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Feature
Points of View: What Are the Key Concepts in Developmental Biology?

Note from the Editor

Points of View (POV) address issues faced by many people within the life science education community. CBE—Life Sciences Education *(*CBE-LSE*) publishes the POV Feature to present two or more opinions published side-by-side on a common topic. We consider POVs to be "Op-Ed" pieces designed to stimulate thought and dialogue on significant educational issues. They are not meant to be exhaustive treatments of a subject.*

In this issue, we ask the question, "What are key concepts in developmental biology?" We present three POVs. The first is by CBE-LSE *Editor-in-Chief, William Wood, and it is in part based on his experience teaching developmental biology to undergraduates at the University of Colorado, Boulder, including his collaborative experiments in the classroom with Jennifer Knight, the first results of which have been published in* CBE-LSE *(Knight and Wood, 2005). The second, a partially tongue-in-cheek list of key concepts to convey to students about embryonic development, is by Scott Gilbert (Swarthmore College), author of the leading textbook worldwide for teaching developmental biology,* Developmental Biology*, 8th ed. (Sinauer Associates, Inc.). The third is by Jeff Hardin (University of Wisconsin–Madison), who has produced Web-based educational materials for teaching developmental biology that are used nationally and internationally for conveying dynamic events during early development (see the WWW feature in this issue by Stark for more details), and who deals with the vexing problem of trying to convey the essential four-dimensional nature of embryonic development to introductory students.*

Teaching Concepts Versus Facts in Developmental Biology

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In our teaching of undergraduate life sciences courses, we are admonished to place more emphasis on concepts over facts, conceptual understanding over memorization of details. But understanding the biology of development requires extensive knowledge of facts as well as concepts, and sometimes it seems hard to distinguish which is which. What do we mean by a concept? According to the Concise Oxford English Dictionary, a concept is

> 1. an abstract idea. (origin: Latin *conceptum*, something conceived).

Merriam-Webster defines a concept as

> 1. something conceived in the mind: thought, notion.
> 2. an abstract or generic idea generalized from particular instances.

Over both of these, I prefer a more operational definition from physicist-educator Carl Wieman: *A concept is an idea that can be applied in multiple contexts to explain and/or predict outcomes*. The conceptual understanding we want to help our students attain then becomes simply the ability to apply an idea in multiple contexts to explain and/or predict outcomes. The kinds of applications we want our students to be capable of can range from lower to higher levels of Bloom's taxonomy (Bloom *et al*., 1956; Allen and Tanner, 2002), depending on our learning goals.

But some of the facts we teach in developmental biology (and other life sciences) can also be viewed as concepts. What is the difference? I'll come back to that question at the end of this essay. First, let's look at an example of the perceived concept/fact dichotomy.

One of our assignments from the editor for this POV was to explain a favorite developmental concept and why we feel it is centrally important. One of mine is the concept of combinatorial control. Probably, I find it so compelling because I encountered it as a revelation of how development, which had earlier seemed largely mysterious, could actually work. I grew up intellectually as a bacterial and bacteriophage molecular geneticist, who turned to developmental biology in mid-career and began teaching it in the late 1970s. It was impossible to understand how development worked with the molecular biology of the day. A turning point for me came when Keith Yamamoto, visiting Boulder in the early 1980s for a departmental seminar, presented us with his evidence that the same transcription factor could repress a reporter gene in one mammalian cell type and activate the same reporter gene in another cell type. This was clearly not simply an elaboration on the *lac* operon, but something quite

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different! The action of a transcriptional regulatory component must depend on other factors in its cellular environment, that is, on the past history of the cell. Later, elaboration of signaling pathways and their effects on gene expression told us the nature of some of these factors. Moreover, we learned that signaling works in the same combinatorial way: responses of different cells to a signal depend on the signaling pathway components already present in each cell's plasma membrane, cytoplasm, and nucleus. And to complete the story, signaling controlled many of the transcription factors that regulated transcription!

The picture of development that emerged from this story was beautiful and understandable. But when we describe in our classes or our textbooks all the possible levels at which development is regulated, via expression of thousands of genes, each controlled by multiple inhibitory and activating cell-type–specific transcription and posttranscription RNA-processing factors, many of which are activated or inactivated by multicomponent signaling pathways, which can in turn be modulated by multiplexing with other signals, and so on, students can be overwhelmed by the seemingly infinite types and variations of developmental regulatory controls. Amid this monstrous complexity, they may miss the simple idea that makes sense of it all: the principle of combinatorial control.

The concept of combinatorial control may be stated as follows:

> How a cell behaves in response to an autonomous determinant or an external signal depends on the *combination* of transcriptional and posttranscriptional regulators, signaling pathway components, cytoskeletal elements, and other proteins and RNAs that it has synthesized earlier: i.e., on its developmental history.

But isn't that a fact? It's a factual statement. But it's also an important concept, an idea that can be applied in multiple contexts to understand and predict outcomes.

The underlying details are more specific facts, but many of these include important smaller subconcepts:

> There are multiple DNA response elements in the vicinity of each developmentally regulated gene. These interact with multiple protein transcription factors (TFs), which can positively or negatively affect transcription rate. The TFs can also interact with each other, positively or negatively, to control the overall transcriptional effect. The action of the TFs can in turn be regulated positively or negatively by effector proteins activated or inactivated by often multiplexed signaling pathways, and so on, and so on, into the jungle of complexity alluded to above.

These statements are more factual than conceptual. But without knowledge of some facts, students may find the concept of combinatorial control somewhat meaningless. So which should be learned first, the general concept or the specific underlying facts? Analyses of learning styles (e.g., Felder, 1993) have revealed two distinct groups of learners: those who prefer to learn the facts first and then have the simplifying generalizations emerge as they go along, and those who prefer to begin with an overarching concept on which they can hang specific facts as they are encountered. As a teacher, I believe strongly that the best way to accommodate both groups is to go back and forth between facts and the relevant concept as the course progresses.

In our development course, we introduce the concept of combinatorial control near the beginning, after reviewing developmentally relevant aspects of gene regulation. We tell our students that we consider it centrally important, and that quite often, when we throw out a question to the class, the answer will be "combinatorial control." Then, as examples of signaling and gene regulation come up in various contexts during the course, we will ask the class, "What is this an example of?" After a few weeks of this, we start to get choral responses of "combinatorial control!" in unison! It becomes a course joke, but students do incorporate the concept into their thinking and seem to remember it, at least through the final exam!

So, what's the real distinction between the facts and the concept? Is this just an unimportant semantic question? I don't think so. But the answer cannot be found in the statements themselves. Instead, we have to go back to Wieman's operational definition, and consider how students are being asked to use the information they learn in our courses. If the question on our final exam is "define the term combinatorial control," we are asking students simply to memorize the statement we gave them. This is the lowest Bloom's level of understanding, and in fact students can get a perfect score on the question without understanding the statement conceptually at all. Conversely, if we ask them to explain at the molecular level how two different cell types in the same tissue can respond differently to the same hormonal signal, or to predict the types of proteins that, for example, a mammary gland cell must have produced during development to increase the steady-state level of casein mRNA in response to prolactin, they will have to apply the principle of combinatorial control to an unfamiliar situation, requiring a deeper understanding of the concept. So whether ideas in developmental biology are learned as factual or conceptual depends partly on how we and our textbooks present them and on how students study them; but most of all, it depends on how we formulate our course learning goals and our homework and exam questions, in terms of factual recall versus application of concepts. Needless to say, I strongly urge less of the former and more of the latter!

ACKNOWLEDGMENTS

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All I Really Needed to Know I Learned during Gastrulation

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Note from the Editor

This list of key principles in animal development was presented as "life lessons" at the Society for Developmental Biology national meeting in 2005, and it has been edited somewhat for inclusion here. For the video presentation, visit http://sdbonline.org/fly/gilbert/gilbert01.htm.

Are there principles of development that can be derived from specific examples? Alexander Kowalevsky predicted that such principles would be found, and his motto became "*In specialibus generalia quaerimus*" ("We seek the general in the specifics"). I think that we may have enough specifics about animal development so that some generalities can be made. In the United States, there was a best-selling book by Robert Fulghum, entitled *All I Really Need to Know I Learned in Kindergarten* (Fulghum, 1988). I would postulate that kindergarten is actually a late stage of education and that "All I Really Need to Know I Learned during Gastrulation." So, here is my list of developmental principles.

1. One's fate is determined by how much one listens to mother versus how much one listens to neighbors (Bard, 1997). Thus, as philosopher W.V.O. Quine said, "To be is to be a value of a variable." A cell is given pluripotency. Its interactions and heritage determine its destiny.
2. You don't have to be fully differentiated to influence your neighbors. You can make a difference while you are still young. The optic cup cells influence the outer ectoderm to become lens before the optic cup tissue is retina. The myotome cells of the somite tell the dorsalmost layer of the sclerotome to become tendon cells before the myotome cells differentiate into muscle. The embryo is created by "immature" cells.
3. In such interactions, competence is as important as signaling. The ability to respond to signals is itself a specialized state and can be achieved through prior inductions or by maternal specification. This is why the chick epiblast cannot respond to bone morphogenetic protein (BMP) antagonists until it has been exposed to fibroblast growth factors. (A similar operating principle explains why 15-yr-old boys should not be forced to read Jane Austin, whereas 15-yr-old girls can understand the humor of social relations.)
4. "The smallest unit of analysis is the relationship." (Haraway, 1976). This principle is found at all levels: enhancer–transcription factor interactions, cell–cell interactions, and organism–organism interactions. It means that what an entity is becomes a property of its relationships. It does not exist alone. Waddington and Weiss were two of the principal expounders of this view.
5. Context matters. It matters a lot and determines the outcome of relationships between components of an embryo. As one example, BMP4 causes bone formation at some times and places. It causes apoptosis at other times and places, and it specifies the epidermis at still other times and places. Whether an action is helpful or not depends on where and when it is done.
6. The preceding leads to "the three fundamental rules of development":
   A. Timing is everything.
   B. The three determinants of value are "location, location, and location."
   C. Both of the above-mentioned statements are true.
7. Build in small pieces. Embryos use cassettes, or modules, to carry out many functions. Such modules are critical, such that if one does not work, the entire system is not thrown out of kilter. Such modules allow for impressive compensatory development.
8. The units of construction are not necessarily the units of the adult. Rhombomeres, compartments, heart fields, and the medial rib are modules that do not exist in the adult, but they are important units of construction.
9. Think globally, but use local contractors in embryonic construction projects. The transcription factors that *Drosophila* embryos use to form their second *even-skipped* transcription stripe are not the same transcription factors used to make the first or third stripes. The fourth mammary glands in mice do not form the same way as glands 1, 2, 3, and 5.
10. No one influence controls the entire project. Multiple inducers are needed for successful differentiation in many cases. "You can get a lot done if you don't care who gets the credit" (George Marshall). The anterior endoderm and heart deserve some credit in forming the lens, even though the optic cup gets most of the glory.
11. There have to be pushes and pulls. The signal to become A must be paired with the signal *not* to become B. Thus, one cell will tell another cell, "Become ectoderm and not mesoderm", and one field will say to another, "Become female, and don't become male."
12. Reciprocal induction is the rule. All entities are both active and passive; actors and acted-upons. "All that you change changes you." (Butler, 1998). This is the way that complex organs can form.
13. Two negatives equal a positive. Activation is usually the repression of a repressor. Repression is often the

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repression of the repressor of a repressor. The enemy of my enemy is my friend.
14. The wisdom of the tadpole is paramount: Don't digest your tail until you've built your hindlimbs.
15. Powerful entities must be powerfully regulated. "Master regulatory genes must be masterfully regulated." It's difficult to get MyoD expressed, and that's the way it should be!
16. Redundancy is important. We have six sets of Hox10 genes, and this prevents our skeleton from being deformed if one of them goes awry. The same principle is true in daily life: Many of us have our presentations on USB keys and CDs.
17. There is strength in community . . . and often one needs community to be effective. In other instances, one must migrate as an individual.
16. Redundancy is important. We have six sets of Hox10 genes, and this prevents our skeleton from being deformed if one of them goes awry. The same principle is true in daily life: Many of us have our presentations on USB keys and CDs.
18. The whole is greater than the sum of its parts; every part of an organism has a definition only in the context of the entire interacting system of which it is a part.
19. "Homology" means appreciating both differences and similarities. Whether one emphasizes the similarities or differences between a forelimb and a hindlimb is a matter of context.
20. Function changes with time. When considering the life history of an organism, have respect for those playing lesser roles as adults, for they once may have been vigorous and important. Those intervertebral discs used to be the notochord, and the anus used to be Hensen's node, itself. Some, like the hypoblast and chorion, killed themselves so that we can be here today. They were important and deserve our study, even though we do not retain them as functional units.
21. There are multiple paths to the same end. Think of the neural tube, which can form in two ways in vertebrates.
22. As Ian Wilmut (2001) said, "Life is messy, and science is a slice of life." If you seek perfection, go into math. Evolution and embryology make do with what they got, and "good enough" is indeed good enough.

With these principles as a starting point, perhaps the most important principle of all was stated by Viktor Hamburger, who affirmed that "Our real teacher has been and still is the embryo—who is, incidentally, the only teacher who is always right" (see Holtfreter, 1968). Gastrulation is the point at which nearly all developmental principles get tested. It's the quality control point to find out if all systems are "go." Anyone who gets past gastrulation and middle school must be respected as a survivor. So at gastrulation, one can see highlighted nearly everything one needs to know about the essential principles of development, and a lot of what you need to get you through life.

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The Missing Dimension in Developmental Biology Education

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FOUR-DIMENSIONAL THINKING: AN INHERENT CHALLENGE IN DEVELOPMENTAL BIOLOGY

I arrived at the University of Wisconsin–Madison as a young assistant professor in 1991. In those days, teaching a modern course in developmental biology was an exciting proposition. Modern discoveries at the molecular level due to work in invertebrate model organisms were just beginning to be synthesized into coherent "nuggets" that could be passed on to undergraduates, and the pursuit of the molecular basis of the Spemann-Mangold organizer was hot and heavy. Those were heady days indeed. As time passed, however, the challenges of teaching modern developmental biology changed. How could one convey the fruits of the explosion in molecular detail to the modern student (see the accompanying POV by Wood

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in this issue), while preserving the essential—and intellectually elegant —heritage of classical embryology from the past (as touched on in the POV by Gilbert in this issue). Using girth as a simple guide to the explosion of "facts" in upper-division developmental biology courses, the authors of developmental biology texts initially struggled to deal with this problem as well.[1] Of course, these are not problems unique to developmental biologists; my cell biology colleagues lodge very similar complaints when it comes to the core curriculum in their upper-division courses, and at least some cell biology texts have similar struggles with heft (e.g., see the review by Schwarzbauer, 2003; http://www.lifescied.org/cgi/content/full/2/1/16).

The issue of how to convey the essential facts and concepts of developmental biology to undergraduates, given this explosion in knowledge, is clearly important; however, a crucial question remains. Are there other issues that are somewhat unique to teaching developmental biology, as opposed to cell biology, molecular biology, genetics, or biochemistry? One can make the case that an essential feature of developing embryos that is not obviously shared with key topics in these other disciplines, is that the embryo must be constructed over time, and in three dimensions. Because this process, which developmental biologists usually call morphogenesis, occurs in both time and space, it is inherently a four-dimensional (4D) process. This has long been recognized by developmental biology researchers, including those in my own laboratory, who use 4D microscopy in their research to chart the positions of cells as they move to new positions within the embryo (e.g., Thomas *et al*., 1996; Hardin, 2006). It is this 4D nature of development that allows for new interactions between differentiated parts of the embryo.

FOUR-DIMENSIONAL THINKING IS NOT PART OF THE CURRICULUM

Although 4D thinking has become part of the research repertoire of many developmental biologists, it has yet to make much of an impact on the average undergraduate. There are likely several reasons why this gap persists. First, the processes involved are inherently difficult to grasp at a truly 4D level, even for professional researchers. As a result, as anyone who has struggled to teach the basic features of amphibian gastrulation to uninitiated undergraduates quickly realizes, inculcating a deep understanding of the spatial relationships between parts of the gastrula is one of the most challenging aspects of teaching developmental biology.

Second, as a pragmatic response to the difficulty of learning in four dimensions, it is simply easier to concede the difficulty of the problem, and "solve" this problem by acting as if the embryo is not actually developing in four dimensions. One classic way of doing this in an earlier period was to couple a lecture course in developmental biology to a laboratory course in "embryology," in which one examined serial sections of embryos at various stages in their development. This approach forces students to develop a three-dimensional (3D) understanding of the embryo by mentally reconstructing such sections, an activity aided by classic atlases of developmental biology (e.g., Schoenwolf, 2007). However, this approach does not usually lead to a 4D understanding of the embryo. This is because one dimension is usually missing in this approach: the transformation of the embryo over time. Moreover, although there are some institutions that still have such courses, they are highly endangered, in the United States at least. As teaching budgets have shrunk, elective laboratory courses have been a convenient target of cuts, particularly at large public universities. In addition, as the emphasis has shifted to molecular approaches in developmental biology, the emphasis of those laboratory courses that remain has shifted in a corresponding direction. As a result, this older method for teaching embryonic structure is disappearing.

Modern computer and animation technology would seem to be a promising avenue to pursue the teaching of the 4D nature of embryonic development. Indeed, I have spent considerable effort over many years to try to provide simple movies and animations as an aid to student learning.[2] However, such materials are usually only used to provide visual impact regarding how dynamic development is (thus, they provide the "wow" factor during a lecture). I use them myself this way for the most part. However, video materials have rarely been exploited to aid genuine 4D understanding. It is only when such movies are coupled to more insightful representations of the internal components of embryos as they change over time that such movies will aid 4D thinking regarding the early embryo.

CAN FOUR-DIMENSIONAL THINKING BE LEARNED?

To see why 4D thinking is needed to truly understand animal development, consider one of the most difficult cases commonly covered in an undergraduate developmental biology course: amphibian gastrulation. Gastrulation is a key stage during early animal development, and, as the POV by Gilbert in this issue underscores, it is a truly crucial time in the life history of animals. Largely due to the work of Ray Keller and colleagues, we now have a detailed understanding of how the *Xenopus* gastrula changes shape in four dimensions (e.g., see review by Keller *et al*., 2003). This impressive work originated with detailed fate maps of both the interior (deep) cells of the embryo, and its outer (superficial) cells. Although the detailed changes in shape of various regions of the embryo have been well depicted (Figure 1, A and B), it is hard to convey to students how these changes take place dynamically during gastrulation. Be-

[1]This can actually be demonstrated empirically in the case of the classic text in the field, *Developmental Biology*, by Scott F. Gilbert (Sinauer Associates, Inc.). The thickness of various editions is as follows (publication date, thickness in centimeters, and page count are shown in parentheses): 1st (1985, 3.7 cm, 726 pp.), 2nd (1988, 3.6 cm, 843 pp.), 3rd (1991, 3.6 cm, 891pp.); 4th (1994, 3.7 cm, 894 pp.), 5th (1997, 3.9 cm, 958 pp.), 6th (2000, 2.9 cm, 749 pp.), 7th (2003, 3.3 cm, 838 pp.), and 8th (2006, 3.3 cm, 817 pp.). There was clearly a period in the late 1990s during which the new knowledge had to be consolidated.

[2]See http://worms.zoology.wisc.edu/embryo_main/embryology_main.html for the old site, covering echinoderms and amphibians, and the new, higher bandwidth site, which has thus far only been updated to include echinoderms, at http://worms.zoology.wisc.edu/dd2/.

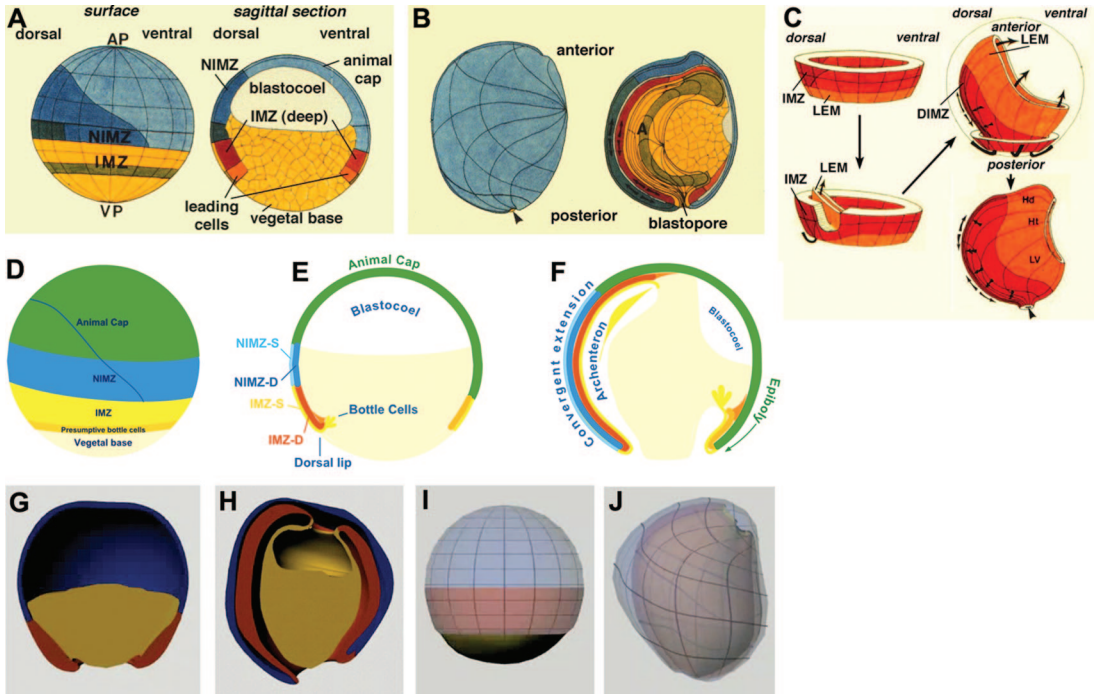

Figure 1. 4D thinking is needed to understand amphibian gastrulation. (A–C) A fully detailed representation of cell movements during gastrulation in *Xenopus laevis*. Fate maps of the superficial and deep cells of a *Xenopus* gastrula (adapted from hand drawings made by R. Keller). Dorsal is to the left. (A) Surface and sagittal views of an early gastrula. AP, animal pole; VP, vegetal pole; IMZ, involuting marginal zone; NIMZ, noninvoluting marginal zone. Light blue, presumptive epidermis; dark blue, presumptive neural ectoderm; darkest blue, presumptive floor plate, a type of neural ectoderm; yellow, presumptive endoderm; green, presumptive archenteron roof. The IMZ material moves into the interior, whereas the NIMZ material remains on the surface but changes shape. (B) Late gastrula. A, archenteron. (C) Fate map showing only deep cells. The deep cells form a doughnut-shaped structure around the equator of the embryo, which turns inside-out starting on the dorsal side. The entire structure then extends to cover the entire interior of the embryo, creating an extremely difficult spatial problem for student learning. Orange, leading edge mesoderm; red, deep cells of the involuting marginal zone. (D–F) Simplification of gastrulation into a 2D problem over time. 2D depictions of *Xenopus* gastrulation over time (from a Flash animation courtesy of D. Gard). (D) Surface view, corresponding to A. Green, animal cap; blue, noninvoluting marginal zone; yellow, involuting marginal zone (IMZ); orange, presumptive bottle cells; tan, vegetal base. (E and F) Sagittal views. (E) NIMZ-S, superficial cells of the noninvoluting marginal zone; NIMZ-D, deep cells of the noninvoluting marginal zone; IMZ-S, superficial cells of the involuting marginal zone; IMZ-D, deep cells of the involuting marginal zone. Material moves into the interior first at the dorsal lip of the blastopore, driven by bottle cells, which constrict. (F) As gastrulation proceeds, the blastocoel is occluded, and the archenteron forms; this is driven by convergent extension of the marginal zone material. (G–I) Two different 3D views of early and late gastrulae (from Flash animations courtesy of Wesleyan University; http://learningobjects.wesleyan.edu/gastrulation/animations.php?ani = 3D). Dorsal is to the left. These animations contain less information than the 2D animation in D–F, but they depict it in a 3D manner over time (i.e., four dimensionally). (G and H) 3D depiction of germ layers. Blue, ectoderm; red, mesoderm; yellow, endoderm. The red material on the left in H has extended more than that on the right. The blastocoel is visible as the cavity in H. (I and J) Partially transparent rendering of ectoderm (light blue) and mesoderm (pink) at early (I) and late gastrula (J) stages. Note that the light blue and pink material on the left extends more dramatically than that on the right, as can be judged by the distortion of the grid lines in J.

cause of the difficulty, students are often exposed to a simple two-dimensional (2D) representation of a frog gastrula over time (Figure 1, C and D). Such representations are no doubt a useful starting point, but they are hardly 4D.

Is training in 4D thinking possible at the undergraduate level? Such spatial visualization is an extremely important skill in many fields in science and mathematics. Chemical bond angles, geological structures such as faults and folds, and 3D functional representations are all examples in which spatial thinking is an asset. Spatial visualization is a complex process that involves both visual processing and the construction and manipulation of mental images (Mathewson, 1999). It involves several related mental activities, including the ability to rotate objects about one or more axes (Shepard and Metzler, 1970), the ability to mentally manipulate objects (e.g., by folding them; Ekstrom *et al*., 1976), and the ability to see through the surface of an object into its interior ("penetrative" thinking; Kali and Orion, 1996).

Despite the importance of spatial visualization in science, mathematics, and engineering, it is not often thoughtfully taught or assessed (Mathewson, 1999). Moreover, longitudinal studies suggest that failure to train students in this area can lead to their abandoning certain fields entirely (e.g., Shea *et al*., 2001). Fortunately, although students have differing aptitudes for such spatial thinking, psychological research suggests that training in spatial thinking is possible for most students (Lord, 1985), and that such training is effective irrespective of gender (Sorby, 2001; Levine *et al*., 2005; Feng *et al*., 2007).

With regard to developmental biology in particular, the article by Lu and colleagues in this issue of *CBE-LSE* shows that students can learn the rudiments of 4D thinking by exposure to raw 4D data sets of embryos if the embryos are inherently simple in organization, as *Caenorhabditis elegans* early embryos are. Even here, however, as the structure of the embryo becomes progressively more complicated, a *via media* is necessary, in which only the salient features of the development of specific structures are highlighted amid the complexity of the entire embryo. Clearly, an intermediate sort of representation, in which salient features of the 4D embryo are depicted, is what is needed to help students grasp the key features of gastrulation.

Computer-aided representations may be particularly useful in this regard. Studies have shown that computer games can be useful in a general sense to train students to think spatially (Feng *et al*., 2007). With regard to the specific problem of understanding gastrulation, computer rendering may be particularly valuable. For example, it is possible to depict structures of an otherwise opaque embryo with varying degrees of transparency to aid penetrative thinking skills (Figure 1, E and F), and it is possible to extract particular features in a 4D representation to highlight important architectural features of the embryo (Figure 1, G and H). Although the examples shown in Figure 1, E–H, are derived from static orientations, the technology already exists to depict embryos on the computer as true 3D objects in 4D space. What is needed is the application of instructional materials development resources toward the production of such models. If such models become widely available, it should be possible to reclaim all four dimensions of the embryo in the undergraduate developmental biology curriculum.

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