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OBITUARY

Obituary: Hans Meinhardt (1938–2016)

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Hans Meinhardt, a pioneer in mathematical biology, died on 11 February 2016 in Tübingen, Germany, after a short illness. He was born in 1938 and grew up in Mühlhausen in the former German Democratic Republic and in Cologne, in former West Germany. He received his Ph.D. in physics from the University of Cologne in 1966. For a number of years he worked on problems in physics and then in experimental biology. However, he found these areas unsatisfying for various reasons and so he decided to move into theoretical biology—a decision he never regretted. The possibility of contributing to the fundamental problem of how spatial structures emerge from apparently structure-less initial states was a challenge that most excited him, and he embraced it head-on for over 40 years.

Hans Meinhardt was one of the most influential mathematical biologists of his generation, and his research enriched both mathematics and biology. He is perhaps best known for his seminal paper with Alfred Gierer, entitled "A Theory of Biological

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Pattern Formation" published in 1972 (Gierer and Meinhardt 1972).[1] In one space dimension the Gierer–Meinhardt model takes the form

$$
\begin{aligned}
\frac{\partial a(x,t)}{\partial t} &= \rho_0 \rho + \frac{c\rho (a(x,t))^2}{h(x,t)\left(1+\kappa (a(x,t))^2\right)} - \mu a(x,t) + D_a \frac{\partial^2 a(x,t)}{\partial x^2}, \\
\frac{\partial h(x,t)}{\partial t} &= c' \rho' (a(x,t))^2 - \nu h(x,t) + D_h \frac{\partial^2 h(x,t)}{\partial x^2},
\end{aligned} \tag{1}
$$

where $a(x,t)$ and $h(x,t)$ are concentrations of activator and inhibitor, respectively, at time t and position x, D_a, D_h, ρ_0, c, c' and κ are positive constants, while ρ, ρ', μ and ν could be functions of x representing spatially non-uniform distributions of sources and sinks.[2] Computer simulations in the paper showed how this model could enhance initial shallow graded distributions into very steep gradients, or into self-organised periodic spatial patterns. Furthermore, it was demonstrated that the model could explain size regulation and account for experimental results related to body plan, development and regeneration of the biological model system Hydra. The model is now a textbook example used to teach undergraduate and graduate students in mathematics the patterning principle of *short-range activation and long-range inhibition* (Murray 2003; Edelstein-Keshet 2005).

Twenty years earlier—in a paper largely unknown in biological circles—Alan Turing (Turing 1952) demonstrated that the interaction of reaction and diffusion can produce instability of a uniform steady state and lead to self-organised spatial pattern formation. Turing's investigation, which was motivated by patterns observed in various biological organisms, revealed conditions under which a uniform steady state of a reaction–diffusion system can be destabilised by diffusion and evolve to a new, spatially heterogeneous, state. Unaware of Turing's work, Meinhardt asked from a biological perspective: how can a biological structure such as a plant leaf or a hydra head suppress the formation of a similar structure in its neighbourhood without inhibiting itself, being in the centre of this inhibition? He could show that if lateral inhibition is complemented by a nonlinear local self-enhancement, both components together make a uniform distribution unstable and a new self-regulating patterned steady state is reached when the self-enhancing reaction has attained an equilibrium with the long-ranging antagonistic component (Fig. 1). This mechanistic insight concerning the effect of *short-range activation and long-range inhibition* reflects Turing's mathematical instability criterion, and enabled Meinhardt to propose appropriate nonlinear reaction schemes and interactions that can explain biochemical processes and cellular properties.

Somewhat earlier Wolpert (1969) suggested that pattern formation results from positional information available to cells, and while different in detail, the insights of Turing, Wolpert and Meinhardt on the importance of the interaction of reaction and transport in pattern formation have led to a paradigm shift in how biologists think about pattern formation in developmental biology. This shift is due in part to Mein-

[1] Cited 1494 times according to Web of Science as of 2 November 2016.

[2] Inhibitor is "Hemmstoff" in German, and therefore is represented by h.

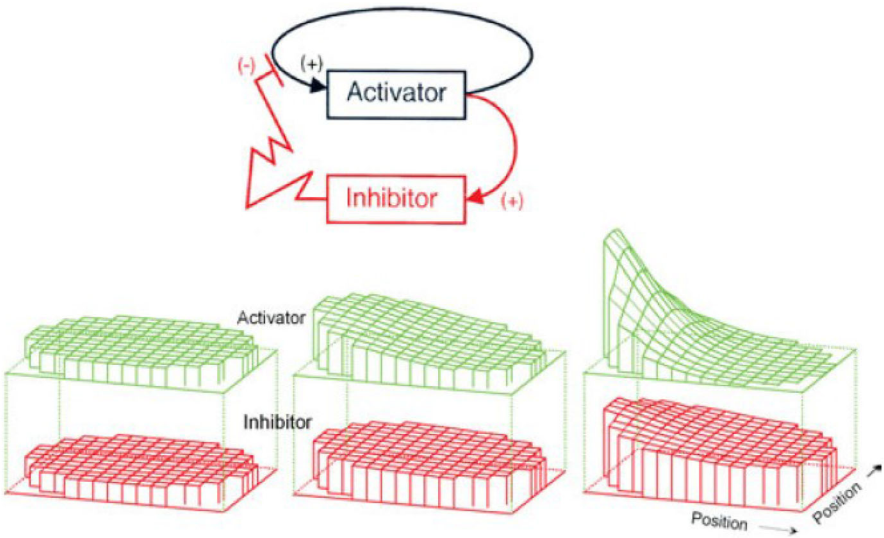

Fig. 1 The interaction of a short-range autocatalytic activator with a long-range inhibitor can lead to stable patterns in space (drawing and simulation by Hans Meinhardt, reproduced, with permission, from Gordon and Beloussov 2006)

hardt's strong advocacy of the underlying principles and long-standing interaction with experimental biologists. His influence in that community is reflected in the fact that two obituaries were published in major biological journals shortly after his death (Roth 2016; Müller and Nüsslein-Volhard 2016).

While the original Gierer–Meinhardt paper was mainly concerned with the formation and regulation of patterns in Hydra, Meinhardt went on to apply the concept of *short-range activation and long-range inhibition* to a vast array of biological problems. His 1982 book "Models of Biological Pattern Formation" (Meinhardt 1982) sets out to describe grand challenges in biological development and presents solutions in the form of computer simulations of mathematical models long before detailed comparisons with experiments became possible. Examples include the aforementioned Hydra, the leaf-hopper embryo *Euscelis*, vertebrate limb development, biochemical switches, molecular control of gene activation, compartment formation in wings, somitogenesis, net-like structures (including branching patterns on plant leaves and tumour angiogenesis). Moreover, the examples in the book go beyond applications of activator–inhibitor models. In particular, his boundary induction mechanism provides an explanation for aspects of the polar coordinate model (French et al. 1976).

As illustrated in the 1982 book, Meinhardt worked to cast a broad range of biological phenomena within the framework of the activator–inhibitor organising principle. It can be argued that he pushed this idea too hard at times, since it is difficult to provide mechanistic details in many of the examples cited. Moreover, there were setbacks, such as the discovery of the periodic expression patterning of pair-rule genes in *Drosophila* embryogenesis which seemed tailor-made for an application of a self-organising pattern generator, but was shown not to be based on this mechanism (Akam

1989). However, it is important to remember the quote of George Box that "All models are wrong, but some are useful" (Box 1979) and if a theoretical model can change the way people think or suggest experiments that may not have otherwise been done, then the model has played an important role in pushing forward theory. In fact, in the preface to his 1982 book, Meinhardt himself says "I hope that these theories will provide a framework for further experimental investigations and create insights which will facilitate future biochemical studies. Discrepancies between these theories and these future experimental results will lead to modifications and refinements of the theories and, hence, will focus new experiments". This echoes John Bonner's "We have arrived at the stage where models are useful to suggest experiments, and the facts of the experiments in turn lead to new and improved models that suggest new experiments. By this rocking back and forth between the reality of experimental facts and the dream world of hypotheses, we can move slowly toward a satisfactory solution of the major problems of developmental biology" (Bonner 1974).

In 1995 Meinhardt published his second, beautifully produced, aesthetically appealing and prize-winning book, "The Algorithmic Beauty of Sea Shells" (Meinhardt 1995) which investigates pigmentation patterns on tropical shells. The book came with a diskette so that the readers can generate their own patterns. In the preface Meinhardt states, "My interest in these patterns began with a dinner in an Italian restaurant. In the meal I found a shell with a pattern consisting of red lines arranged like nested W's". Triggered by the intermittent W's, he solved apparently all known shell patterns by the new idea of combining model modules, where each module is responsible for a particular phenomenon, for example, periodic patterns, oscillations or travelling waves. He later applied this modularization idea to dynamic phenomena, such as cell division in *Escherichia coli* and cortical polarisation of chemotactic cells and growth cones (Meinhardt 1999; Meinhardt and de Boer 2001). There are alternative theories for the pigmentation patterns on shells which hypothesise different underlying biological mechanisms, leading to different mathematical formulations (see, for example, Gong et al. 2012). The jury is still out as to what is the actual mechanism.

The Gierer–Meinhardt model has also fascinated mathematicians, who were particularly struck by the "spiky" localised nature of the periodic spatial patterns it produced. Limiting cases of the model and various simplifications have been studied in detail numerically (Harrison and Holloway 1995), while the existence of k-spike equilibrium solutions was proved in Takagi (1986) and their stability properties investigated in Iron et al. (2001). Wei and Winter (2001) proved existence and stability of multi-peaked patterns for the singularly perturbed system in two dimensions, while a differential-algebraic system of coupled ordinary differential equations was derived by Iron and Ward (2002) for the evolution of the centres of the spikes together with criteria to predict their collapse. This approach was extended in Ward et al. (2002) using the method of matched asymptotic expansions to generalise the results.

Hans Meinhardt worked at a time when there was very little spatio-temporal data available to validate his models, but this did not deter him from strongly putting forward his ideas. He was naturally delighted when many years later some of his predictions were experimentally validated. For example, somitogenesis is a process in which cell aggregates (somites) form in a temporal sequence from head to tail along the body axis. Meinhardt presented a model that predicted, counter-intuitively, that this was the result of a wave moving in the opposite direction (Meinhardt 1982), and this was shown to be true experimentally many years later (Palmeirim et al. 1997).

Meinhardt had the ability to identify grand challenges in developmental biology and bring them to the attention of the mathematical biology and the biology communities. These were problems that were biologically important, exhibited behaviour that could not be understood by experiments alone, were deceptively easy to formulate, and computationally (and in some cases also mathematically) tractable. He was not a mathematician but he had an uncanny sense of how interactions needed to be set up to form the structures observed. He then used computer simulations to verify his intuition. He was deeply immersed in the biology to make sure that his models were relevant. He was also far ahead of his time in terms of making his work electronically available. Long before the calls for open repositories, he set up a didactic website showcasing his work in a very user-friendly way (http://www.eb.tuebingen.mpg.de/research/emeriti/hans-meinhardt.html).[3] The models and simulations on this website can be seen as pioneering model repository and open source simulation.

Meinhardt was truly a pioneer who, while fully aware that many biologists did not support the modelling approach he championed (Gordon and Beloussov 2006), was not discouraged and continued to strongly advocate his viewpoints, eventually converting some biologists to adopt his ideas. In this era of "big" science with large groups, he showed how effectively a single scientist could change a paradigm.

Hans Meinhardt loved travelling with his wife, and he loved the desert, but he was similarly fascinated by the local nature around him, discovering new facets in his garden and gaining inspiration from self-taken photographs for his scientific questions. He loved his work and on finding a shell shop on a tourist walk with one of the authors of this piece, he took great delight in picking up each shell and explaining how the patterns on it formed. He presented his work as invited speaker all over the world, not only at major biological conferences but also at summer schools which encouraged the next generations of scientists.

In 2003, Meinhardt was awarded the Cornelia-Harte Prize for his outstanding contributions to the modelling and computer-assisted simulations of dynamic pattern formation processes in developmental biology by the German Society for Developmental Biology.

Up to his death, Hans Meinhardt had many future plans: his dream was to publish a third book, presenting the quantitative molecular mechanisms underlying the qualitative organisation principles predicted in his 1982 book. This plan remained, regrettably, unfinished.

On hearing the sad news of Hans' passing, Professor Shigeru Kondo (Osaka, Japan) expressed in an email "we can only hope that Hans Meinhardt meets Alan Turing in heaven to create another theory". The scientific community misses his creativity, intuition, humour and humanity. He leaves his wife Edeltraud and his two sons Christoph and Martin.

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[3] This website allows also open access to his 1982 book.

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