

The Source-Sink Model

The source-sink model, first proposed by biologist Francis Crick in 1970, is a theoretical system for how morphogens distribute themselves across small fields of early embryonic cells. A morphogen is a substance that determines the fate and phenotype of a group of cells through a concentration gradient of itself across that group. Crick's theory has been experimentally confirmed with several morphogens, most notably with the protein bicoid, the first discovered morphogen. The model provides a theoretical structure for the understanding of some features of early embryonic development.

In 1901, Thomas Hunt Morgan, then working at Bryn Mawr College in Lower Merion Township, Pennsylvania, hypothesized that what he called a sort of stuff acted at different concentrations to organize regeneration in hydroids, planaria, and annelids. Four decades later in 1941, Charles Manning Child of Stanford University in Palo Alto, California, proposed his Gradient Theory, arguing that varying levels of embryonic processes was due to a gradient of metabolic activity. Yet it wasn't until 1952 that Alan Turing, a mathematician at University of Manchester in Manchester, United Kingdom, defined Morgan's idea of a sort of stuff as a morphogen. In Turing's paper, "The Chemical Basis of Morphogenesis," he defined a morphogen as a molecular substance in the embryo that diffused between cells and, at certain concentrations, directed the embryo's development. Yet as Crick noted in 1970, despite this foundational work by Morgan, Child, and Turing, morphogens and gradients were unpopular among embryologists. Unable to isolate any potential morphogenic molecules, research on morphogens stalled by the 1960s.

In 1969, when embryologist Lewis Wolpert, based out of the Middlesex Hospital Medical School in London, England, published "Positional Information and the Spatial Pattern of Cellular Differentiation," the concept of morphogens began a revival of interest. Wolpert proposed that embryonic cells create highly specific patterns of cellular differentiation in the embryo through the communication of positional information. Positional information, a term coined by Wolpert, is a form of intercellular communication that instructs each cell to differentiate according to its orientation within the embryo. Positional information, Wolpert argued, hinged on several key principles. First, positional information in a group of cells may be established by each cell's position relative to one or more points. A group of cells specified by relation to a common point is called a field. Second, individual cells in a field can interpret their position and react accordingly via molecular mechanisms. Third, a field of cells has an established polarity, as defined by the direction of flow of positional information. Thus, polarized cells exist in a unidirectional gradient. Instructions, perhaps chemically communicated, exist in concentration gradients across the field of cells. At different concentrations cells are stimulated in such a way to establish the fate of future their differentiation, presumably by the activation of particular genes. Wolpert asserted that such a system would only operate across small distances, often around fifty to one-hundred cells.

Wolpert's work received a hostile reception in the United States, with critics arguing that molecular diffusion could neither be as precise, nor rapid enough to explain the pace of morphogenesis. However, Wolpert's claim that morphogens operate over small distances piqued the interest of a close friend of Wolpert, Francis Crick, who worked at the University of Cambridge in Cambridge, England. Coming to his friend's assistance, Crick authored the 1970 publication, "Diffusion in Embryogenesis". The paper, making use of mathematical models of diffusion, posited that simple diffusion could establish a reliable gradient across a line of cells. While Crick recognized that an embryo has three dimensions, a model of diffusion could be reduced to one without sacrificing conceptual or spatial information. At one end of the line of cells, a cell would initiate and maintain production of a morphogen, termed the source. At the other end, the farthest cell would be the sink, or

rather it would destroy the morphogen or be unable to respond to it at a low concentration. Crick used prevalent and empirical data to obtain realistic estimates of variables such as cytoplasmic viscosity, cellular diameter, morphogen size, and membrane permeability. Crick mathematically demonstrated that a morphogen, produced at the source, could readily diffuse across the line of cells through the random molecular movement. Significantly, Crick obtained measurements of the time required to establish a gradient, and distance over which that gradient could be maintained, consistent with that of Wolpert's model. Although Wolpert did not connect positional information to morphogens, Crick linked the two in part because diffusion of morphogens offered the simplest mechanistic explanation of how positional information transmits during morphogenesis.

In 1988 Christiane Nüsslein-Volhard, the director of the Max Planck Institute for Molecular Biology in Tübingen, Germany, identified the protein bicoid as the first proven morphogen. Bicoid is a protein in fruit flies of the genus *Drosophila* and is instrumental in early embryonic development. Shortly after a fly lays an egg, bicoid becomes highly concentrated in the anterior cytoplasm of the egg and quickly extends to over 60 percent of the embryo. The gradient of bicoid drops sharply by several orders of magnitude towards the posterior of the embryo. Nüsslein-Volhard and her graduate student Wolfgang Driever showed that the bicoid gradient partly confirms the source-sink model, both in the way that the protein gradient is established at a specific embryonic location, and in the short time period the gradient is established. The key difference between Crick's model and the bicoid gradient, however, is that there is no specific sink, rather the concentration degrades generally across the field. The discovery of bicoid marked the first empirical instance of a widely debated concept nearly ninety years old.

Crick's 1970 source-sink model established that morphogens need not rely on complex molecular mechanisms of transport. Today, however, more detailed understanding of intercellular signaling and molecular mechanisms have overshadowed the source-sink model's mechanism of simple diffusion. While simple diffusion has been observed in morphogens such as fibroblast growth factor 8 (fgf8), Wolpert has said that he now considers simple diffusion too messy as a model.

Sources

1. Child, Charles M. *Patterns and Problems of Development*. Chicago: University of Chicago Press, 1941. <http://www.biodiversitylibrary.org/item/28806> (Accessed May 6, 2012).
2. Crick, Francis H. C. "Diffusion in Embryogenesis." *Nature* 225 (1970): 420-2
3. Driever, Wolfgang., and Christiane Nüsslein-Volhard. "A Gradient of Bicoid Protein in *Drosophila* Embryos." *Cell* 54 (1988): 83-93.
4. Driever, Wolfgang, and Christiane Nüsslein-Volhard. "The Bicoid Protein Determines Position in the *Drosophila* Embryo in a Concentration-Dependent Manner." *Cell* 54 (1988): 95-104.
5. Drocco, Jeffrey Alfred. "Biophysical Studies of Morphogen Gradient Formation in *Drosophila melanogaster*." PhD diss., Princeton University, 2011.
6. Grimm, Oliver, Mathieu Coppey, and Eric Wieschaus. "Modeling the Bicoid Gradient." *Development* 137 (2010): 2253-64.
7. Morgan, Thomas Hunt. *Regeneration*. New York: Macmillan, 1901. <http://books.google.com/books?id=T4rPAAAAMAAJ> (Accessed May 6, 2012).
8. Richardson, Michael K. "Diffusible Gradients Are Out - an Interview with Lewis Wolpert." *International Journal of Developmental Biology* 53 (2009): 659-62.
9. Schier, Alexander F., and Daniel Needleman. "Rise of the Source-Sink Model." *Nature* 461 (2009): 480-1.
10. Turing, Alan M. "The Chemical Basis of Morphogenesis." *Philosophical Transactions of the Royal Society of London Series B—Biological Sciences* 237 (1952): 37-72.
11. Wolpert, Lewis. "Positional Information and the Spatial Pattern of Cellular Differentiation." *Journal of Theoretical Biology* 25 (1969): 1-47.
12. Yu, Shuizi Rachel, and Markus Burkhardt. "Fgf8 Morphogen Gradient Forms by a Source-Sink Mechanism with Freely Diffusing Molecules." *Nature* 461 (2009): 533-6.