© 2023. Published by The Company of Biologists Ltd | Development (2023) 150, dev201727. doi:10.1242/dev.201727

MEETING REVIEW

Developmental mechanisms understood quantitatively

Veronica Biga[1,*,‡], Tom P. J. Wyatt[2,*,‡] and Diana Pinheiro[3,*,‡]

ABSTRACT

Across developmental systems, quantitative and imaging-based approaches have provided unprecedented resolution of dynamic changes in gene regulation and cell fate specification, along with complex changes in tissue morphology. This has set the stage for a wealth of comprehensive theoretical models, parameterised by experimental data, able to reproduce key aspects of biological behaviour and jointly enabling a higher level of abstraction, going from the identification of the molecular components to understanding complex functional relationships between these components. Despite these successes, gaining a cross-scale understanding of developmental systems will require further collaboration between disciplines, from developmental biology to bioengineering, systems biology and biophysics. We highlight the exciting multi-disciplinary research discussed at The Company of Biologists workshop 'Fostering quantitative modelling and experimentation in Developmental Biology'.

KEY WORDS: Modelling, Quantitative biology, Theory

Introduction

For much of the 20th century, biological research was dominated by a revolution in molecular biology and genetics. A wealth of knowledge has been generated by these endeavours, identifying the components and signalling pathways that regulate a multitude of biological processes. To achieve a more complete understanding of complex phenomena, the next step is now to employ a broader range of quantitative approaches. This is particularly the case in developmental biology, where many processes involve multiple levels of organisation, across wide-ranging time- and length-scales. This was the theme of The Company of Biologists meeting in July 2022, where we met to discuss the most recent advances in quantitative biology and how they are allowing the field to answer some of developmental biology's biggest questions. The first section of this Meeting review will highlight advances enabled by new quantitative experimental techniques that were presented at the meeting. The second section focuses on how quantitative approaches are allowing combinations of theory and experiment to make progress on linking signalling and gene regulatory networks to cell fate and patterning. Finally, with a greater interest in physical properties, computational modelling and live imaging-based methods, the importance of cell and tissue mechanics in developmental processes is increasingly being revealed; this is covered in the last section.

[1]Faculty of Biology, Medicine and Health, The University of Manchester, Manchester M13 9PT, UK. [2]Wellcome-MRC Cambridge Stem Cell Institute, University of Cambridge, Puddicombe Way, Cambridge CB2 0AW, UK. [3]Research Institute of Molecular Pathology (IMP), Vienna BioCenter (VBC), Vienna 1030, Austria.
*These authors contributed equally to this work

‡Authors for correspondence (veronica.biga@manchester.ac.uk; diana.pinheiro@imp.ac.at; womtyatt@gmail.com)

V.B., 0000-0001-9592-385X; T.P.J.W., 0000-0002-2589-2370; D.P., 0000-0003-4333-7503

Expanding the biologist's toolkit

Advancement in developmental biology has frequently been fuelled by the emergence of technologies that allow us to make improved measurements. A recent example is the revolution in high-throughput so-called 'omic' techniques. Tatiana Sauka-Spengler (University of Oxford, UK and Stowers Institute, MO, USA) presented her group's work combining ATAC-seq (assay for transposase-accessible chromatin using sequencing) and scRNAseq (single cell RNA-sequencing) to map the temporal changes both at the chromatin and transcriptional levels, to identify new regulatory networks controlling neural crest formation, and to test gene regulatory circuitry using transcription factor pertubation, binding and downstream target outputs (Ling and Sauka-Spengler, 2019). Eileen Furlong's group (European Molecular Biology Laboratory, Heidelberg, Germany) showed the power of combining a single cell developmental time-course (in this case scATAC-seq) with mutant data to phenotype mutants *de novo*, providing information at a cellular level (which cell types are missing and when) and at a molecular level (which enhancers and genes have changed in their activity) (Secchia et al., 2022). These approaches from development are mirrored in work on adult adipogenesis where the team of Susanne Mandrup (University of Southern Denmark, Odense, Denmark) is exploring how cooperation between enhancers in enhancer communities drives adipocyte lineage determination (Madsen et al., 2020).

Other exciting advances in quantitative molecular techniques include the development of tools to measure the dynamics of transcription and translation. Sarah Bray's group (University of Cambridge, UK) is using the MS2-MCP system to reveal mechanisms underlying transcriptional dynamics in the *Drosophila* embryo. They have shown that Twist and Dorsal cooperate with Notch to modulate the duration of bursts of transcription rather than increasing burst frequency (Falo-Sanjuan et al., 2019). Using the MS2-MCP system in the same model system, Mounia Lagha (Institute of Molecular Genetics of Montpellier, France) showed that the GAGA pioneer factor (GAF) acts as a stable mitotic bookmarker during zygotic genome activation, thus ensuring rapid transcriptional activation upon mitotic exit (Bellec et al., 2022). She also presented recent work showing that mRNA translation can also be imaged live in a developing embryo, which revealed unexpected dynamics and spatial patterns (Dufourt et al., 2021).

At a larger length-scale, uncovering the conditions that allow stem cells to self-organise *in vitro* has led to advances in tissue models. Using the gastruloid-disc system, in which the colony shape of human pluripotent stem cells (hPSCs) is controlled, patterning mechanisms can be studied in a systematic way (Warmflash et al., 2014). Nadia Ayad (University of California, San Francisco, USA) presented work in this system exploring how mesoderm differentiation is instructed by geometry, stress and substrate stiffness (Muncie et al., 2020). She is also exploring how patterns of stress and cell fate can affect apoptosis *in vitro*, as well as the subsequent consequences of apoptosis on tissue behaviour. In a similar vein, *in vivo* work by Magali Suzanne's group (Centre for

Development (2023) 150, dev201727. doi:10.1242/dev.201727

Integrative Biology, Toulouse, France) showed that apoptosis actively generates pulling forces and that the localisation of apoptotic events drives epithelial folding in the *Drosophila* leg and the avian neural tube (Monier et al., 2015; Roellig et al., 2022).

Novel bioengineering techniques are increasingly being applied in the context of developmental biology. Tom Wyatt (University of Cambridge, UK) reported the use of microfluidics to stimulate the basal side of hPSCs with spatial concentration gradients of the morphogen BMP4. Here, the quantitative control afforded by microfluidics has allowed different cell fate patterning mechanisms, such as dose-response and secondary inductions to be systematically distinguished. Alexander Aulehla's lab (European Molecular Biology Laboratory, Heidelberg, Germany) has used microfluidics in an *ex vivo* context to understand the mechanism controlling temporal dynamics of Notch in the presomitic mesoderm (PSM) (Sanchez et al., 2022). By entraining the endogenous oscillations, they found that the pace of somite formation is controlled through a mechanism of phase coordination between oscillatory Notch and Wnt signalling (Sonnen et al., 2018). His lab has now engineered a light-sheet microscopy setup enabling visualisation of the onset of oscillations of the Notch target Lunatic fringe (Falk et al., 2022). In addition, in somitogenesis, Ryoichiro Kageyama's group (RIKEN Center for Brain Science, Saitama, Japan) is interested in the oscillating clock gene *Hes7*, which can be monitored live through the development of a fast-maturing fluorescent protein named Achilles (Yoshioka-Kobayashi et al., 2020). This allowed them to uncover the role of Notch in tuning intercellular coupling for effective synchronisation of Hes7 oscillations (Kageyama et al., 2022; Yoshioka-Kobayashi et al., 2020). Altogether, these studies showcase an increasingly sophisticated toolkit for developmental biologists, enabling us to observe and perturb biological systems in a more controlled manner.

The dynamics of cell state and tissue patterning

Morphogen signalling gradients are present across developing systems and instruct tissue patterning by inducing cell specification into distinct cell types. Zena Hadjivasiliou (The Francis Crick Institute, London, UK) and collaborators combined theoretical modelling with experiments to quantitatively explore the mechanisms of gradient formation and how they scale with tissue growth. They found that as the *Drosophila* wing disc grows, the Dpp gradient shifts from being formed mainly through diffusion of extracellular ligands to being driven by the recycling of intracellular ligands (Romanova-Michaelides et al., 2022). The molecular basis of gradient scaling is also being studied in the context of regeneration, where Elly Tanaka's group (Institute of Molecular Pathology, Vienna, Austria) has built on previous work showing that axolotl limb regeneration is regulated by oppositely localised Fgf8 and Shh signalling (Nacu et al., 2016), and is studying how the Shh gradient scales with blastema size. Marcos Nahmad showed that, in the *Drosophila* wing disc, a mechanism for expanding tissue domains, called recruitment, also acts as a controller of tissue growth upon perturbations in cell proliferation (Muñoz-Nava et al., 2020).

While signalling gradients act at the tissue scale, they need to be interpreted at the single cell level to determine fate. Our current view of cell fate decisions is shaped by the Waddington metaphor depicting progenitor cells transitioning towards differentiation as a ball rolling down rough terrain containing multiple decision points, leading to alternative states. Inspired by this, theoretical models of developmental decisions have been constructed using geometric representations, as described by Eric Siggia (The Rockefeller University, New York, USA) and colleagues (Rand et al., 2021; Sáez et al., 2022). In these approaches, quantitative gene expression data are used to infer an abstract landscape containing 'attractors', or regions of low potential, representing specific cell states. The attractors are separated by 'saddle regions', or areas of high potential, where single cell trajectories flow away from and can create 'saddle-node or fold bifurcations', which act to sort cells into alternative states. Using this approach, work from James Briscoe (The Francis Crick Institute, London, UK) described work that utilised these geometric models of cell fate decisions based on *in vitro*-derived neural and mesodermal gene expression data to characterise both the landscape and the dynamic trajectories (Sáez et al., 2022). A major challenge of using high-throughput data, however, is its high dimensionality; thus, strategies are required to project the data onto a low-dimensional space. Using such strategies, the group of Paul François (University of Montreal, Canada) has proposed that the *Drosophila* gap genes network can be compressed into a 2D latent map that captures the underlying network function (Seyboldt et al., 2022).

While geometric models investigate fate specification from the perspective of single cells, in developing tissues, cell fate transitions must be appropriately coordinated in space and time. Focusing on the early *Drosophila* embryo, Erik Clark (University of Cambridge, UK) discussed computational and experimental evidence that extrinsic and dynamic spatial inputs cross-regulate gene expression networks, thus affecting local patterning (Clark et al., 2022). Complex patterning has also been observed in the embryonic mouse spinal cord, where the Notch target HES5 oscillates every 3-4 h (Manning et al., 2019). By using a combination of signal processing techniques and live imaging of *ex vivo* spinal cord tissue, Veronica Biga (University of Manchester, UK) and co-authors have shown that progenitors expressing HES5 are organised both locally, forming microclusters with synchronous and nested temporal dynamics, and globally, as microclusters with low and high expression are observed periodically along the dorsoventral axis (Biga et al., 2021). Theoretical predictions suggest that these spatially periodic microclusters are formed through interactions between proximal and distal cells, and moderate the rate of differentiation (Hawley et al., 2022; Biga et al., 2021). Spatiotemporal mechanisms of pattern formation were further discussed by Francis Corson (École Normale Supérieure, Paris, France) in the *Drosophila* eye during ongoing R8 cell differentiation. In another Notch-driven process, self-organised patterning during bristle formation has been modelled computationally and validated experimentally (Corson et al., 2017; Couturier et al., 2019). Altogether, these studies emphasise the strength of combining theory and biological experimentation to understand developmental cell fate decisions and patterning as dynamic processes.

The emergence of robust tissue shape

During embryogenesis, tissue patterning is often accompanied by large-scale morphogenesis. Recent years brought considerable advances in our understanding of the mechanical forces and cell behaviours driving morphogenesis, largely due to improved high-resolution live imaging, quantitative image analysis and mathematical modelling. By applying Bayesian computation methods to imaging datasets following hundreds of gene knockdowns, Ruth Baker's team (University of Oxford, UK) developed an unsupervised method to determine the contribution of distinct cell processes to wound closure in an *in vitro* assay (Perez et al., 2022). The team of Richard Carthew (Northwestern University, Evanston, IL, USA) and collaborators are now

Development (2023) 150, dev201727. doi:10.1242/dev.201727

combining quantitative image analysis with geometric methods to examine the natural variation in wing morphology in a highly outbred *Drosophila* population. Their findings show that strong constraints act on wing morphology, with all observed phenotypes converging along an axis in morphological space (Alba et al., 2021).

Using quantitative approaches, the field is exploring how cross-scale interactions produce robust morphogenetic outputs. Recent work highlighted that changes in tissue properties, including (un)jammed (solid-fluid) transitions or collective motility, can arise from subtle, yet quantifiable, changes in, for example, cell shape, cell-cell contact number or motility. In the zebrafish gastrula, Diana Pinheiro (Institute of Molecular Pathology, Vienna, Austria) found that the gradient of Nodal/TGFβ signalling, which patterns the mesendoderm germ layer, orchestrates its large-scale internalisation movements, by triggering both a motility-driven unjamming transition and specifying a spatial adhesion code. This dual mechanical role of Nodal produces an ordered mode of collective migration that couples patterning and morphogenesis during gastrulation (Pinheiro et al., 2022). Rachna Narayanan (University of Warwick, UK) is studying the tissue architecture of the PSM in fish, by comparing the control parameters that characterise the adaxial and mesenchymal cells integrating the tissue. In flies, Jana Fuhrmann (Max Planck Institute for Molecular Cell Biology and Genetics, Dresden, Germany) is examining how in-plane cell behaviours and tissue properties can collectively drive morphogenetic transitions here: from a folded epithelium into a flat bi-layered epithelia. Furthermore, Nat Clarke (Massachusetts Institute of Technology, Cambridge, MA, USA) is exploring the link between the patterns of cell-cell adhesion and EGFR signalling in the ectoderm of *Drosophila* embryos.

Another exciting development is the notion that tissue boundaries and geometry provide key morphogenetic information (Collinet and Lecuit, 2021). An analysis of tissue flow in the fly embryo by Thomas Lecuit's team uncovered that the geometric coupling between tissue-intrinsic mechanics and a curvature gradient at the posterior pole triggers the onset of polarised flow in this system (Gehrels et al., 2023). Similarly, the boundary conditions imposed on the growing *Drosophila* imaginal disc by the extracellular matrix (ECM) have been shown to determine the morphology of the tissue in three dimensions (Harmansa et al., 2023). The importance of the mechanical properties of the ECM as an active material was also highlighted by recent work in the zebrafish optic cup. Caren Norden's team showed that modulating ECM topology (e.g. porosity) results in distinct cell-matrix interactions, a critical parameter for directional cell migration (Soans et al., 2022).

The interplay between cell and ECM mechanics has also emerged in the context of tissue patterning in both plants and animals. Using reconstituted assays of follicle patterning *ex vivo*, Alan Rodrigues (The Rockefeller University, New York, USA) and collaborators showed that contractile dermal cells rearrange the underlying ECM, which, in turn, promotes cell alignment. This reciprocal interplay creates a supracellular unit with fluid-like material properties that spontaneously breaks symmetry and forms regular patterns (Palmquist et al., 2022). Using time-lapse imaging and automated image analysis, Hannah Fung (Stanford University, CA, USA) and colleagues have now found that a geometrical parameter – cell size – regulates the transition from asymmetric self-renewing divisions to differentiation in meristemoids in *Arabidopsis* (Gong et al., 2022 preprint). A longstanding question in developmental biology is how external physical parameters, such as temperature, affect the pace of cellular processes. Connie Phong (Stanford University, CA, USA) is now employing quantitative approaches and biochemical assays to interrogate how the cell cycle machinery and the rate of division are modulated by temperature. Overall, these studies emphasise the importance of quantitative approaches in understanding the molecular and biophysical mechanisms controlling early development and tissue shape, and outline emerging research directions in the field.

Discussion

Over recent years, quantitative approaches have begun to uncover how signalling pathways, gene regulatory networks and molecular effectors function together, over multiple scales, to generate developmental outputs. This is well exemplified by recent work on dynamic Waddington models, where quantitative gene expression datasets are being used to model both discrete (steady)-cell fates, as well as the temporal transitions between these states. Novel approaches, e.g. using microfluidics, can be used to perturb the endogenous dynamics of signalling with high spatio-temporal resolution, thus providing new experimental tools to directly test and/or refine predictions of cell fate decisions. An important future challenge will be to mechanistically understand how patterning and morphogenetic programs are coordinated during development. Here, recent advances in gastruloid/organoid systems are providing an additional tool to obtain a quantitative understanding of the cross-scale interactions controlling robust embryo development.

A common theme that emerged during the meeting was the challenge of working effectively in a highly interdisciplinary field, where researchers with such diverse approaches, questions and terminologies must come together. A popular suggestion was to adapt a framework from neuroscience, laid out by David Marr (Marr, 2010), that could help to conceptually organise our work in a more unified way. This framework identifies three conceptual tiers in information-processing systems: computation, algorithm and hardware. To apply this to developmental biology, we can take the example of tissue patterning. The highest level of abstraction, computation, refers to the goals of the system. At this level, researchers may ask what information is required to generate a given pattern and where this information could be stored. The algorithm then determines the specific input-output relationships that are required to carry out that computation, e.g. how cells could measure a local morphogen concentration and convert it to a discrete cell state decision. Finally, the hardware level studies the components required to execute the algorithm, e.g. the transcription factors acting downstream of signalling activation. It was broadly agreed that this framework could help us, as a community, to better structure our ideas and research. In collaborating within and between these levels, we believe quantitative modelling and experimentation will drive developmental biology into new and exciting realms.

Acknowledgements

We thank the workshop organizers and the participants for stimulating discussions and their comments on this Meeting review.

Competing interests

The authors declare no competing or financial interests.

Funding

V.B. is funded by Prof. Nancy Papalopulu's Wellcome Trust Investigator Award (224394/Z/21/Z).

References

Alba, V., Carthew, J. E., Carthew, R. W. and Mani, M. (2021). Global constraints within the developmental program of the Drosophila wing. *eLife* **10**, e66750. doi:10.7554/eLife.66750

Bellec, M., Dufourt, J., Hunt, G., Lenden-Hasse, H., Trullo, A., Zine El Aabidine, A., Lamarque, M., Gaskill, M. M., Faure-Gautron, H., Mannervik, M. et al. (2022). The control of transcriptional memory by stable mitotic bookmarking. *Nat. Commun.* **13**, 1176. doi:10.1038/s41467-022-28855-y

Biga, V., Hawley, J., Soto, X., Johns, E., Han, D., Bennett, H., Adamson, A. D., Kursawe, J., Glendinning, P., Manning, C. S. et al. (2021). A dynamic, spatially periodic, micro-pattern of HES5 underlies neurogenesis in the mouse spinal cord. *Mol. Syst. Biol.* **17**, e9902. doi:10.15252/msb.20209902

Clark, E., Battistara, M. and Benton, M. A. (2022). A timer gene network is spatially regulated by the terminal system in the Drosophila embryo. *eLife* e78902. doi:10.7554/eLife.78902

Collinet, C. and Lecuit, T. (2021). Programmed and self-organized flow of information during morphogenesis. *Nat. Rev. Mol. Cell Biol.* **22**, 245-265. doi:10.1038/s41580-020-00318-6

Corson, F., Couturier, L., Rouault, H., Mazouni, K. and Schweisguth, F. (2017). Self-organized Notch dynamics generate stereotyped sensory organ patterns in Drosophila. *Science* **356**, eaai7407. doi:10.1126/science.aai7407

Couturier, L., Mazouni, K., Corson, F. and Schweisguth, F. (2019). Regulation of Notch output dynamics via specific E(spl)-HLH factors during bristle patterning in Drosophila. *Nat. Commun.* **10**, 3486. doi:10.1038/s41467-019-11477-2

Dufourt, J., Bellec, M., Trullo, A., Dejean, M., De Rossi, S., Favard, C. and Lagha, M. (2021). Imaging translation dynamics in live embryos reveals spatial heterogeneities. *Science* **372**, 840-844. doi:10.1126/science.abc3483

Falk, H. J., Tomita, T., Mönke, G., McDole, K. and Aulehla, A. (2022). Imaging the onset of oscillatory signaling dynamics during mouse embryo gastrulation. *Development* **149**, dev200083. doi:10.1242/dev.200083

Falo-Sanjuan, J., Lammers, N. C., Garcia, H. G. and Bray, S. J. (2019). Enhancer priming enables fast and sustained transcriptional responses to Notch signaling. *Dev. Cell* **50**, 411-425.e8. doi:10.1016/j.devcel.2019.07.002

Gehrels, E., Chakrabortty, B., Merkel, M. and Lecuit, T. (2022). Curvature gradient drives polarized tissue flow in the Drosophila embryo. *Proc. Natl. Acad. Sci. USA* **120**, e2214205120. doi:10.1073/pnas.2214205120

Gong, Y., Dale, R., Fung, H. F., Amador, G. O., Smit, M. E. and Bergmann, D. C. (2022). A cell size threshold triggers commitment to stomatal fate in Arabidopsis. *bioRxiv* doi:10.1101/2022.10.09.510391

Harmansa, S., Erlich, A., Eloy, C., Zurlo, G. and Lecuit, T. (2023). Growth anisotropy of the extracellular matrix shapes a developing organ. *Nat. Commun.* **14**, 1220. doi:10.1038/s41467-023-36739-y

Hawley, J., Manning, C., Biga, V., Glendinning, P. and Papalopulu, N. (2022). Dynamic switching of lateral inhibition spatial patterns. *J. R. Soc. Interface* **19**, 20220339. doi:10.1098/rsif.2022.0339

Kageyama, R., Isomura, A. and Shimojo, H. (2022). Biological significance of the coupling delay in synchronized oscillations. *Physiology* **38**, 63-72. doi:10.1152/physiol.00023.2022

Ling, I. T. C. and Sauka-Spengler, T. (2019). Early chromatin shaping predetermines multipotent vagal neural crest into neural, neuronal and mesenchymal lineages. *Nat. Cell Biol.* **21**, 1504-1517. doi:10.1038/s41556-019-0428-9

Madsen, J. G. S., Madsen, M. S., Rauch, A., Traynor, S., Van Hauwaert, E. L., Haakonsson, A. K., Javierre, B. M., Hyldahl, M., Fraser, P. and Mandrup, S. (2020). Highly interconnected enhancer communities control lineage-determining genes in human mesenchymal stem cells. *Nat. Genet.* **52**, 1227-1238. doi:10.1038/s41588-020-0709-z

Manning, C. S., Biga, V., Boyd, J., Kursawe, J., Ymisson, B., Spiller, D. G., Sanderson, C. M., Galla, T., Rattray, M. and Papalopulu, N. (2019). Quantitative single-cell live imaging links HES5 dynamics with cell-state and fate in murine neurogenesis. *Nat. Commun.* **10**, 2835. doi:10.1038/s41467-019-10734-8

Marr, D. (2010). *Vision: A Computational Investigation into the Human Representation and Processing of Visual Information*. MIT Press.

Monier, B., Gettings, M., Gay, G., Mangeat, T., Schott, S., Guarner, A. and Suzanne, M. (2015). Apico-basal forces exerted by apoptotic cells drive epithelium folding. *Nature* **518**, 245-248. doi:10.1038/nature14152

Muncie, J. M., Ayad, N. M. E., Lakins, J. N., Xue, X., Fu, J. and Weaver, V. M. (2020). Mechanical tension promotes formation of gastrulation-like nodes and patterns mesoderm specification in human embryonic stem cells. *Dev. Cell* **55**, 679-694.e11. doi:10.1016/j.devcel.2020.10.015

Muñoz-Nava, L. M., Alvarez, H. A., Flores-Flores, M., Chara, O. and Nahmad, M. (2020). A dynamic cell recruitment process drives growth of the Drosophila wing by overscaling the vestigial expression pattern. *Dev. Biol.* **462**, 141-151. doi:10.1016/j.ydbio.2020.03.009

Nacu, E., Gromberg, E., Oliveira, C. R., Drechsel, D. and Tanaka, E. M. (2016). FGF8 and SHH substitute for anterior–posterior tissue interactions to induce limb regeneration. *Nature* **533**, 407-410. doi:10.1038/nature17972

Palmquist, K. H., Tiemann, S. F., Ezzeddine, F. L., Yang, S., Pfeifer, C. R., Erzberger, A., Rodrigues, A. R. and Shyer, A. E. (2022). Reciprocal cell-ECM dynamics generate supracellular fluidity underlying spontaneous follicle patterning. *Cell* **185**, 1960-1973.e11. doi:10.1016/j.cell.2022.04.023

Perez, S. M., Sailem, H. and Baker, R. E. (2022). Efficient Bayesian inference for mechanistic modelling with high-throughput data. *PLOS Comput. Biol.* **18**, e1010191. doi:10.1371/journal.pcbi.1010191

Pinheiro, D., Kardos, R., Hannezo, É. and Heisenberg, C.-P. (2022). Morphogen gradient orchestrates pattern-preserving tissue morphogenesis via motility-driven unjamming. *Nat. Phys.* **18**, 1482-1493. doi:10.1038/s41567-022-01787-6

Rand, D. A., Raju, A., Sáez, M., Corson, F. and Siggia, E. D. (2021). Geometry of gene regulatory dynamics. *Proc. Natl. Acad. Sci. USA* **118**, e2109729118. doi:10.1073/pnas.2109729118

Roellig, D., Theis, S., Proag, A., Allio, G., Bénazéraf, B., Gros, J. and Suzanne, M. (2022). Force-generating apoptotic cells orchestrate avian neural tube bending. *Dev. Cell* **57**, 707-718.e6. doi:10.1016/j.devcel.2022.02.020

Romanova-Michaelides, M., Hadjivasiliou, Z., Aguilar-Hidalgo, D., Basagiannis, D., Seum, C., Dubois, M., Jülicher, F. and Gonzalez-Gaitan, M. (2022). Morphogen gradient scaling by recycling of intracellular Dpp. *Nature* **602**, 287-293. doi:10.1038/s41586-021-04346-w

Sáez, M., Blassberg, R., Camacho-Aguilar, E., Siggia, E. D., Rand, D. A. and Briscoe, J. (2022). Statistically derived geometrical landscapes capture principles of decision-making dynamics during cell fate transitions. *Cell Syst.* **13**, 12-28.e3. doi:10.1016/j.cels.2021.08.013

Sanchez, P. G. L., Mochulska, V., Mauffette Denis, C., Mönke, G., Tomita, T., Tsuchida-Straeten, N., Petersen, Y., Sonnen, K., François, P. and Aulehla, A. (2022). Arnold tongue entrainment reveals dynamical principles of the embryonic segmentation clock. *eLife* **11**, e79575. doi:10.7554/eLife.79575

Secchia, S., Forneris, M., Heinen, T., Stegle, O. and Furlong, E. E. M. (2022). Simultaneous cellular and molecular phenotyping of embryonic mutants using single-cell regulatory trajectories. *Dev. Cell* **57**, 496-511.e8. doi:10.1016/j.devcel.2022.01.016

Seyboldt, R., Lavoie, J., Henry, A., Vanaret, J., Petkova, M. D., Gregor, T. and François, P. (2022). Latent space of a small genetic network: Geometry of dynamics and information. *Proc. Natl. Acad. Sci. USA* **119**, e2113651119. doi:10.1073/pnas.2113651119

Soans, K. G., Ramos, A. P., Sidhaye, J., Krishna, A., Solomatina, A., Hoffmann, K. B., Schlüßler, R., Guck, J., Sbalzarini, I. F., Modes, C. D. et al. (2022). Collective cell migration during optic cup formation features changing cell-matrix interactions linked to matrix topology. *Curr. Biol.* **32**, 4817-4831.e9. doi:10.1016/j.cub.2022.09.034

Sonnen, K. F., Lauschke, V. M., Uraji, J., Falk, H. J., Petersen, Y., Funk, M. C., Beaupeux, M., François, P., Merten, C. A. and Aulehla, A. (2018). Modulation of phase shift between Wnt and Notch signaling oscillations controls mesoderm segmentation. *Cell* **172**, 1079-1090.e12. doi:10.1016/j.cell.2018.01.026

Warmflash, A., Sorre, B., Etoc, F., Siggia, E. D. and Brivanlou, A. H. (2014). A method to recapitulate early embryonic spatial patterning in human embryonic stem cells. *Nat. Methods* **11**, 847-854. doi:10.1038/nmeth.3016

Yoshioka-Kobayashi, K., Matsumiya, M., Niino, Y., Isomura, A., Kori, H., Miyawaki, A. and Kageyama, R. (2020). Coupling delay controls synchronized oscillation in the segmentation clock. *Nature* **580**, 119-123. doi:10.1038/s41586-019-1882-z