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EDITORIAL

Size and shape—integration of morphometrics, mathematical modelling, developmental and evolutionary biology

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The German philosopher Arthur Schopenhauer (1788–1860) once said: "Any foolish boy can crush a beetle with his foot, but all the professors in the world cannot make a beetle". This quote summarizes the limited knowledge in the mid-nineteenth century about the mechanisms that generate a new individual. But, it still reflects our limited knowledge of the genetic control of morphogenesis. Studies in a number of model systems, especially in the fruit fly *Drosophila melanogaster*, have revealed basic principles of how the body axis, segments or organs like the wing are specified, for example. However, we are still lacking a comprehensive understanding of how organisms and their organs know when to stop growing or how to attain their final shape, which is often species specific or even specific to an individual.

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The basis of size: cell size and cell numbers

In theory, the size of an organ can mainly be changed in two ways: either by changing the size of the individual cells or by changing the number of cells, and thus, an understanding of size control should be possible by studying the mechanisms of cell growth and cell proliferation.

In practice, however, the control of cell number and cell size is more complex. For each process, there are several cellular mechanisms. For instance, cell number can be determined not only by controlling the production of new cells but also by killing cells that were already produced (cell death). Thus, positive and negative regulatory mechanisms of cell growth and cell number complement each other. In addition, there is evidence that the mechanisms that control cell growth and those that control cell number can communicate and influence each other. Diploid and tetraploid salamanders, for instance, develop organs of comparable size although in the tetraploid animals, the cells are much larger. The organs compensate for the bigger cell size by reducing the number of cells (Fankhauser 1952). Similarly, a decrease in cell number in plant mutants is associated with an increase in cell size and vice versa. This compensation ensures that despite alterations during development, functional leaves are formed (Gonzalez et al. 2012).

Size control: autonomous vs. non-autonomous

In the early 1920s, Harrison and later also Twitty and Schwind transplanted organ anlagen of salamander legs and eyes from a small species into a large species and vice versa. Intriguingly, the size of the transplanted organs always resembled the size in the source species rather than the new host. Thus, the information about their final size must have resided within the transplanted legs and eyes themselves (Harrison 1924;

Harrison 1929; Twitty and Schwind 1931). Further support for an organ-autonomous (intrinsic) control of size was provided by transplantation experiments in *Drosophila* that showed that larval wing imaginal discs grow to a predefined size irrespective of the environment into which they are transplanted (Bryant and Simpson 1984; Bryant and Levinson 1985).

On the other hand, there is ample evidence for external influences that play a role in defining the final size of an individual or an organ. For example, transplantation experiments in horned beetles have shown that organ primordia that grow next to each other compete for resources (Nijhout and Emlen 1998). Similarly, damaged or slow-growing imaginal discs are able to send a "wait-for-me signal" to other organs to induce a reduction of their growth rate and/or a prolonged developmental time (Parker and Shingleton 2011). Various environmental factors like nutrition, temperature, oxygen levels and pathogen infections also influence the developmental programs underlying organ and body growth (Mirth and Shingleton 2012; Andersen et al. 2013). The final size of individual organisms and their organs is therefore the result of a complex interplay between intrinsic and environmental factors. We are only beginning to understand these intricate connections between genetic and epigenetic information in the cell, integration of environmental information, and hormonal control of developmental timing.

Shape: description and quantification of complex structures

Size differences can be expressed in terms of rather simple one-dimensional measurements (e.g. length, height etc.). Shape, on the other hand, is a much more complex feature, and it is far more difficult to measure and compare.

In 1915, D'Arcy Wentworth Thompson proposed that the scientific description of the manifold forms, which occur in nature could benefit from using analytical methods borrowed from mathematics and statistics (Thompson 1915). Indeed, the analysis of morphological variation using multivariate statistical methodology in the first half of the twentieth century marks the rise of morphometrics as a biological discipline. During this early phase, shape was still mainly described by multiple linear measurements and distances and the major problem of capturing the geometry or overall shape of a complex structure persisted. In the 1980s, advances in the development of statistical analytic tools and their combination with outline and landmark data revolutionized the field of geometric morphometrics (Zelditch et al. 2012; Rohlf and Marcus 1993; Adams et al. 2004; Mitteroecker and Gunz 2009; Adams et al. 2013) and sparked studies in facial expression (Adams et al. 2013), shape-to-body size correlation (allometry) (Sidlauskas et al. 2011), symmetry (Klingenberg et al. 2002), quantitative genetics (Klingenberg and Leamy 2001; Boell et al. 2011; Pallares et al. 2015) and evolutionary-developmental biology (Klingenberg 2010; Salazar-Ciudad and Jernvall 2010) to name but a few.

The development and evolution of size and shape

Most morphological structures attain their final (i.e. functional) shape late in embryonic development or during postembryonic stages. Unfortunately, however, most studies of the genetic mechanisms that control development have focused on the earlier steps of embryogenesis and therefore our knowledge about the developmental basis of the "finalizing steps" of shape formation is still limited. Presumably, a combination of tissue patterning pathways, pathways involved in systemic growth control, like the insulin/TOR pathway, and the endocrine system affect local growth in given tissues. In addition, these processes also respond to environmental changes within a given reaction norm (Debat et al. 2003; Debat et al. 2008).

Research into the evolutionary change of shape has so far mostly focused on simple gains or losses of features, e.g. the species specific bristle numbers in *Drosophila* larvae (McGregor et al. 2007), the reduction of pelvic armor plates in stickleback fish (Shapiro et al. 2004), and pigmentation variation in mice (Hoekstra 2006) and flies (Gompel et al. 2005; Jeong et al. 2008). More and more studies, however, also deal with more complex shapes, for instance the differentiation of leaf shape between the plant model system *Arabidopsis thaliana* and the closely related species *Cardamine hirsute* (Hay and Tsiantis 2006; Barkoulas et al. 2008). Genetic mapping of quantitative trait loci (QTL), genome wide association studies (GWAS), and genome wide expression comparisons using modern high-throughput sequencing methods are powerful tools to identify genes and pathways involved in defining the size and shape of an organism. In addition, the combination of evolutionary developmental biology with population genetics provides an entirely new level of detail by revealing those nucleotides that are under selection and the potential basis for morphological diversification (Rebeiz et al. 2009; Linnen et al. 2013).

Finally, mathematical modeling has become a powerful tool to predict how changes in the gene regulatory network of a structure might relate to variation in its final shape. Similar to modern weather forecasts, this allows for describing regulatory networks and interactions of systems that would otherwise be too complex to handle. Recent cornerstones of a successful integration of mathematical models into evolutionary and developmental studies about shape variation are the prediction of a link between dorsal-ventral patterning mechanisms and tissue polarity organizers for proper flower shape formation, for example (Green et al. 2010; Sauret-Güeto et al. 2013), or insights into how leaf shape is established (Bilsborough et al. 2011; Kuchen et al. 2012). Population level variation in teeth morphology and tooth type differences in seals have been translated into mathematical models to

disentangle the stages of development and the respective signaling changes responsible for the observed shape changes (Salazar-Ciudad and Jernvall 2010). In *Drosophila*, computational models exist that explain patterning of the dorsal head region (Aguilar-Hidalgo et al. 2013) and growth control in the wing imaginal disc (Wartlick et al. 2011).

The size and shape symposium and beyond

In order to account for the extensive progress made in several fields of biological research towards understanding the regulation of body and organ size and shape, the Symposium "Size and Shape—Integration of morphometrics, mathematical modelling, developmental and evolutionary biology" took place in April 2014 in Göttingen, Germany (for a full program refer to: http://www.evolution.uni-goettingen.de/program.html). During the five sessions of the symposium, renowned experts and early stage researchers presented recent advances in each of the research areas, including cell and developmental biology, evolutionary biology, mathematical modeling of biological processes and various applications of geometric morphometric approaches. The symposium was exceptionally successful in bringing researchers from these diverse fields together to foster interactions and fruitful discussions about the future of research on size and shape related questions.

This Special Issue (SI) of Development Genes and Evolution is intended to provide a selection of recent advances in size and shape research, and brings together key contributions from the symposium. However, the SI can only present a small fraction of the ideas and discussions that emerged during the symposium. We are, therefore, delighted to announce that the SI is also the "kick-off" for a new publication category of Development Genes and Evolution: the Topical Collection (TC) "Size and Shape". This TC will be a permanent feature of the journal and will publish original articles, perspectives and review papers dealing with all aspects of the study of biological size and shape. Papers suitable for the TC "Size and Shape" will be published online as soon as they are ready and will be collected in their own, specially highlighted virtual issue on the home page of the journal. Of course, all contributions will also be included in the regular print issues and a "Topical Collection" logo on the issue cover and on the paper itself will draw attention to the fact that the paper belongs to the Topical Collection "Size and Shape".

We are excited to serve as the editors for this new Topical Collection of Development Genes and Evolution and will strive to make it a place where you can read about the latest findings related to the formation and diversification of biological size and shape.

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