

The Source-Sink Model ^[1]

By: Resnik, Jack Keywords: [Morphogenesis](#) ^[2] [Differentiation](#) ^[3]

The source-sink model, first proposed by biologist [Francis Crick](#) ^[5] in 1970, is a theoretical system for how [morphogens](#) ^[6] 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](#) ^[6], most notably with the protein [bicoid](#) ^[7], 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](#) ^[8], then working at [Bryn Mawr College](#) ^[9] in Lower Merion Township, Pennsylvania, hypothesized that what he called a sort of stuff acted at different concentrations to organize regeneration in [hydroids](#) ^[10], [planaria](#) ^[11], and annelids. Four decades later in 1941, [Charles Manning Child](#) ^[12] of [Stanford University](#) ^[13] 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](#)" ^[14], 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](#) ^[6] and gradients were unpopular among embryologists. Unable to isolate any potential morphogenic molecules, research on [morphogens](#) ^[6] stalled by the 1960s.

In 1969, when embryologist [Lewis Wolpert](#) ^[15], based out of the [Middlesex Hospital Medical School](#) ^[16] in London, England, published "Positional Information and the Spatial Pattern of Cellular Differentiation," the concept of [morphogens](#) ^[6] began a revival of interest. Wolpert proposed that embryonic cells create highly specific patterns of cellular [differentiation](#) ^[17] in the embryo through the communication of [positional information](#) ^[18]. 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](#) ^[18] 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](#) ^[19], as defined by the direction of flow of [positional information](#) ^[18]. 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](#) ^[17], presumably by the activation of particular [genes](#) ^[20]. 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](#) ^[6] operate over small distances piqued the interest of a close friend of Wolpert, [Francis Crick](#) ^[5], 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](#) ^[18] to [morphogens](#) ^[6], Crick linked the two in part because diffusion of [morphogens](#) ^[6] offered the simplest mechanistic explanation of how [positional information](#) ^[18] transmits during morphogenesis.

In 1988 [Christiane Nüsslein-Volhard](#) ^[21], the director of the [Max Planck Institute for Molecular Biology](#) ^[22] in Tübingen, Germany, identified the protein [bicoid](#) ^[7] as the first proven morphogen. Bicoid is a protein in fruit flies of the genus [Drosophila](#) ^[23] and is instrumental in early embryonic development. Shortly after a fly lays an [egg](#) ^[24], [bicoid](#) ^[7] becomes highly concentrated in the anterior cytoplasm of the [egg](#) ^[24] and quickly extends to over 60 percent of the embryo. The gradient of [bicoid](#) ^[7] drops sharply by several orders of magnitude towards the posterior of the embryo. Nüsslein-Volhard and her graduate student [Wolfgang Driever](#) ^[25] showed that the [bicoid](#) ^[7] 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](#)^[7] gradient, however, is that there is no specific sink, rather the concentration degrades generally across the field. The discovery of [bicoid](#)^[7] marked the first empirical instance of a widely debated concept nearly ninety years old.

Crick's 1970 source-sink model established that [morphogens](#)^[6] 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](#)^[6] such as [fibroblast growth factor 8](#)^[26] (fgf8), Wolpert has said that he now considers simple diffusion too messy as a model.

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