Oates et al., 2012). Since segmentation is coupled to tip driven polar growth, somitogenesis occurs in a spatiotemporally sequential manner, starting with the patterning of the anterior somites and laying down more and more posterior somites as time progresses (Aulehla and Pourquié, 2010; Oates et al., 2012). On a similar note, as they grow plant roots sequentially prepattern groups of cells competent at future lateral root formation (De Smet et al., 2007; Moreno-Risueno et al., 2010; Xuan et al., 2015, 2016).

Again, similar patterning mechanisms appear to be at play in both plant roots and vertebrates, although similarities may not always extend down to the level of the molecular mechanism (Fig. 3). In vertebrate segmentation, oscillations in components of the FGF, Wnt and Delta-Notch signalling pathway occur in the posterior presomitic mesoderm (Dequeant et al., 2006; Aulehla and Pourquié, 2010). As cells move out of this zone and FGF and Wnt levels drop oscillations first slow down and then cease, transforming into a temporally stable, spatially repetitive gene expression pattern that defines the boundaries and polarities of the future somites (Aulehla and Herrmann, 2004; Aulehla et al., 2008; Naiche et al., 2011) (Fig. 3). On a very similar note, oscillations in auxin (response) as well as gene expression occur in the auxin dominated meristem (De Smet et al., 2007; Moreno-Risueno et al., 2010; Xuan et al., 2015, 2016). As growth causes cells to leave the meristem, those cells that experienced peaks of elevated auxin (signalling) become prepatterned into future lateral root forming sites

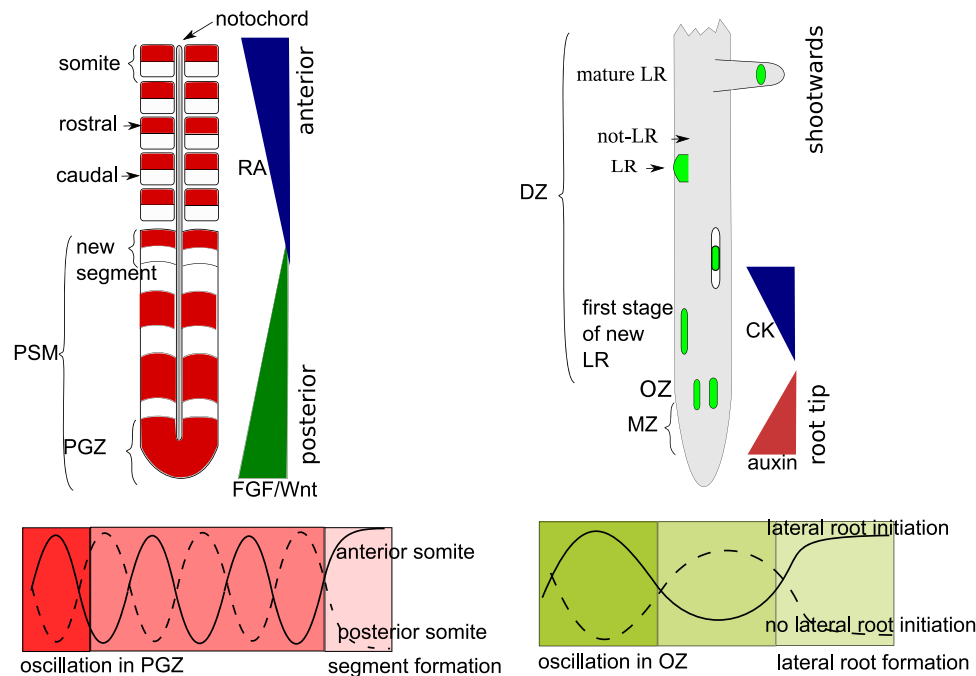


Fig. 3. Comparison of axial segmentation in vertebrates and plant roots. Left: oscillations in the vertebrate presomitic mesoderm prepattern somite formation. PGZ: posterior growth zone, PSM: presomitic mesoderm. Right: oscillations in the root tip oscillation zone prepattern sites competent for future lateral root formation. OZ: oscillation zone, MZ: meristematic zone, DZ: differentiation zone, LR: lateral root.

(De Smet et al., 2007; Moreno-Risueno et al., 2010; Xuan et al., 2015, 2016) (Fig. 3). In both cases, the tip localized gradients support temporal oscillatory dynamics, while the oppositely organized gradients promote the transition into spatially repetitive patterns.

In vertebrates, the oscillatory dynamics are organized by a complex gene regulatory network, comprising interconnected modules of the FGF, Wnt and Delta-Notch signalling pathways (Dequeant et al., 2006). Oscillations arise from the presence of delayed negative feedbacks, present in each of these three modules (Goldbeter and Pourquie, 2008). As a consequence, oscillatory behaviour arises in a cell-autonomous manner, and indeed individual, separated presomitic mesoderm cells have been shown to keep oscillating (Maroto et al., 2005), albeit at more and more diverging phases. Tissue level coherence of the oscillatory dynamics arises both from Delta-Notch signalling enhancing synchrony between nearby cells (Jiang et al., 2000; Horikawa et al., 2006) as well as FGF and Wnt gradients controlling oscillator period in a position dependent manner (Aulehla et al., 2008). The transition from temporal oscillations to spatial prepattern was originally thought to be controlled by the FGF/Wnt-RA antagonism Goldbeter et al. (2007), yet more recent studies question the relevance of RA signalling and point to FGF signalling alone controlling the onset of segment patterning (Fig. 3) (Aulehla and Herrmann, 2004; Aulehla et al., 2008; Naiche et al., 2011). While this patterning system is generally referred to as the clock-and-wavefront mechanism that was first introduced by Cooke and Zeeman (1976) the precise details through which oscillations transition into a temporally stable spatial prepatterns are still under debate (see e.g. for alternative models for segment boundary formation (Lauschke et al., 2013; Cotterell et al., 2015; Sonnen et al., 2018; Boareto et al., 2018; Simsek and Özbudak, 2018)).

Initially, the observation of oscillations in a large number of genes correlating with lateral root priming led to the suggestion of a similar, cell autonomous clock-like patterning mechanism being at work in plants (Moreno-Risueno et al., 2010). However, although modeling studies have suggested a few molecular networks theoretically capable of generating oscillations (Muraro et al., 2013; Mellor et al., 2016), for realistic model parameter settings these neither generated oscillation

periods consistent with those reported for priming nor were they supported by experimental data demonstrating oscillations in the proposed network components. Thus, while on a higher level the animal and plant mechanisms bear clear resemblances, lower level mechanistic details may in fact differ (Laskowski and Ten Tusscher, 2017). Indeed, recent work from our group proposes that in the plant root tip, oscillations arise from a synergism between root growth dynamics and root tip auxin transport (Van den Berg and Ten Tusscher, 2018). During root growth, divisions inside the growth zone give rise to clones of approximately synchronously growing sibling cells. At the same, stem cell divisions produce new cells below these existing cells, pushing the cells shootwards. As a consequence, sibling cells exit the growth zone at different time points in their growth cycle, leading to a periodic variation in the sizes with which cells start their subsequent elongation phase. Auxin transport in the root tip is dictated by a PIN mediated reflux loop which causes auxin to flow down through the vasculature, upward through the outer tissue layers, and back inward from outer tissues to vasculature at the end of the growth zone. This inward flux produces an auxin loading domain at the end of the meristem. The capacity to load auxin in this domain is larger for elongated cells, which have more passive auxin uptake due to their larger surface area. It is the combination of growth induced periodic variations in cell sizes with this size dependent auxin loading that generates oscillations in auxin levels at the end of the meristem. Thus, in plants the oscillations arise on the tissue level, rather than cell-autonomously.

4. Vertebrate limb and digit patterning and plant phyllotaxis

Besides the belowground rootsystem, also a lot of developmental patterning occurs in plant shoots. An intensively studied phenomenon is phyllotaxis, the spatial placement of shoot organs along the stem. While the spiral, Fibonacci-series mimicking, placement is particularly famous, other spatial patterns occur for different developmental stages. In the model plant species *Arabidopsis thaliana* the cotyledons (the two embryonic leaves present in a dicot species), as well as the first

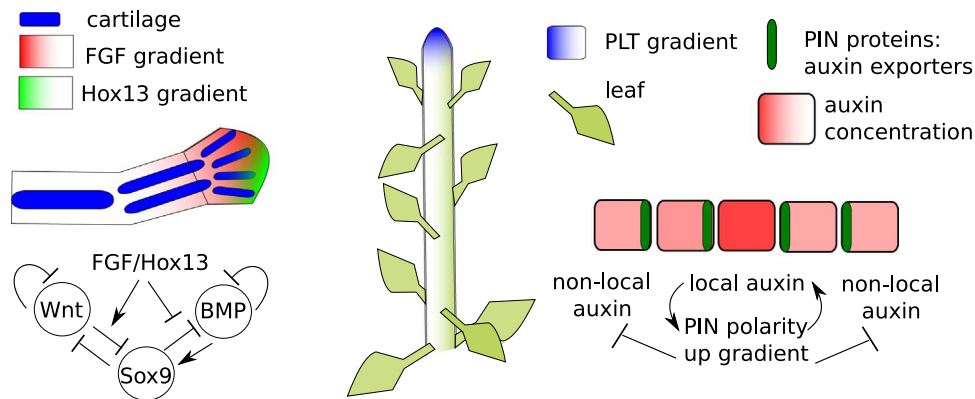


Fig. 4. Comparison of limb patterning in vertebrates and plant shoot phyllotaxis. Left: Turing wavelength in vertebrate limb and digit patterning is modulated by FGF and Hox gradients. Patterning arises from the interplay between Wnt, BMP and Sox9 signals. Right: Wavelength of phyllotaxis Turing pattern depends on PLT expression. Formation of auxin maxima prepattern sites for future leaf primordia formation arises from polarisation of auxin exporting PIN proteins towards neighboring cells with the highest auxin concentration (“up the gradient”).

subsequent leaf pair are placed following a so-called decussate patterns, with 2 leaves formed simultaneously and opposite one another and the next leaf pair oriented perpendicular to the previous one. Only after this the golden angle, spiral pattern is followed (Prasad et al., 2011) (Fig. 4). Similarly, besides axial patterning, extensive developmental patterning occurs in vertebrate limbs. Here, as the limb bud grows out and extends a developmental transition from a single thick bone in the upper limb, two more slender bones in the lower limb, and three thin bones in the distal limb forming the hand or foot are laid down (Zhu et al., 2010) (Fig. 4). Within the hand or foot, subsequently digit patterning takes place (Sheth et al., 2012; Raspopovic et al., 2014).

In vertebrates, patterning of limb bones has been proposed to arise from a Turing type patterning mechanism over 50 years ago (Newman and Frish, 1979). In the last decade experimental data demonstrating that TFG- α , Activin and BMP act as activators, whereas Notch, FGF, Noggin and CHL2 signals play an inhibitory role have confirmed this hypothesis (Zhu et al., 2010). The transition from one to two to three bones when going from upper limb to lower limb to the autopod (foot or hand region) arises from a gradual change in the Turing pattern wavelength, caused by the gradual decline of the FGF gradient emanating from the distal end of the limb (Zhu et al., 2010) (Fig. 4). The patterning mechanism has been elucidated in most detail for digit patterning, where the Turing wavelength has been shown to be modulated through an interaction with the Hox genes to give individual digits their unique identity (Sheth et al., 2012; Raspopovic et al., 2014) (Fig. 4). Whether or not plant phyllotaxis can be called a Turing type patterning mechanism is a matter of taste, but molecular details are certainly different compared to the limb and digit patterning mechanisms. In phyllotaxis, maxima of auxin are generated in a self-organized manner due to the polarisation of auxin exporting membrane proteins, called PINs, towards neighboring cells with highest auxin levels (Reinhardt et al., 2000, 2003; Vernoux et al., 2000), through an as of yet incompletely identified mechanism (but for suggestions see e.g. (Heisler et al., 2010; Bhatia et al., 2016)). Thus, high auxin levels locally enhance themselves while simultaneously at a distance depleting auxin (Fig. 4). The mechanism thus resembles an activator-substrate depletion type Turing mechanism (Gierer and Meinhardt, 1972), but with the additional property of controlled, directional transport of the activator (Smith et al., 2006; Jönsson et al., 2006). Indeed, in the case of phyllotaxis, pattern wavelength was shown to depend on the relative strength of diffusion and PIN polarisation (Jönsson et al., 2006). The previously discussed auxin antagonist cytokinin helps enhance and stabilize this pattern (Besnard et al., 2014). In addition the PLETHORA genes, by feeding back on auxin dynamics, influence the transition from decussate to spiral pattern (Prasad et al., 2011; Pinon et al., 2013) through influencing patterning wavelength. Consistent with the latter, an earlier modeling study

identified the importance of high auxin production levels and strong auxin dependent PIN polarisation for spiral type phyllotaxis patterns (Smith et al., 2006)

5. Integrating local and systemic signalling in coordinating limbs and diversifying roots

In animals, symmetry and scaling of limbs with overall body size is critical for optimal mobility, yet how exactly this is achieved is currently incompletely understood. Experimental data show that limb growth is controlled both by local, limb-produced signals such as Hedgehog (Hh), FGF, BMP and Wnt (Laufer et al., 1994; Pizette and Niswander, 1999; ten Berge et al., 2008; Capdevila and Izpisua Belmonte, 2001), as well as systemic signalling for example through Insulin Like Growth Factor (IGF) (for a review see (Agrogiannis et al., 2014)). Somehow, through the interplay of this local and systemic signals (as well as possibly other not yet discovered signals) scaling and symmetry of limbs is obtained. This mechanism was recently studied in a setup, in which a drop in chondrocyte density was artificially induced in one but not the other hind limb of a mouse embryo. It was shown that the density drop resulted in an increase in local cell proliferation in the injured limb. Additionally, the insulted limb resulted in a reduction of placental IGF, which subsequently causes a reduced growth of the entire embryo including the non-injured limb. As a consequence of the enhanced proliferation of the injured limb and the reduced growth of the rest of the body, the organ/organism scaling as well as the left/right organ ratios is to a large extent restored (Roselló-Díez et al., 2018). Exactly how these processes ensure precise symmetry of the two limbs, as well as the nature of the signals inducing local proliferation and placental IGF reduction remains to be uncovered. Still, the study clearly illustrates the major importance of not only having both local and global signals, but also integrating these signals. While the rest of the body reduces its growth in response to lowered placental IGF concentrations, the injured limb that is perceiving these same lowered IGF levels instead increased its growth due to its concurrent perception of a lowered local cell density.

Obviously, in sessile plants, selective pressures are highly different, and rather than symmetry and scaling, flexible adaptation to varying, spatially heterogeneous environmental conditions is of critical importance. Thus, after the prepattern for sites competent for forming lateral roots has been laid down, the probability with which these sites actually develop into lateral roots as well as their subsequent growth rate need to be flexibly adjusted to environmental conditions. Importantly, this adaptation should occur in response to both global conditions (average availability of a nutrient in the soil and the amount currently present in the plant which together determine how much it is in need) and local conditions (availability of the nutrient in the vicinity of an individual

lateral root). A famous experimental setup illustrating this principle is the split root experiment, where it is demonstrated that proliferation of roots on one side of the root system where nitrate is present is promoted by a lack of nitrate on the opposite side of the root system (see e.g. (Mounier et al., 2014)), with level of asymmetry scaling with nitrate availability asymmetry (Shemesh et al., 2010). While the outcome is opposite to the animal limb case, i.e. asymmetry is promoted, the underlying regulatory architecture is highly similar. Roots experiencing a nitrate lack signal this to the plant shoot (Tabata et al., 2014), which subsequently sends a systemic signal down to the entire root system to promote nitrate uptake and lateral root outgrowth (Ohkubo et al., 2017; Remans et al., 2006). This signal increases for lower intraplant nitrate levels. A response is only induced in locations perceiving this systemic lack of nitrate signal while at the same time perceiving a local nitrate availability (Ohkubo et al., 2017). Thus, again, integrated local and systemic signalling are key.

6. Discussion

In this review I discussed the striking parallels in signalling and patterning processes that exist when comparing animal and plant development. It was shown that extension of the vertebrate body axis as well as growth of plant roots are both organized from a polarly localized growth region, the presomatic mesoderm or root meristem. Additionally, segmenting these extending axes, either into vertebrate somites or sites competent for future lateral root formation, is in both cases achieved by combining this polarised growth process with a temporal oscillation. Finally, parallels were found between vertebrate limb patterning and plant phyllotaxis, as well as the integration of global and local signalling to fine tune developmental processes. In all cases, many similarities in the underlying patterning mechanism were shown to exist.

In addition to these similarities there are of course also many differences between animal and plant developmental patterning, even in the processes discussed in this review. While in plants new lateral roots continue to be formed throughout the life of a plant, in vertebrates axial extension comes to a halt when the last somite has been laid down. As a consequence additional mechanisms controlling the halting of the process are required for vertebrate segmentation (Young et al., 2009; Tenin et al., 2010).

Furthermore, in vertebrates, somites have to be patterned in a highly robust, scalable, reproducible and symmetric manner, essential for normal mobility as can be understood from the disabling nature of developmental defects such as scoliosis. As a consequence, in vertebrates the oscillatory mechanism pre-patterning somites needs to incorporate auxiliary mechanisms for the synchronisation of intracellular oscillations between nearby cells (Jiang et al., 2000; Horikawa et al., 2006), buffering and catch-up mechanisms preventing left-right differences (Kawakami et al., 2005; Vermot et al., 2005; Roselló-Díez et al., 2018), as well as thus far incompletely understood mechanisms for scaling somite size with growth zone size (Lauschke et al., 2013; Sonnen et al., 2018; Boareto et al., 2018; Simsek and Özbudak, 2018). In contrast, due to their sessile nature plants need to be able to flexibly adjust to temporally and spatially varying environmental conditions. Thus, the oscillatory mechanism laying down sites competent for lateral root formation lays down only a prepattern, and the precise placement, actual initiation, subsequent development and outgrowth of individual lateral roots from these sites is strongly dependent on environmental conditions (see e.g. (Remans et al., 2006; Zamioudis et al., 2013; Kircher and Schopfer., 2016)). These different selective pressures for vertebrates and plants may have caused that while the general principle of patterning a spatially repetitive pattern through temporal oscillations from a growth zone is shared, the mechanism underlying oscillations is different.

Finally, while vertebrates use an activator-inhibitor type Turing patterning in limbs and digits in which undirected movement of

signalling molecules plays an important role (Zhu et al., 2010; Sheth et al., 2012; Raspopovic et al., 2014), in plants feedback regulation of directed, polarised auxin transport is applied to generate an activator-depletion type of Turing patterning for phyllotaxis (Reinhardt et al., 2000, 2003; Vernoux et al., 2000). In this context, the presence of cell walls and plasmodesmata (channels connecting the cytoplasm of neighboring cells) in plants but not (or only in specialised tissues) in animals is likely to put different constraints on direct cell-cell as well as tissue level signalling processes. Again, one may speculate that such differences led to the different types of molecular underpinnings for limb and digit patterning in vertebrates versus phyllotaxis in plants.

Comparing developmental processes, even or rather particularly across the divide of different kingdoms serves several purposes. The developmental patterning processes discussed in the current paper are all extremely complex, involving large numbers of molecular players and interactions, as well as multiple relevant spatial and temporal scales. For example, in case of the patterning of the plant root tip, the antagonism between auxin and cytokinin is highly complex, with interactions on metabolic, transport, signalling and gene expression processes (Miyawaki et al., 2004; Nordström et al., 2004; Dello Iorio, Nov 28 et al., 2008; Jung and McCouch, 2013; Di Mambro et al., 2017). The essence of the patterning mechanism is further obscured by the large number of other hormones, such as gibberellin, ethylene, abscisic acid, and brassinosteroids that modulate auxin, cytokinin and their interactions (Jung and McCouch, 2013). As an additional complexity, possibly depending on the developmental and tissue context, for single interaction links in this complex network, e.g. the impact of auxin on cytokinin biosynthesis, both positive and negative interactions are known (Miyawaki et al., 2004; Nordström et al., 2004). As a consequence, simply integrating all known relevant details into a computational model, even though perfectly reflecting the systems biology paradigm, may not always lead to the hoped for understanding of the patterning mechanisms at play.

Comparison of similar developmental processes in distantly related organisms, by inducing a sort of “looking through your eyelashes” perspective, can be a helpful tool to distill the essence of the developmental process. By comparing root growth to vertebrate axial extension, focus automatically shifts to the essence of the system, the need to robustly maintain yet also demarcate a growth zone. As a consequence, the auxin-cytokinin antagonism and the self-organizing properties of this antagonism become the focal point of attention. Comparison thus aids in the identification of essential players and interactions, as well as the requirements and constraints the patterning mechanism has to fulfill.

Additionally, comparison across kingdoms helps identify and extend the suite of general design principles that evolution repeatedly applies for similar patterning “problems” (Mentink and Tsiantis, 2016). In this review, we identified antagonistic gradient pairs as a generic mechanism to pattern polarised growth, and oscillations combined with polarised growth as a general mechanism for axial segmentation. Additionally we found wavelength-modulated Turing patterning as a design principle for other repetitive patterning processes, and finally combining systemic and local signalling as a general means for fine tuning and coordinating patterning processes. Recovering such design principles even in an across kingdom comparison further underlines the fact that evolution of developmental processes is far from random but instead heavily biased by a limited number of mechanism existing for each particular patterning demand. The presence of striking resemblances between complex animal and plant developmental patterning mechanisms thus teaches us that in trying to understand our own system of study looking across the borders of kingdoms can provide valuable hints and insights.

Finally, due to the presence of cell walls in plants but not animals, animal and plant development fundamentally differ in terms of mechanics and morphogenesis. While in animals major steps of body plant formation involve extensive reordering of cells, plants need to

reprogram locally present cells to form new stem cell niches capable of growing a new organ. The fact that despite these major differences so many parallel developmental patterning mechanisms can be identified underlines the importance of signalling processes in driving development.

Acknowledgements

This work was supported by the Netherlands Scientific Organization (NWO) through grant number 864.14.003 to K.t.T.

References

- Agrogiannis, G.D., Sifakis, S., Patsouris, E.S., Konstantinidou, A.E., 2014. Insulin-like growth factors in embryonic and fetal growth and skeletal development. *Mol. Med. Rep.* 10 (2), 579–584.
- Aulehla, A., Herrmann, B.G., 2004. Segmentation in vertebrates: clock and gradient finally joined. *Genes Dev.* 18, 2060–2067.
- Aulehla, A., Pourquie, O., 2010. Signaling gradients during paraxial mesoderm development. *Cold Spring Harb. Perspect. Biol.* 2 (2), a000869.
- Aulehla, A., Wiegand, W., Baubet, V., Wahl, M.B., Deng, C., Taketo, M., Lewandoski, M., Pourquie, O., 2008. A beta-catenin gradient links the clock and wavefront systems in mouse embryo segmentation. *Nat. Cell Biol.* 10, 186–193.
- Bénazéraf, B.I., François, P., Baker, R.E., Denans, N., Little, C.D., Pourquie, O., 2010. A random cell motility gradient downstream of FGF controls elongation of an amniote embryo. *Nature* 466 (7303), 248–252.
- Benkova, E., Michniewicz, M., Sauer, M., Teichmann, T., Seifertova, D., Jurgens, G., Friml, J., 2003. Local, efflux-dependent auxin gradients as a common module for plant organ formation. *Cell* 115 (5), 591–602.
- Besnard, F., Refahi, Y., Morin, V., Marteau, B., Brunod, G., Chambrier, P., Rozier, F., Mirabet, V., Legrand, J., Lainé, S., Thévenon, E., Farcot, E., Cellier, C., Das, P., Bishopp, A., Dumas, R., Parcy, F., Helariutta, Y., Boudaoud, A., Godin, C., Traas, J., Guédon, Y., Vernoux, T., 2014. Cytokinin signalling inhibitory fields provide robustness to phyllotaxis. *Nature* 505 (7483), 417–421.
- Bhatia, N., Bozorg, B., Larsson, A., Ohno, C.I., Jönsson, H., Heisler, M.G., 2016. Auxin Acts through MONOPTEROS to regulate plant cell polarity and pattern phyllotaxis. *Curr. Biol.* 26 (23), 3202–3208.
- Blilou, I., Xu, J., Wildwater, M., Willemsen, V., Paponov, I., Friml, J., Heidstra, R., Aida, M., Palme, K., Scheres, B., 2005. The pin auxin efflux facilitator network controls growth and patterning in Arabidopsis roots. *Nature* 433 (7021), 39–44.
- Boareto, M., Tomka, T., Iber, D., 2018. Positional information encoded in the dynamic differences between neighbouring oscillators during vertebrate segmentation. *bioRxiv*. <http://dx.doi.org/10.1101/286328>.
- Capdevila, J., Izpisua Belmonte, J.C., 2001. Patterning mechanisms controlling vertebrate limb development. *Annu. Rev. Cell Dev. Biol.* 17, 87–132.
- Ciruna, B., Rossant, J., 2001. FGF signaling regulates mesoderm cell fate specification and morphogenetic movement at the primitive streak. *Dev. Cell* 1, 37–49.
- Cooke, J., Zeeman, E.C., 1976. A clock and wavefront model for control of the number of repeated structures during animal morphogenesis. *J. Theor. Biol.* 58 (2), 455–476.
- Cotterell, J., Robert-Moreno, A., Sharpe, J., 2015. A local, Self-organizing reaction-diffusion model Can explain somit patterning in embryos. *Cell Syst.* 1 (4), 257–269.
- Cunningham, T.J., Kumar, S., Yamaguchi, T.P., Duester, G., 2015a. Wnt8a and Wnt3a cooperate in the axial stem cell niche to promote mammalian body axis extension. *Dev. Dyn.* 244, 797–807.
- Cunningham, T.J., Brade, T., Sandell, L.L., Lewandoski, M., Trainor, P.A., Colas, A., Mercola, M., Duester, G., 2015b. Retinoic acid activity in undifferentiated neural progenitors is sufficient to fulfill its role in restricting Fgf8 expression for somitogenesis. *PLoS One* 10, e0137894.
- De Smet, I., Tetsumura, T., De Rybel, B., Frei dit Frey, N., Laplace, L., Casimiro, I., Swarup, R., Naudts, M., Vanneste, S., Audenaert, D., Inzé, D., Bennett, M.J., Beeckman, T., 2007. Auxin-dependent regulation of lateral root positioning in the basal meristem of Arabidopsis. *Development* 134 (4), 681–690.
- Delfini, M.C.I., Dubrulle, J., Malapert, P., Chal, J., Pourquie, O., 2005. Control of the segmentation process by graded MAPK/ERK activation in the chick embryo. *Proc. Natl. Acad. Sci. USA* 102 (32), 11343–11348.
- Dello Ioio, R., Nakamura, K., Moubayidin, L., Perilli, S., Taniguchi, M., Morita, M.T., Aoyama, T., Costantino, P., Sabatini, S., 2008. A genetic framework for the control of cell division and differentiation in the root meristem. *Science* 322 (5906), 1380–1384.
- Dequeant, M.L., Glynn, E., Gaudenz, K., Wahl, M., Chen, J., Mushegian, A., Pourquie, O., 2006. A complex oscillating network of signaling genes underlies the mouse segmentation clock. *Science* 314, 1595–1598.
- Di Mambro, R., De Ruvo, M., Pacifici, E., Salvi, E., Sozzani, R., Benfey, P.N., Busch, W., Novak, O., Ljung, K., Di Paola, L., Marée, A.F.M., Costantino, P., Grieneisen, V.A., Sabatini, S., 2017. Auxin minimum triggers the developmental switch from cell division to cell differentiation in the Arabidopsis root. *Proc. Natl. Acad. Sci. USA* 114 (36), E7641–E7649.
- Diez del Corral, R., Olivera-Martinez, I., Goriely, A., Gale, E., Maden, M., Storey, K., 2003. Opposing FGF and retinoid pathways control ventral neural pattern, neuronal differentiation, and segmentation during body axis extension. *Neuron* 40 (1), 65–79.
- Du, Y., Scheres, B., 2017. PLETHORA transcription factors orchestrate de novo organ patterning during Arabidopsis lateral root outgrowth. *Proc. Natl. Acad. Sci. USA* 114 (44), 11709–11714.
- Du, Y., Scheres, B., 2018. Lateral root formation and the multiple roles of auxin. *J. Exp. Bot.* 69 (2), 155–167.
- Dubrulle, J., Pourquie, O., 2004. fgf8 mRNA decay establishes a gradient that couples axial elongation to patterning in the vertebrate embryo. *Nature* 427 (6973), 419–422.
- François, P., Hakim, V., Siggia, E.D., 2007. Deriving structure from evolution: metazoan segmentation. *Mol. Syst. Biol.* 3, 154.
- Fujimoto, K., Ishihara, S., Kaneko, K., 2008. Network evolution of body plans. *PLoS One* 3 (7), e2772.
- Gierer, A., Meinhardt, H., 1972. A theory of biological pattern formation. *Kybernetik* 12 (1), 30–39.
- Goldbeter, A., Pourquie, O., 2008. Modeling the segmentation clock as a network of coupled oscillations in the Notch, Wnt and FGF signaling pathways. *J. Theor. Biol.* 252 (3), 574–585.
- Goldbeter, A., Gonze, D., Pourquie, O., 2007. Sharp developmental thresholds defined through bistability by antagonistic gradients of retinoic acid and FGF signaling. *Dev. Dyn.* 236 (6), 1495–1508.
- Grieneisen, V.A., Xu, J., Marée, A.F., Hogeweg, P., Scheres, B., 2007. Auxin transport is sufficient to generate a maximum and gradient guiding root growth. *Nature* 449 (7165), 1008–1013.
- Heisler, M.G., Hamant, O., Krupinski, P., Uyttewaald, M., Ohno, C., Jönsson, H., Traas, J., Meyerowitz, E.M., 2010. Alignment between PIN1 polarity and microtubule orientation in the shoot apical meristem reveals a tight coupling between morphogenesis and auxin transport. *PLoS Biol.* 8 (10), e1000516.
- Horikawa, K., Ishimatsu, K., Yoshimoto, E., Kondo, S., Takeda, H., 2006. Noise-resistant and synchronized oscillation of the segmentation clock. *Nature* 441 (7094), 719–723.
- Ishikawa, H., Evans, M.L., 1995. Specialized zones of development in roots. *Plant Physiol.* 109, 725–727.
- Jiang, Y.J., Aerne, B.L., Smithers, L., Haddon, C., Ish-Horowitz, D., Lewis, J., 2000. Notch signalling and the synchronization of the somite segmentation clock. *Nature* 408 (6811), 475–479.
- Jönsson, H., Heisler, M.G., Shapiro, B.E., Meyerowitz, E.M., Mjolsness, E., 2006. An auxin-driven polarized transport model for phyllotaxis. *Proc. Natl. Acad. Sci. USA* 103 (5), 1633–1638.
- Jung, J.K., McCouch, S., 2013. Getting to the roots of it: genetic and hormonal control of root architecture. *Front. Plant Sci.* 4, 186.
- Kawakami, Y., Raya, A., Raya, R.M., Rodriguez-Esteban, C., Belmonte, J.C.I., 2005. Retinoic acid signalling links left-right asymmetric patterning and bilaterally symmetric somitogenesis in the zebrafish embryo. *Nature* 435, 165–171.
- Kircher, S., Schopfer, P., 2016. Priming and positioning of lateral roots in Arabidopsis. An approach for an integrating concept. *J. Exp. Bot.* 67 (5), 1411–1420.
- Kumar, S., Duester, G., 2014. Retinoic acid controls body axis extension by directly repressing Fgf8 transcription. *Development* 141 (15), 2972–2977.
- Laskowski, M., Ten Tusscher, K.H., 2017. Periodic lateral root priming: what makes it tick? *Plant Cell* 29 (3), 432–444.
- Lauffer, E., Nelson, C.E., Johnson, R.L., Morgan, B.A., Tabin, C., 1994. Sonic hedgehog and Fgf-4 act through a signaling cascade and feedback loop to integrate growth and patterning of the developing limb bud. *Cell* 79 (6), 993–1003.
- Lauschke, V.M., Tsiarris, C.D., François, P., Aulehla, A., 2013. Scaling of embryonic patterning based on phase-gradient encoding. *Nature* 493 (7430).
- Mähönen, A.P., Ten Tusscher, K., Siligato, R., Smetana, O., Díaz-Triviño, S., Salojärvi, J., Wachsman, G., Prasad, K., Heidstra, R., Scheres, B., 2014. PLETHORA gradient formation mechanism separates auxin responses. *Nature* 515 (7525), 125–129.
- Manu, S., Surkova, S., Spirov, A.V., Gursky, V.V., Janssens, H., Kim, A.R., Radulescu, O., Vanario-Alonso, C.E., Sharp, D.H., Samsonova, M., Reinitz, J., 2009. Canalization of gene expression in the Drosophila blastoderm by gap gene cross regulation. *PLoS Biol.* 7 (3), e1000049.
- Mara, A., Schroeder, J., Chalouni, C., Holley, S.A., 2007. Priming, initiation and synchronization of the segmentation clock by deltaD and deltaC. *Nat. Cell Biol.* 9 (5), 523–530.
- Maroto, M., Dale, J.K., Dequeant, M.L., Petit, A.C., Pourquie, O., 2005. Synchronised cycling gene oscillations in presomitic mesoderm cells require cell-cell contact. *Int. J. Dev. Biol.* 49, 309–315.
- Mellor, N., Bennett, M.J., King, J.R., 2016. GH3-mediated auxin conjugation can result in either transient or oscillatory transcriptional auxin responses. *Bull. Math. Biol.* 78 (2), 210–234.
- Mentink, R.A., Tsiantis, M., 2015. From limbs to leaves: common themes in evolutionary diversification of organ form. *Front. Genet.* 6, 284.
- Meyerowitz, E.M., 2002. Plants compared to animals: the broadest comparative study of development. *Science* 295 (5559), 1482–1485.
- Mironova, V.V., Omelyanchuk, N.A., Novoselova, E.S., Doroshkov, A.V., Kazantsev, F.V., Kochetov, A.V., Kolchanov, N.A., Mjolsness, E., Likhoshvai, V.A., 2012. Combined in silico/in vivo analysis of mechanisms providing for root apical meristem self-organization and maintenance. *Ann. Bot.* 110 (2), 349–360.
- Miyawaki, K., et al., 2004. Expression of cytokinin biosynthetic isopentenyltransferase genes in Arabidopsis: tissue specificity and regulation by auxin, cytokinin, and nitrate. *Plant J.* 37, 128–138.
- Moreno-Risueno, M.A., Van Norman, J.M., Moreno, A., Zhang, J., Ahnert, S.E., Benfey, P.N., 2010. Oscillating gene expression determines competence for periodic Arabidopsis root branching. *Science* 329 (5997), 1306–1311.
- Moubayidin, L., Di Mambro, R., Sozzani, R., Pacifici, E., Salvi, E., Terpstra, I., Bao, D., van Dijken, A., Dello Ioio, R., Perilli, S., Ljung, K., Benfey, P.N., Heidstra, R., Costantino, P., Sabatini, S., 2013. Spatial coordination between stem cell activity and cell differentiation in the root meristem. *Plant Cell.* 25 (11), 4469–4478.

- Mounier, E., Pervent, M., Ljung, K., Gojon, A., Nacry, P., 2014. Auxin-mediated nitrate signalling by NRT1.1 participates in the adaptive response of Arabidopsis root architecture to the spatial heterogeneity of nitrate availability. *Plant Cell Environ.* 37 (1), 162–174.
- Muraro, D., Byrne, H., King, J., Bennett, M., 2013. The role of auxin and cytokinin signalling in specifying the root architecture of Arabidopsis thaliana. *J. Theor. Biol.* 317, 71–86.
- Naiche, L.A.I., Holder, N., Lewandoski, M., 2011. FGF4 and FGF8 comprise the wavefront activity that controls somitogenesis. *Proc. Natl. Acad. Sci. USA* 108 (10), 4018–4023.
- Newman, S.A., Frish, H.L., 1979. Dynamics of skeletal pattern formation in developing chick limb. *Science* 205 (4407), 662–668.
- Nordström, A., et al., 2004. Auxin regulation of cytokinin biosynthesis in Arabidopsis thaliana: a factor of potential importance for auxin–cytokinin-regulated development. *PNAS* 101, 8039–8044.
- Oates, A.C., Morelli, L.G., Ares, S., 2012. Patterning embryos with oscillations: structure, function and dynamics of the vertebrate segmentation clock. *Development* 139, 625–639.
- Ohkubo, Y., Tanaka, M., Tabata, R., Ogawa-Ohnishi, M., Matsubayashi, Y., 2017. Shoot-to-root mobile polypeptides involved in systemic regulation of nitrogen acquisition. *Nat. Plants* 3, 17029.
- Olivera-Martinez, I., Storey, K.G., 2007. Wnt signals provide a timing mechanism for the FGF-retinoid differentiation switch during vertebrate body axis extension. *Development* 134, 2125–2135.
- Pinon, V., Prasad, K., Grigg, S.P., Sanchez-Perez, G.F., Scheres, B., 2013. Local auxin biosynthesis regulation by PLETHORA transcription factors controls phyllotaxis in Arabidopsis. *Proc. Natl. Acad. Sci. USA* 110 (3), 1107–1112.
- Pizette, S., Niswander, L., 1999. BMPs negatively regulate structure and function of the limb apical ectodermal ridge. *Development* 126 (5), 883–894.
- Prasad, K., Grigg, S.P., Barkoulas, M., Yadav, R.K., Sanchez-Perez, G.F., Pinon, V., Blilou, I., Hofhuis, H., Dhonukshe, P., Galinha, C., Mähönen, A.P., Muller, W.H., Raman, S., Verkleij, A.J., Snel, B., Reddy, G.V., Tsiantis, M., Scheres, B., 2011. Arabidopsis PLETHORA transcription factors control phyllotaxis. *Curr. Biol.* 21 (13), 1123–1128.
- Raspopovic, J., Marcon, L., Russo, L., Sharpe, J., 2014. Modeling digits. digit patterning is controlled by a Bmp-Sox9-Wnt Turing network modulated by morphogen gradients. *Science* 345 (6196), 566–570, (Aug 1).
- Reinhardt, D., Mandel, T., Kuhlemeier, C., 2000. Auxin regulates the initiation and radial position of plant lateral organs. *Plant Cell*. 12 (4), 507–518.
- Reinhardt, D., Pesce, E.R., Steiger, P., Mandel, T., Baltensperger, K., Bennett, M., Traas, J., Friml, J., Kuhlemeier, C., 2003. Regulation of phyllotaxis by polar auxin transport. *Nature* 426 (6964), 255–260.
- Remans, T., Nacry, P., Pervent, M., Girin, T., Tillard, P., Lepetit, M., Gojon, A., 2006. A central role for the nitrate transporter NRT2.1 in the integrated morphological and physiological responses of the root system to nitrogen limitation in Arabidopsis. *Plant Physiol.* 140 (3), 909–921.
- Roselló-Díez, A., Madisen, L., Bastide, S., Zeng, H., Joyner, A.L., 2018. Cell-nonautonomous local and systemic responses to cell arrest enable long-bone catch-up growth in developing mice. *PLoS Biol.* 16 (6), e2005086.
- Sabatini, S., Scheres, B., 1999. An auxin-dependent distal organizer of pattern and polarity in the Arabidopsis root. *Cell* 99 (5), 463–472.
- Salazar-Ciudad, I., Newman, S.A., Solé, R.V., 2001a. Phenotypic and dynamical transitions in model genetic networks. I. Emergence of patterns and genotype-phenotype relationships. *Evol. Dev.* 3 (2), 84–94.
- Salazar-Ciudad, I., Solé, R.V., Newman, S.A., 2001b. Phenotypic and dynamical transitions in model genetic networks. II. application to the evolution of segmentation mechanisms. *Evol. Dev.* 3 (2), 95–103.
- Santuari, L., Sanchez-Perez, G.F., Luijten, M., Rutjens, B., Terpstra, I., Berke, L., Gorte, M., Prasad, K., Bao, D., Timmermans-Hereijgers, J.L., Maeo, K., Nakamura, K., Shimotohno, A., Pencik, A., Novak, O., Ljung, K., van Heesch, S., de Bruijn, E., Cuppen, E., Willemsen, V., Mähönen, A.P., Lukowitz, W., Snel, B., de Ridder, D., Scheres, B., Heidstra, R., 2016. The PLETHORA gene regulatory network guides growth and cell differentiation in Arabidopsis roots. *Plant Cell*. 28 (12), 2937–2951.
- Shemesh, H., Arbib, A., Gersani, M., Ovadia, O., Novoplansky, A., 2010. The effects of nutrient dynamics on root patch choice. *Plos One* 5 (5), e10824.
- Sheth, R., Marcon, L., Bastida, M.F., Junco, M., Quintana, L., Dahn, R., Kmita, M., Sharpe, J., Ros, M.A., 2012. Hox genes regulate digit patterning by controlling the wavelength of a Turing-type mechanism. *Science* 338 (6113), 1476–1480.
- Simsek, M.F., Özbudak, E.M., 2018. Spatial fold change of FGF signaling encodes positional information for segmental determination in zebrafish. *Cell Rep.* 24 (1), 66–78, (e8).
- Smith, R.S., Guyomarc'h, S., Mandel, T., Reinhardt, D., Kuhlemeier, C., Prusinkiewicz, P., 2006. A plausible model of phyllotaxis. *Proc. Natl. Acad. Sci. USA* 103 (5), 1301–1306.
- Sokolowski, T.R., Erdmann, T., ten Wolde, P.R., 2012. Mutual repression enhances the steepness and precision of gene expression boundaries. *PLoS Comput. Biol.* 8 (8), e1002654.
- Sonnen, K.F., Lauschke, V.M., Uraji, J., Falk, H.J., Petersen, Y., Funk, M.C., Beaupeux, M., François, P., Merten, C.A., Aulehla, A., 2018. Modulation of Phase shift between Wnt and notch signaling oscillations controls mesoderm segmentation. *Cell* 172 (5), 1079–1090.
- Tabata, R., Sumida, K., Yoshii, T., Ohyama, K., Shinohara, H., Matsubayashi, Y., 2014. Perception of root-derived peptides by shoot LRR-RKs mediates systemic N-demand signaling. *Science* 346 (6207), 343–346.
- ten Berge, D., Bruggmann, S.A., Helms, J.A., Nusse, R., 2008. Wnt and FGF signals interact to coordinate growth with cell fate specification during limb development. *Development* 135 (19), 3247–3257.
- Ten Tusscher, K.H., Hogeweg, P., 2011. Evolution of networks for body plan patterning: interplay of modularity, robustness and evolvability. *PLoS Comput. Biol.* 7 (10), e1002208.
- Tenin, G., Wright, D., Ferjentsik, Z., Bone, R., McGrew, M.J., Maroto, M., 2010. The chick somitogenesis oscillator is arrested before all paraxial mesoderm is segmented into somites. *BMC Dev. Biol.* 10, 24.
- Ullrich, C.I., Aloni, R., 2000. Vascularization is a general requirement for growth of plant and animal tumours. *J. Exp. Bot.* 51 (353), 1951–1960.
- Van den Berg T., Ten Tusscher K.H., 2018. Lateral root priming synergistically arises from root growth and auxin transport dynamics. (<https://doi.org/10.1101/361709>).
- Verbelen, J.P., De Cnodder, T., Le, J., Vissenberg, K., František Baluška, F., 2006. The root apex of Arabidopsis thaliana consists of four distinct zones of growth activities; meristematic zone, transition zone, fast elongation zone and growth terminating zone. *Plant Signal. Behav.* 1 (6), 296–304.
- Vermot, J., Llamas, J.G., Fraulob, V., Niederreither, K., Chambon, P., Dolle, P., 2005. Retinoic acid controls the bilateral symmetry of somite formation in the mouse embryo. *Science* 308, 563–566.
- Vernoux, T., Kronenberger, J., Grandjean, O., Lauf, P., Traas, J., 2000. PIN-formed 1 regulates cell fate at the periphery of the shoot apical meristem. *Development* 127 (23), 5157–5165.
- Wolpert, L., 1969. Positional information and the spatial pattern of cellular differentiation. *J. Theor. Biol.* 25 (1), 1–47.
- Xu, J., Hofhuis, H., Heidstra, R., Sauer, M., Friml, J., Scheres, B., 2006. A molecular framework for plant regeneration. *Science* 311 (5759), 385–388, (Jan 20).
- Xuan, W., Audenaert, D., Parizot, B., Möller, B.K., Njo, M.F., De Rybel, B., De Rop, G., Van Isterdael, G., Mähönen, A.P., Vanneste, S., Beeckman, T., 2015. root Cap-derived auxin pre-patterns the Longitudinal axis of the Arabidopsis root. *Curr. Biol.* 25 (10), 1381–1388.
- Xuan, W., Band, L.R., Kumpf, R.P., Van Damme, D., Parizot, B., De Rop, G., Opendacker, D., Möller, B.K., Skorzinski, N., Njo, M.F., De Rybel, B., Audenaert, D., Nowack, M.K., Vanneste, S., Beeckman, T., 2016. Cyclic programmed cell death stimulates hormone signaling and root development in Arabidopsis. *Science* 351 (6271), 384–387.
- Young, T., Rowland, J.E., van de Ven, C., Bialecka, M., Novoa, A., Carapuco, M., van Nes, J., de Graaff, W., Duluc, I., Freund, J.-N., Beck, F., Mallo, M., Deschamps, J., 2009. Cdx and hox genes differentially regulate posterior axial growth in mammalian embryos. *Dev. Cell*. 17 (4), 516–526.
- Zamioudis, C., Mastranesti, P., Dhonukshe, P., Blilou, I., Pieterse, C.M., 2013. Unraveling root developmental programs initiated by beneficial Pseudomonas spp. bacteria. *Plant Physiol.* 162 (1), 304–318.
- Zhu, J., Zhang, Y.T., Alber, M.S., Newman, S.A., 2010. Bare bones pattern formation: a core regulatory network in varying geometries reproduces major features of vertebrate limb development and evolution. *PLoS One* 5 (5), e10892.