

EDITORIAL

New wave theory

Paul François

There is a long history of theory for biology, initially as a way to provide explanatory and conceptual frameworks. For example, in evolution, natural selection offers an explanation for the diversity of life; in development, the concept of a morphogen suggests a mechanism to ‘produce form’. But theory can also go beyond qualitative explanations to be both quantitative and predictive. The term morphogen itself and the associated mechanism of interactions of diffusing substances were proposed by the mathematician Turing in his formal theory of what we now call ‘Turing patterns’ (Turing, 1952). Other examples of predictive theory in development from the pre-molecular biology era include the clock and wavefront model for somitogenesis (Cooke and Zeeman, 1976) and Meinhardt’s reaction-diffusion model for segment formation (Meinhardt, 1982). The strength of those models is in their generality despite their simplicity: based on higher-level observations and in the absence of molecular data, they postulate a small number of organizing factors and predict how their interactions shape embryos. Although those models can be understood qualitatively, they nevertheless require mathematical descriptions and numerical simulations to be fully comprehended.

Such models have inspired generations of biologists, with tremendous success. A spectacular example was the discovery of a genetic oscillation at the core of the segmentation process (reviewed by Pourquié, 2022), as predicted by models from Cooke, Zeeman and Meinhardt. However, despite the impact of some models, the initial contributions of theory have been somehow eclipsed by the rapid advances and successes of molecular biology. Mechanistic descriptions have been favoured to the detriment of higher-level conceptual thoughts. The tide started turning with the advances of systems biology in the early 2000s (Woese, 2004), providing, for example, theoretical insights on the connection between digit formation and reaction-diffusion models (Newman and Frisch, 1979; Sheth et al., 2012) or on *Drosophila* gap gene networks (Jaeger et al., 2004). But I believe a new wave for theory in (developmental) biology is currently rising (see Fig. 1) due to the convergence of several new factors.

Most Development readers are of course aware that we can now monitor, almost in real time, a vast array of genetic expressions in thousands of cells (e.g. using single cell RNA seq), while also being able to perturb and achieve finer control of gene expression (e.g. with optogenetics). In parallel, organoid and other *in vitro* cultures allow us to reproduce and perturb developmental systems in dishes in a multiplexed and parallel way. As the number of potential experiments has exploded, it has become evident that the data do not speak for themselves. With the advances in computational possibilities (GPU computing and machine learning algorithms), new theoretical tools first appeared to describe and understand data structure. Examples include popular techniques, such as UMAP

(McInnes et al., 2020 preprint), which relies on differential geometry and topology to find close neighbourhoods in gene space. Gene expression and interactions can also be compressed using auto-encoders (Seyboldt et al., 2022). This, in turn, allows theorists to address new conceptual issues, such as optimal coding or information bottlenecks in gene networks (Bauer et al., 2021). Importantly, many of the machine-learning tools presently used have not been designed specifically for biology, and one can expect more-tailored theoretical/computational approaches (such as RNA velocity; Gorin et al., 2022) to improve our understanding of data.

Surprisingly, the structure of high-dimensional data in biology often appears much simpler than expected. In many cases, using the biological dynamics, one can indeed extract and describe a rather small number of (nonlinear) ‘modes’, an example of which was reported recently for the mechanics of embryogenesis in ascidians (Liu et al., 2022 preprint). For this reason, a ‘new wave’ in theory takes a conceptual but quantitative framework, focusing on low-dimensional description, validated by data. In particular, the central notion of ‘attractors’ appears relevant to describe cellular states, thus quantifying the classical landscape (or rather ‘seascape’) view of Waddington. In collaboration with experimentalists, theorists are currently devising geometric descriptions of development (Sáez et al., 2022), inferring flows in abstract spaces: continuous (Freedman et al., 2021 preprint) or discrete (Greulich et al., 2021). Mathematical properties (e.g. bifurcation theory) impose constraints on – to paraphrase Jacob (1982) – the possible and the actual in fate decision, with surprising accuracy (Rand et al., 2021). Such geometric models can be connected to more classical gene network-type formalisms (Exelby et al., 2021), including stochastic approaches (Coomer, Ham, and Stumpf, 2022). Even more abstract models of biological interactions suggest generic features, such as emergence of time-scales and differentiation in models of gene networks with epigenetic interactions (Matsushita et al., 2022). Finally, dynamical systems theory applied to development suggests and motivates new experiments that are tailored to the new questions arising, as recently illustrated for entrainment of the segmentation clock (Sanchez et al., 2022).

Low-dimensional descriptions also confirm the pioneer’s intuition to perform modelling on higher-level structures, now identified via clustering of gene expression. As we have just celebrated the 50 year anniversary of Anderson’s seminal paper on emergence (Anderson, 1972), this is not surprising: we know now from complex systems science that, on the one hand, precise descriptions of interactions between objects on a smaller scale (the ‘mechanisms’) do not necessarily illuminate higher-level principles but, on the other hand, different small-scale models can lead to the same higher-scale behaviour (Strogatz et al., 2022). An alternative theoretical strategy is to leverage the ever-increasing computational power to simulate interacting agents with the hope of capturing the correct emerging behaviours – an approach that has been particularly successful for capturing biomechanical effects with connections to statistical mechanics (Petridou et al., 2021). It is easy to envision how those approaches will scale up in the future (see, for

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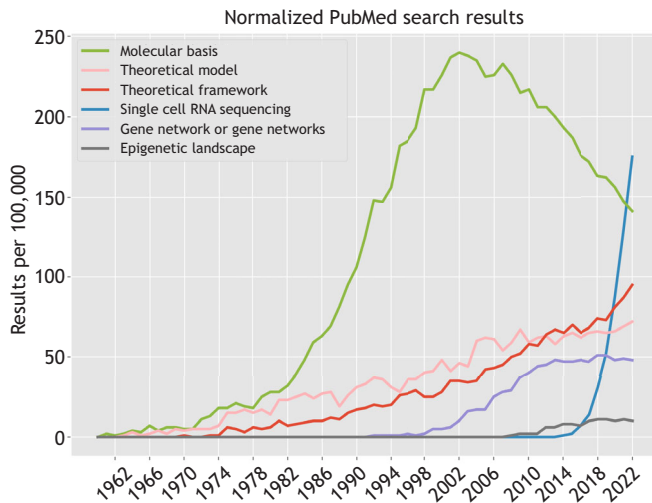


Fig. 1. Relative counts of PubMed search results by year for a few scientific terms. While ‘molecular basis’ peaked in the early 2000s, we can see a slow but steady increase of ‘theoretical model’ and ‘theoretical framework’. Plot data retrieved from PubMed using <http://esperr.github.io/pubmed-by-year/>.

example, combinations of mechanics and signalling by Uriu et al., 2021 or Romanos et al., 2021). Moving forward, machine learning offers a general lesson here. The ‘neural networks’ used in modern artificial intelligence are very crude approximations of biology, yet there is now little doubt that their interactions can perform computations/functions similar to those occurring in the brain. This provides an elegant illustration of the power of large-scale numerical simulations of semi-realistic agents. Nevertheless, we still do not know whether the actual ‘algorithms’ used by artificial neural networks are similar in any way to what happens in the brain, and similar questions will likely arise in complex models of developing systems. One of the challenges will be to find the right strategy (bottom-up versus top-down) and focus (genes, cells or tissues) to identify the most useful theory for developmental biology.

At *Development*, we are excited by theoretical approaches for developmental biology. As a journal that has always tried to embrace the latest advances, concepts and techniques available to our field, we encourage submissions of theoretical papers providing new insights and specific predictions to describe developing and regenerating systems, as well as studies combining both theory and experiments. We expect that the coming years will bring increasingly fruitful collaborations between theorists and experimentalists to shed further light on the underlying principles of development, and hope that *Development* will be seen as the obvious home for the publication of such studies. I was asked to join the *Development* team of editors a couple of years ago to signal our interest in this field, and other editors of the journal (including James Briscoe and Thomas Lecuit) also have expertise in this area – together, we encourage you to submit your latest research to the journal, and we look forward to handling your papers.

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