The physics of development 100 years after D'Arcy Thompson's "On Growth and Form"

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By applying methods and principles from the physical sciences to biological problems, D'Arcy Thompson's *On Growth and Form* demonstrated how mathematical reasoning reveals elegant, simple explanations for seemingly complex processes. This has had a profound influence on subsequent generations of developmental biologists. We discuss how this influence can be traced through twentieth century morphologists, embryologists and theoreticians to current research that explores the molecular and cellular mechanisms of tissue growth and patterning, including our own studies of the vertebrate neural tube.

D'Arcy Thompson's *On Growth and Form* (Thompson, 1917) has been described as the "the finest work of literature in all the annals of science that have been recorded in the English tongue" (Medawar, 1967). It has provided inspiration to generations of biologists, artists, architects and engineers. In part, the influence of the book arises from the clarity of its illustrations and the elegance and accessibility of the writing, despite the occasional Greek or Latin footnote. But, more than the style, the originality and authoritative breadth of the subject matter, drawing on numerous examples from across the natural world, builds a compelling case for the author's main thesis: biological form is the consequence of physical processes and mechanical forces. D'Arcy Thompson developed this argument over the course of 20+ years leading up to the publication of *On Growth and Form.* In part it was his response to Darwinian ideas of natural selection, which had started to dominate attempts to explain the shape of living organisms. D'Arcy Thompson reasoned that only a limited number of design solutions are compatible with physical principles and meet the challenges faced by living organisms. Consequently, it is these physical principles that constrain biological form thereby limiting and governing the evolution of functional morphology (Gould, 1971). This relegated to a secondary role explanations of biological form based on selection of unconstrained random heritable changes. In this view, *On Growth and Form* can be seen as a bridge between the transcendental anatomists of the early nineteenth century, such as Etienne

Geoffroy Saint-Hilaire and Richard Owen, with their belief in an *ideal plan* underpinning the morphology and function of organisms, and modern Evo-Devo theory, with its emphasis on structuralism and an explanation of evolutionary change based on understanding alterations in embryo development (Amundson, 2006).

Nevertheless, the importance of *On Growth and Form* is, arguably, not in this thesis, but in the influence that the book has had and continues to have on the wider field. By applying tools from mathematical and physical sciences to the biological world, D'Arcy Thompson demonstrated how mathematical reasoning could be used to provide succinct descriptions of living forms and to reveal elegant, simple answers to seemingly complex problems. In doing this D'Arcy Thompson rejected vitalist explanations of biological processes and established the science of form as a rigorous discipline. This laid the foundations for further studies of biological morphology and embryo development. As a consequence, later generations of developmental biologists have read the book as a manifesto promoting a quantitative approach to the study of embryology. A well-cited quote from the epilogue of *On Growth and From* sums this up:
"I know that in the study of things, ***number, order and position*** *are the threefold clue to exact knowledge; that these three, in the mathematicians hands furnish the 'first outlines for a sketch of the universe'".*
However, the explanations provided by D'Arcy Thompson in *On Growth and Form* were largely descriptive; they lacked specific mechanistic details and failed to give accounts of the generative processes. It is only in recent years with advances in experimental embryology, microscopy and imaging, together with the power of developmental genetics and molecular approaches to perform precise perturbations, that causative explanations have begun to emerge. To illustrate how D'Arcy Thompson's influence can still be seen in current topics in developmental biology we will follow two threads that lead from *On Growth and Form* to our own interests in the development of the vertebrate neural tube.

On Morphological Transformations and Morphospaces
On Growth and Form covers many topics, but probably the most widely known is the geometrical method D'Arcy Thompson developed to describe changes in shape between homologous structures in different species. In this approach, a Cartesian coordinate grid is projected onto an organ or organism, then subjected to a simple mathematical transformation to produce the shape of another related animal. This is illustrated by D'Arcy Thompson's diagram of morphing a porcupine fish into a sunfish (Figure 1). Although the approach has drawn criticism for oversimplification and a lack of causal explanation (Arthur, 2006)(Bookstein, 1977) it exemplifies D'Arcy Thompson's goal of finding concise mathematical descriptions for biological processes. It has also served as a source of inspiration for later morphologists.

One example of this influence is the development of the 'morphological space' concept to document and analyse biological form (Stone, 1997)(McGhee, 2006). Morphological spaces, commonly abbreviated as morphospaces, are mathematical constructions that represent the possible morphology of a set of organisms. A typical morphospace, might have two or more axes, each of which represents a quantitative feature of shape or structure – this could be a direct measure of a shape characteristic (e.g. length) or a composite variable of several characteristics produced by a dimension reducing projection. In this way, an individual organism corresponds to a single point within morphospace denoting its configuration. The approach has been used both to describe variation in biological form and in rigorous mathematical analyses of morphology (Mitteroecker and Huttegger, 2009) (McGhee, 2006).

An iconic example, which demonstrates some of the uses of a morphospace, is Raup's description of coiled mollusc shells (Raup, 1966). In this model a shell is represented by logarithmic spiral (a form favoured by D'Arcy Thompson), which is described by three parameters that determine its size, coiling, and relative proportions (Figure 2). Different combinations of parameter values define different shell shapes and allow a morphospace to be populated with potential morphologies. This represents a theoretical design space. Comparing the morphospace to the shapes of real shells provides a simple means to estimate the shape parameters in real specimens. Moreover, exploring the morphospace reveals structural and functional principles of morphology. For example, it can indicate the geometric limits of possible morphologies. These could be the consequence of either physical or genetic constraints. Alternatively, identifying the areas of morphological space that are occupied or devoid of real specimens provides insight into the morphological forms favored by natural selection.

However, morphospaces, whether generated by a mathematical model or based on statistical measurements of geometric parameters, do not in themselves provide a causal explanation for biological form. This requires molecular, genetic or mechanical insight into the processes generating the morphology. The increasing ease with which defined genetic perturbations can now be introduced into organisms and their effects assayed raises the possibility of rapid progress in defining the molecular and genetic control of morphology. Likewise the rise in synthetic developmental biology and tissue engineering techniques, such as in vitro organoid methods, allows the generation of tissues *ex vivo*, under artificially imposed external conditions without the usual in vivo constraints. Specific parameters inaccessible in vivo, whether molecular or physical, can be systematically varied *in vitro,* allowing the exploration of a greater range of morphological forms and obtaining new insights into the mechanisms determining shape. The morphospace representation has the potential to

support these studies. It provides a means to illustrate complicated effects on tissue morphology or configuration in an intuitive manner and offers an attractive way to link phenomenological and mechanistic models. In this respect it would fulfill D'Arcy Thompson's goal of developing succinct and efficient descriptions of biological form.

On Morphogens and Form

By the 1930s and 40s the influence of *On Growth and Form* was spreading beyond the biology community. Alan Turing, the mathematician, computer scientist and polymath became fascinated by D'Arcy Thompson's observations of recurring mathematical patterns in nature. He highlighted the appearance of the Fibonacci sequence in the arrangement of leaves on plants (phylotaxis) and suggested that "certain well-known physical laws are sufficient to account for many of [these] facts" (Turing, 1952). Turing was able to pursue this interest, after his codebreaking work during the Second World War and his move to Manchester University, when the first commercial general purpose computer, the Ferranti Mark I, was installed at the university in the early 1950s. Turing used it to test the possibility that diffusing chemicals reacting with one another could explain the formation of anatomical patterns in developing tissues (Copeland, 2005). He used the phrase "chemical embryology", originally introduced by Joseph Needham (Needham, 1931), to summarise this idea. Similar to D'Arcy Thompson's insistence that physical forces can explain biological forms, Turing's hypothesis, evident in the phrase 'chemical embryology', was that patterns in tissues arise from simple chemical processes that can be described precisely and mathematically.

In the paper describing these studies, "The Chemical Basis of Morphogenesis" (1952), Turing cites *On Growth and Form* as one of only six references. The paper introduces a set of chemical kinetic equations, now termed a 'reaction-diffusion system' that can generate biological-like patterns (for a review see (Green and Sharpe, 2015). In their canonical form, the equations describe a rapidly diffusing inhibitor molecule and a slowly diffusing self-activating molecule and depending on the model details these can produce various periodic patterns. Turing coined the term "morphogen" for such diffusing patterning substances. As justification for this he cited Conrad Waddington's experimental evidence that embryos produce "evocators" that induce organ formation (Waddington, 1940). Indeed it is now well established that in plants and animals chemical/molecular signals, termed morphogens in Turing's honour, spread within tissues instructing cell identity and generating spatial patterns of cell differentiation (Rogers and Schier, 2011).

Crucially, Turing's work demonstrated that tissue patterns correlate with and can be explained by the dynamic changes in the distribution of a morphogen. In

doing this he defined a question that is of central importance in developmental biology even today: how are morphogen profiles shaped and interpreted in tissues? Turing's approach demonstrated the power of a quantitative and mathematical approach. This is reflected in subsequent studies of morphogen-mediated patterning. It's not just those cases where Turing-like reaction-diffusion mechanisms operate, but also studies of systems in which cells acquire positional values in response to external cues that spread from localized sources, rather than being produced throughout the tissue (Rogers and Schier, 2011)(Green and Sharpe, 2015)(Kicheva et al., 2012). In these latter cases, which more closely follow the "positional information" model proposed by Wolpert (Wolpert, 1969), a quantitative understanding of the mechanisms controlling morphogen gradient formation has also been instrumental.

The work of both Turing and D'Arcy Thompson advocated finding simple mathematical descriptions of biological processes based on physical principles. The notion that physical laws constrain biological systems has far reaching consequences. This way of thinking is now guiding efforts to identify the relationships between spatial and temporal scales of processes underlying tissue morphogenesis and inspiring quantitative approaches to understand the feedback mechanisms that coordinate tissue patterning and growth. These efforts are building on the foundations that Turing and D'Arcy Thompson laid down for modern developmental biology and are rooted in exploring the physical principles that govern development.

On Neural Tube Patterning and Growth

One current area of work where the legacy and impact of *On Growth and From* is evident is the study of vertebrate neural tube development. Our own attempts at understanding the growth and patterning of the neural tube have been influenced by D'Arcy Thompson and the agenda that he and his successors established.

The developing neural tube is a tissue ideally suited to study how morphogen signalling, cell fate specification and tissue growth are coordinated (for reviews see (Dessaud et al., 2008)(Briscoe and Small, 2015). In this tissue, 14 discrete domains of progenitors are generated and arrayed along the dorsal-ventral axis. The identity of each of these domains is encoded by the combinatorial expression of transcription factors, which are necessary and sufficient to specify the types of neurons each progenitor type generates. The pattern of gene expression is established in a progressive manner in response to opposing gradients of morphogens – Shh emanating from the ventral pole and BMP signalling dorsally. At the same time as pattern forms, the tissue is growing and the dorsal-ventral length of the tissue more than doubles in size as the progenitor domains are established (Kicheva et al., 2014). Moreover, spinal cord

patterning is largely conserved in all vertebrates, despite differences in size and rate of development. This raises several questions. How do the morphogens generate pattern? How is correctly and precisely proportioned pattern established in a growing tissue? What mechanisms coordinate pattern formation with growth?

Over the last few years we have attempted to tackle aspects of these questions, seeking to follow D'Arcy Thompson's dictum of taking quantitative measurements and combining these with physical and mathematical approaches. Measurements of Shh morphogen and the transcriptional activity of the Gli proteins, the effectors of Shh signalling, have revealed a dynamic ventral-to-dorsal gradient of Shh signaling in the ventral neural tube (Chamberlain et al., 2008; Cohen et al., 2015)(Balaskas et al., 2012). In response to this gradient, specific target transcription factors that comprise the combinational progenitor code are induced or repressed. Pairs of these target transcription factors frequently cross-repress each other's expression to form bistable switches, which results in the formation of discrete domains of gene expression (Briscoe et al., 2000)(Balaskas et al., 2012). This combination of cross-repressive interactions between target transcription factors and the Gli activity gradient produces a morphgen-driven gene regulatory network (Figure 3).

Experiments, combined with mathematical analysis of the neural tube regulatory network, have provided an explanation for several seemingly counterintuitive aspects of neural tube patterning. On one hand, the pattern appears in the same temporal order as the spatial arrangement of the domains (Dessaud et al., 2007). The mathematical model suggested that the dynamics of the transcriptional network composed of Nkx2.2, Olig2, Irx3 and Pax6 (Fig. 3) in the ventral neural tube could account for both spatial and temporal patterns of gene expression (Balaskas et al., 2012; Cohen et al., 2014). This further helped to reconcile the observations that both the levels and duration of Shh signaling affect the establishment of pattern (Dessaud et al., 2007). Analysis of the network also suggested an explanation as to why gene expression boundaries do not correspond to constant levels of Shh signaling over time (Balaskas et al., 2012). The strength of cross-repression between the network components determined the response of these genes to the Shh signaling gradient and was crucial for determining the boundary positions between domains (Balaskas et al., 2012). Moreover, the models suggested an explanation for how gene expression is maintained as Shh signaling decreases as development proceeds. This relies on the cross-repressive interactions between the transcription factors, which introduce a property known as multistablity, in which the final state of a system is determined by an earlier state, rather than by ongoing changes. Together, these studies highlighted to us how pattern formation is dependent not only on

the graded distribution of morphogens but also on the structure and dynamics of the downstream transcriptional network controlled by the morphogen.
D'Arcy Thompson recognized that form and growth are inseparable and described morphogenesis in terms of the amount of growth that occurs in different directions. Indeed, a full understanding of pattern formation cannot be achieved without considering the context of the growing tissue. Following this idea, we set out to measure, with high spatial and temporal resolution, the cell cycle dynamics and patterning of the neural tube. A three-dimensional reconstruction and analysis of the data showed that spinal cord development could be divided into two phases (Kicheva et al., 2014). Initially, morphogen signalling causes changes in gene expression within progenitors, hence altering their identity and modifying the relative size of each progenitor domain. This results in the expansion of some progenitor domains at the expense of others. Subsequently, cells become substantially less sensitive to morphogen signaling, nevertheless alterations in progenitor domain proportions continue. Quantitation revealed that different progenitor subtypes undergo terminal differentiation at different rates and this is sufficient to account for the changes in pattern during this second phase. The progenitor identitity genes play a key role in regulating their own rates of differentiation. Thus the pattern established during the first phase is naturally elaborated by modulating the rate of cell cycle exit and neuronal differentiation. Recent studies are beginning to unravel the mechanisms controlling the timing and rate of differentiation. A prominent example is the role of Olig2, marker of motor neuron progenitors, in cross-regulating the expression of proneural genes and components of the Notch signaling pathway which are involved in neurogenesis (Fig. 3, Mateo et al., 2014; Sagner et al., 2017). Although many questions are still open, these studies suggest that a quantitative understanding of the specific gene regulatory network involved in neurogenesis will be instrumental for understanding the cell-type specific elaboration of pattern during the second phase.

These results begin to connect growth and form (or at least molecular pattern) in the neural tube. The two phase mechanism for coordinating patterning and growth means that the tissue is patterned when it is relatively small. The dorsoventral morphogen signaling gradients in the neural tube have maximum ranges at the earliest developmental stages, allowing accurate patterning to be imposed across a tissue that is subsequently elaborated by growth. In turn, the second phase offers an opportunity to compensate for any patterning errors that occur during the first phase. For example regulative feedback strategies could adjust proliferation, differentiation or apoptosis rates to regulate proportions. Unraveling these feedback mechanisms, and investigating how the precision and dynamics of gene expression is achieved in the neural tube will be aims of future studies in the field.

Much of *On Growth and Form* is focused on understanding tissue form and adaptation to physical constraints at the scale of a whole organ or organism. By contrast, developmental biology of the last several decades, including our own studies, have often drifted into more reductionist approaches, aiming to achieve a cellular and molecular understanding of patterning and growth. A renewed drive in the field to understand how complex behaviours emerge from molecular mechanisms has prompted a resurgence in a more systematic and holistic view of tissue development. One aspect of this in the neural tube is that, similar to several other tissues, there are sources of morphogens at both poles of the patterning axis. These generate antiparallel gradients: a dynamic dorsal to ventral gradient of BMP, emanating from the dorsal pole, reciprocal to the ventral-to-dorsal Shh gradient (Tozer et al., 2013)(Kicheva et al., 2014). Strikingly, both Shh and BMP signaling reach their maximum levels during the early phases of neural tube patterning and subsequently levels decrease throughout the tissue (Fig. 3). Thus, as the tissue grows, the antiparallel morphogen signaling gradients drift apart. Because of this and the dynamics of the signaling cascades, cells are exposed to high levels of signaling only during early developmental stages. This is consistent with the idea that the formation of the initial pattern happens early, when the gradients are steepest, since slope of a gradient as well as the absolute levels of signaling, affects the precision with which morphogens can specify gene expression patterns (Bollenbach et al., 2008)(Kicheva and Briscoe, 2015).

Theoretical studies suggest that the interpretation of antiparallel gradients can maximise the precision of patterning if cells use a combination of the two signals (Morishita and Iwasa, 2009)(Tkačik et al., 2015). Indeed, there is evidence that neural progenitors can interpret a combination of Shh and BMP signals (Liem et al., 2000)(Mizutani et al., 2006). Yet, it is unclear in what way the signals are combined. Morphogen gradients have been viewed as defining a coordinate system within the tissue (Wolpert, 1969). However, the positional identities that cells adopt in response to these signals can be predicted within this coordinate system only if the function that transforms morphogen signalling levels into cell identities is known (Corson and Siggia, 2012). In some sense, this is similar to plotting a morphospace – the dependence of form on defined measurable parameters. Can we find such a function for morphogen patterned tissues? How would it relate to the molecular mechanism of the underlying gene regulatory network? Does the function explain emergent properties, for example does it account for the observed precision and robustness of pattern? What happens if the coordinate system changes over time, as in a growing tissue? These are questions that we are currently exploring, using a combination of in vivo quantitative measurements, ex vivo assays and mathematical analysis.

D'Arcy Thompson's ideas and his insistence on finding physical explanations for biological processes has guided our studies of neural tube morphogenesis, as well as the studies of many other researchers in the field. His advice to interpret experimental observations in the context of biophysical laws is as valid now a century ago and will be essential for the future development of integrative approaches that address how concurrent processes are influencing one another. If we're fortunate this might contribute to D'Arcy Thompson's "*sketch of the universe".* And 100 years after *On Growth and Form,* it's worth remembering that "*the harmony of the world is made manifest in Form and Number, and the heart and soul and all the poetry of Natural Philosophy are embodied in the concept of mathematical beauty".*

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Figures

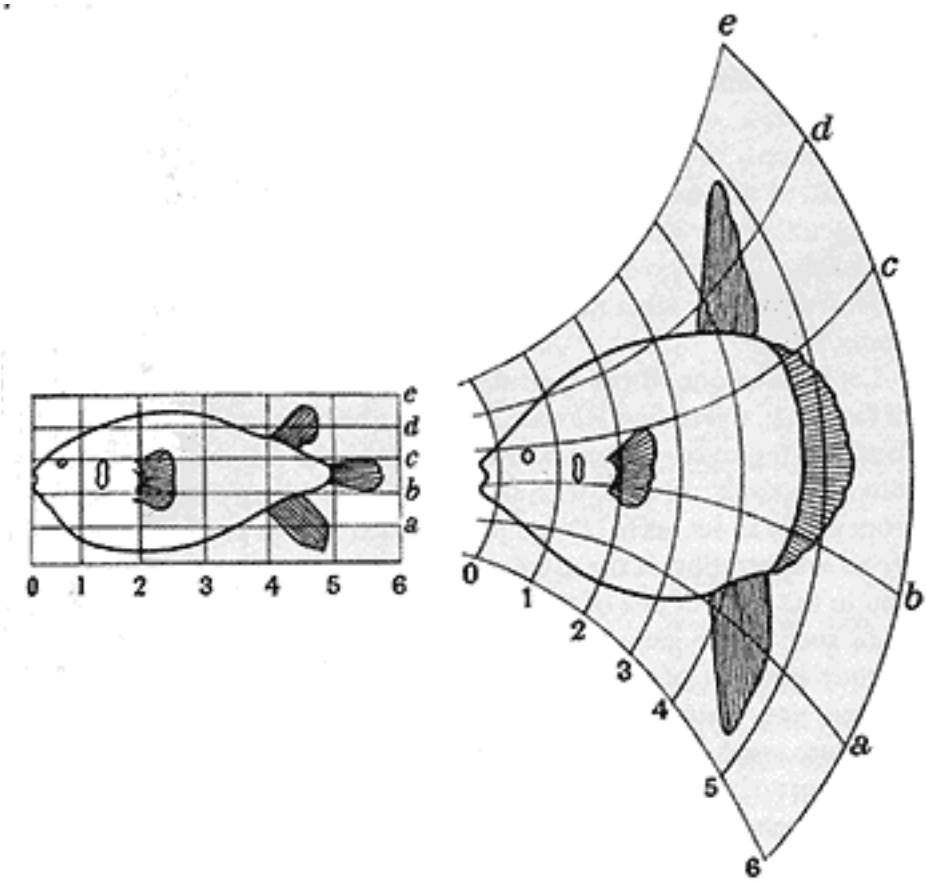

Figure 1. Figure 381 and 382 from *On Growth and Form* illustrating the method of transforming morphologies. D'Arcy Thompson notes that this is a "particularly instructive case". Reprinted with permission from On Growth and Form.

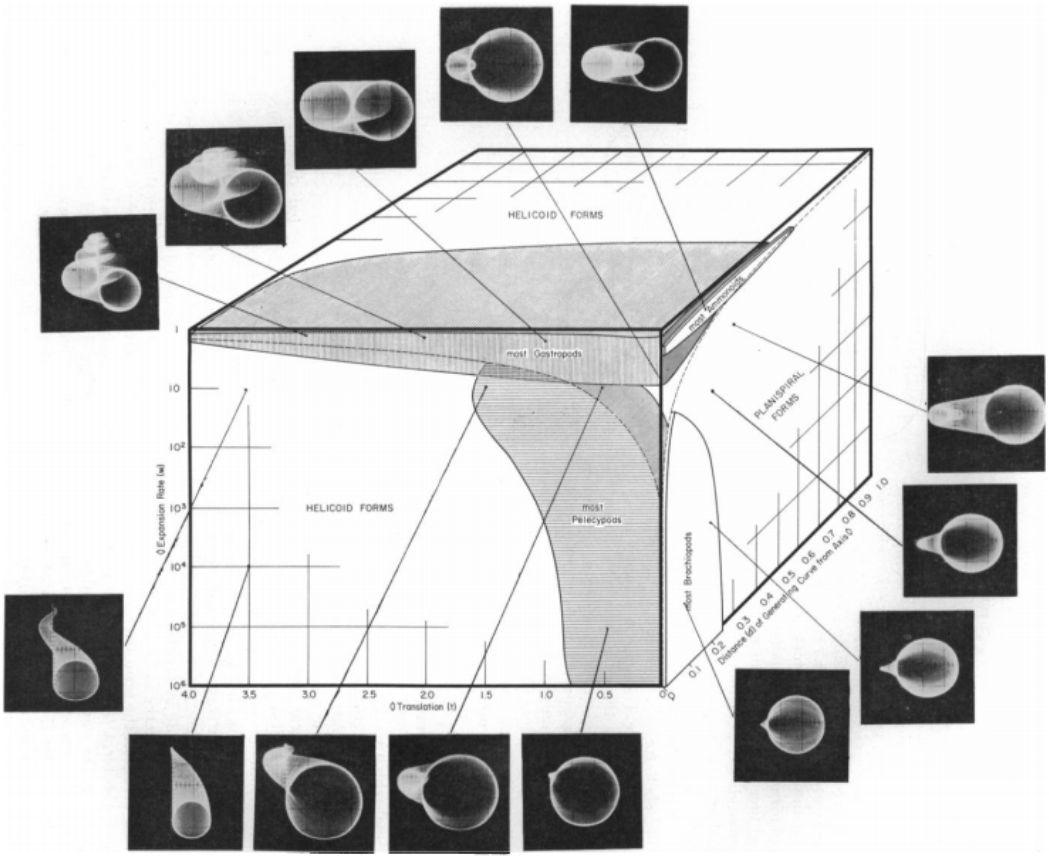

Figure 2. Raup's three dimensional morphospace illustrating possible shell morphologies with images exemplifying the shapes at the indicated positions. The regions occupied by naturally occurring species are shown by the shaded regions. Reprinted with permission from Raup (1966).

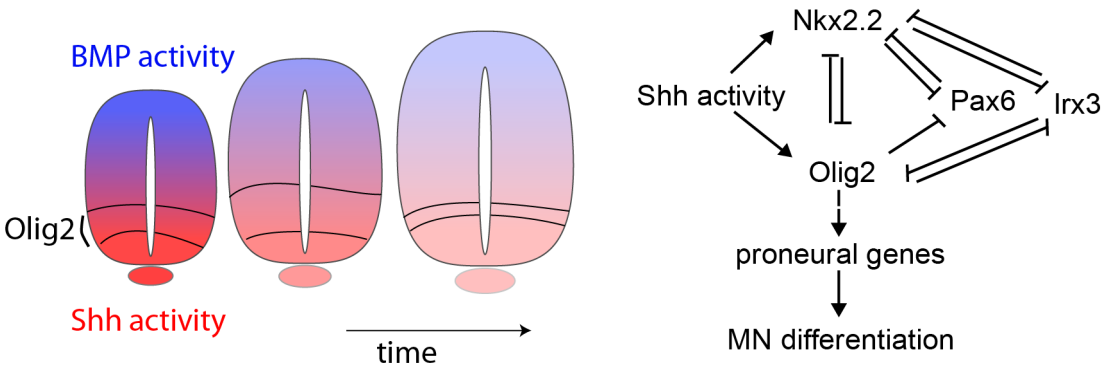

Figure 3. The dorsoventral axis of the vertebrate neural tube is patterned by opposing gradients of BMP and Shh signaling activity. The levels of signaling are the highest early in development. The boundaries of the Olig2 expression domain, which contains the motor neuron progenitors, are defined by a multicomponent gene regulatory network (simplified scheme on the right). This network explains how Shh activation and derepression by Nkx2.2 and Pax6 help to specify Olig2 identity at the expense of Irx3. At later stages Olig2 plays a role in inducing rapid motor neuron (MN) differentiation, which contributes to the decrease in the size of this progenitor domain.