What has been your biggest mistake in research? Despite my rant about the importance of risk, I'm not sure that I've taken risks on sufficiently important problems to make really big mistakes. I definitely worry that future studies will show that I've made major misinterpretations of results. For example, several colleagues and I recently showed that the spatial extent of functional magnetic resonance imaging (fMRI) activity in human primary visual cortex varies with the *perceived* size of an object, even with retinal image size held constant. This really surprised us. Our interpretation is that primary visual cortex gets depth information from higher-level visual areas through feedback as part of a neural computation of physical object size. This is significant if true, but the BOLD signal measured by fMRI is a coarse-grained and distant proxy for neural activity.

Do you have a scientific hero? Several. In computational neuroscience and vision it is Horace Barlow. And I've always been drawn to physicists for inspiration, in particular Richard Feynman and Clerk Maxwell. Both were interested in visual perception. Even English majors should read volume one of Feynman's lectures on physics. To deduce the laws of colour trichromacy, Maxwell and his wife did psychophysics experiments on human subjects in their London home — how cool is that? And without human subject approvals! But when times do get tough, consider Kepler, who in the midst of the 30 Years War and the Counter-Reformation, suffered the death of several children, the witchcraft trial of his mother, and forced moves from town to town, yet through it all still managed to write '*The Harmony of the World*'.

What do you think are the big questions to be answered in your field? I'm just one of many interested in this one, but I'd like to understand the computational function of the feedforward, feedback and lateral connections in cortex, especially between and within the multiple visual areas. It's a tall order. A promising idea, traceable at least to the 1950s, is that feedback is the synthesis or predictive component of the analysis-by-synthesis of sensory information. Edge detection may provide some insight. Simulations of feedforward networks using models of neurons in primary visual cortex have failed to explain the accuracy of human perception of object boundaries.

A promising direction in computer vision is to use prior scene and object knowledge represented as structured probability distributions to tease apart true edges from the false ones. But we are far from understanding how such solutions could get fleshed out in neural circuits. A link may be in recent work proposing that neural populations encode probability distributions. So the so-called edge detectors in primary visual cortex really don't make detection decisions, but rather provide probability-weighted 'suggestions' that get combined with prior statistical knowledge about possible shapes of objects. If we can understand how the visual system provides us with the phenomenally crisp, and in fact illusory perception of boundaries around objects, maybe we'd be closer to understanding the computational role of cortical interactions in general. But that's just a guess.

How did you end up in Minnesota — isn't it cold there? I went to Minnesota in 1976 for graduate work in mathematics. I had just gotten married, and my wife was teaching in Minneapolis. During the first year, I became increasingly interested in perception, and decided to study vision with Gordon Legge in Psychology. It was perhaps another positive aspect of my graduate imprinting, but after several interim years at Cambridge and then Brown, I returned to join the Minnesota faculty in 1989. It was a good move. I have great students and superb colleagues, many in vision science. And in the words of local storyteller Garrison Keillor, it is a place where all the women are strong, all the men are good-looking, and all the children are above average. And yes it does get cold in Minnesota.

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Quick guide

Entosis

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What is entosis? Entosis is a process whereby cells become internalized into neighboring cells, forming what are called 'cell-in-cell' structures (Figure 1A).

What is known about how these cells within cells form? Cell–cell contacts are important, as E-cadherin localizes to regions where one cell is entering another, and blocking E-cadherin inhibits cell-in-cell formation. In addition, contractile force, associated with adherens junction formation, is important for driving entosis. Rho GTPase activity is required in the cell that becomes internalized, suggesting that it may 'invade' into its neighbor. The only known inducer of entosis is matrix detachment in culture. Matrix adhesion, which counterbalances cell–cell adhesion, may normally inhibit entosis, and cell-in-cell formation might result from imbalances in contractile forces. Cell-in-cell structures can be formed homotypically, between the same cell type, or heterotypically between different cell types. Heterotypic cell-in-cell structures, for example between hematopoietic cells and epithelial cells or tumor cells, are likely to form by different mechanisms.

Can all cells undergo entosis? Entosis has been observed in many cell lines at varying frequencies, including breast epithelial cells (MCF10A, HMEC), breast carcinoma cells (MCF7, SUM52, SUM225), and human embryonic kidney cells (HEK293). Entosis has also been observed in primary human breast tumors.

What happens to the internalized cell? Surprisingly, internalized cells initially appear healthy and viable, some even divide while inside of the host. However, whether they experience any kind of stress is not known. Over a period of 20 hours, some internalized cells are able to escape (~20%), but most cells die (~50%) (Figure 1B).

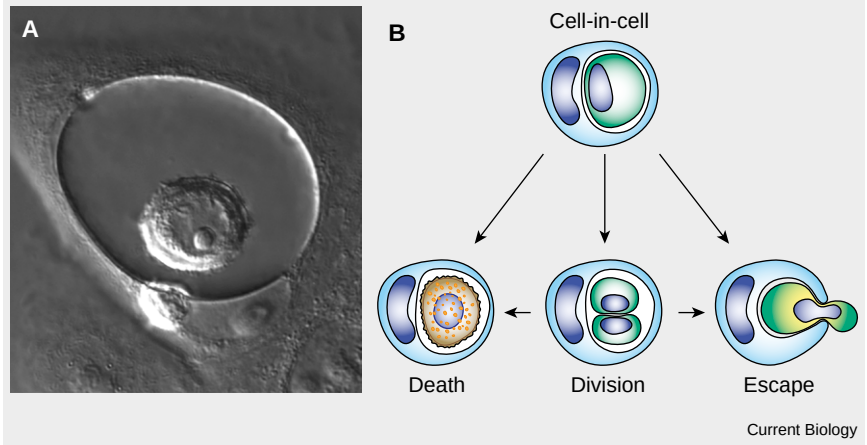

Figure 1. Formation of cells within cells by entosis.
(A) A viable cell is internalized completely inside of another, forming a cell-in-cell structure (DIC image). The depicted cells are human mammary epithelial cells (MCF10A). (B) The fates of cells after entotic internalization.

How do these cells die? They perish through a specialized form of cell death that lacks hallmarks of apoptosis, as dying cells are negative for cleaved caspase-3, and do not exhibit condensed or fragmented nuclei. Instead, LAMP1, a lysosomal membrane protein, localizes around dying cells and acidification occurs at the earliest stages of death, suggesting lysosomal involvement.

How does entosis differ from other types of cell engulfment? Entosis should not be confused with phagocytosis, where dead, dying or pathogenic cells are engulfed. Phagocytosis is driven by cytoskeletal rearrangements within the host cell in response to signals given off by the target cell. In entosis, cells can be found inside apparently non-phagocytic hosts and are internalized as viable cells. Also, the internalized cell appears to play a much more active role. Entosis thus more resembles parasite or pathogen cell invasion, or the process of leukocyte transcellular migration.

***Is entosis seen* in vivo?** Reports of cells within cells date back to the early 1900s. Most homotypic cell-in-cell structures are reported in human tumors. They are frequently found in exudates that contain metastatic carcinoma cells, or tumor samples harvested from urine. These fluid environments correspond to the *in vitro* conditions of matrix deprivation that promote entosis. The striking similarity to entotic structures suggests that entosis underlies the formation of cell-in-cell structures in many different tumors. Cell-in-cell structures have also been found in solid tumors. It is not known whether entosis is strictly a feature of tumor cells, or whether the process also occurs between normal cells in the body.

How might entosis affect a tumor? As the main outcome of entosis is death of the internalized cell, it may represent a novel mechanism for eliminating cells outside of their normal microenvironment. This idea is supported by the observation that suppression of entosis, via inhibition of ROCK activity, increases anchorage-independent growth of cancer cells. However, this process is complex and the possible effects of entosis on tumor progression are currently under investigation.

Where can I find out more?

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Primer

Extracellular regulation of BMP signaling

Lise Zakin and E.M. De Robertis*

In the developing organism, cells differentiate, divide and die as part of groups of hundreds or thousands of cells called ‘morphogenetic fields’. Fields have the remarkable property of self-regulation: for example, if the forelimb field is bisected, each half can give rise to a complete limb after transplantation, as discovered by Ross Harrison in 1918. Therefore, cells in the morphogenetic field are capable of long-range communication with each other in order to ascertain their position [1]. This positional information is relayed in the extracellular space in the form of concentration gradients of specific classes of extracellular molecules called ‘morphogens’ that trigger cellular responses by binding and activating cell surface receptors. Here, we focus on a family of morphogens called ‘Bone Morphogenetic Proteins’ (BMPs), which has provided a new paradigm for signaling regulation in the extracellular space.

BMPs were discovered by Marshall Urist in 1965, who found that decalcified bone matrix fragments had bone-inducing activity when transplanted subcutaneously or intramuscularly into rats or rabbits. This activity was then solubilized and purified by Hari Reddi in 1981, and in 1988 BMP2–7 were cloned [2]. BMPs belong to the Transforming Growth Factor β (TGF-β) superfamily, the most numerous group of growth factors in humans. During development, BMPs have been shown to participate in many signaling processes, including organogenesis, tissue type differentiation and dorsal-ventral patterning. In humans, altered BMP signaling is associated with cancer, skeletal and vascular diseases.

Binding of BMPs to cell membrane BMP receptors causes the phosphorylation and activation of transcription factors called ‘Smad1/5/8’ inside the cell. The