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Abstract

Two important skills for scientists in developmental and cell biology, as well as in fields such as neurobiology, histology and pathology, are: 1) observation of features and details in microscopic images of cells, and 2) quantification of cellular features observed in microscopic images. However, current training in developmental and cell biology does not emphasize observation and quantitative analysis of microscopic images, and it is unclear how best to teach students these skills. Here, we describe our experiences applying visual artistic approaches to instruct undergraduate and graduate students in how to observe and analyze cellular forms in microscopic images. At Loyola Marymount University, we used representational drawing to enhance undergraduate students' skills in observation of fine cellular details in microscopic images of embryos. At Touro University California, we paired abstract paintings with microscopic images of tissues to engage masters and medical students in learning quantitative measurements of cellular features. Overall, this paper explains specific ways in which visual arts can be used to instruct and engage students in observation and analysis of microscopic images of cells and tissues.

Keywords

Drawing, Visual Arts, Morphometrics, Microscopy, Developmental and Cell Biology, Quantitative Analysis, Observational skills

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Introduction

Developmental biology encompasses diverse species, a multitude of organ systems, morphogenetic mechanisms, cell and tissue types, changes in shape and an infinite array of molecular regulatory pathways. In addition, developmental processes occur in 4-dimensions, with cell behaviors and activities occurring in 3 dimensional spaces over a continuum of time. In short, the development of living things is as complex and dynamic as it is beautiful. This complexity has historically engendered a reductionist approach, where individual research groups focus on narrow topics which they investigate in detail. However, understanding developmental processes in their full complexity requires a visual methodology to study morphogenetic, cellular and molecular events within the changing organizational contexts of the developing embryo's tissues. In turn, noticing these precise changes at a single time point as well as over time requires robust observation skills. Thus, keen observation is *foundational* to the interpretation of data collected from biological studies.

Another increasingly important skill associated with observation of patterns and forms of cells in developing and adult tissues is quantitative analysis of microscopic images (Aikens and Dolan, 2014; Feser et al., 2013). These mathematical measurements translate qualitative observations of cell shapes, positions, and behaviors into precise quantitative data. These quantitative measurements can then be used to determine statistical similarities and differences between cell forms and patterns in tissues from embryos of different developmental stages, subjected to different molecular or mechanical perturbations, and/or reflecting healthy and diseased conditions (Bru et al., 2007). Moreover, quantitative measurements of cell and tissue forms can serve as parameters to develop and refine computational models and animations of cell and tissue morphogenesis (Patel et al., 2018). Finally, the process of making quantitative measurements may also improve researchers' ability to observe and recognize fine cellular details and patterns in microscopic images of tissues (Dao et al., 2019).

Although observation and quantitative analysis are fundamental skills for understanding the complexity of biological systems, instructors struggle with how best to teach these skills, and it is unclear what approaches are available to engage students. Here, we describe how drawing and visual art can be used to enhance instruction in students' observation and quantitative analysis of forms and patterns in cell and developmental biology. At Loyola Marymount University (LMU), students created representational drawings to enhance their observation of cell shapes and locations in whole mount embryos, stained or unstained sections on slides, and microscopic images of developing embryos to hone observational skills. At Touro University

California (TU-CA), students paired abstract paintings and photographs that contain biomorphic forms with microscopic images of cells and tissues to learn how to make morphometric measurements of cells and tissues. This paper presents specific pedagogical approaches incorporating drawing and visual art that can be used to teach students critical skills of observation (Edwards, 1999a; Edwards, 1999b) and quantitative analysis in cell and developmental biology.

RESULTS

Using Art to Engage Students in Fostering Their Observational Skills in an Embryology Lab

This section describes two activities in which LMU students improved their observational skills through representational drawing of whole mount embryos, sections, and embryonic images.

Overall improvement in observational skills in an Undergraduate Embryology Lab Course

A class of 12 undergraduate Embryology students at LMU provided a preliminary study to examine how drawing can be used to improve observational skills in an instructional setting. Specimens included whole embryos, sections and images of sea stars, sea urchins, chicken, grasshopper testes, frog, pig, and human embryos. At the beginning of the course, almost all the students were unable to see subcellular details. One student consistently noted subcellular details but could not draw representations that filled the page, instead producing miniature drawings too small to show the subcellular details he could verbalize. Another student "resisted" observing, instead producing drawings that were stylized and failed to capture the complexity of the embryo. Only on the last assignment, after a last, long conversation, did she begin to draw intentionally and show improvement in observation skills. Another student made immediate perceptual improvements by paying attention to the correct *number* of items in an image. At the midpoint of the semester, an Art instructor was invited to lead class and gauge student progress from their drawing books. The Art instructor noted progressive improvements in observation skills from all but the one student mentioned above. By the end of the class, all students showed a clear improvement in drawing and observation skills.

Granular study with two internship students to produce an atlas focused on the development of neural crest cells in the chicken embryo

In this second study, two undergraduate research interns at LMU generated a hand-drawn atlas of embryology focused on neural crest cells in the chicken embryo's head and heart. The students worked relatively independently and documented their experiences in a diary. Since the atlas needed to be high quality, students had to redraw inaccurate images.

One of the students quickly realized that her renditions of the reference image were not proportional and lacked detail (Compare Figs. 1C,H to 1D,I). After producing multiple drafts of each drawing while continually examining the reference images, her drawings became more proportional and detailed (Fig. 1F). Yet, although she now could “see” nuclear and cell membrane details, her cells were symmetrical and stylized (Fig. 1F), and did not reflect the morphological differences between the otic placode, neural tube, neural crest and epidermis. When redrawing her images, she covered all but a small part of the reference image, slowly drawing the reference image in sections. The student began to recognize local intricacies without getting distracted by the complexity of the image at large. Consequently, she produced accurate drawings that depicted the *true* variety, morphology, organization and disorganization of cell types present in the embryo (Fig. 1G compared to Fig. 1F). In addition, she replaced contour lines around structures with accurate boundaries made by light and dark values. Her progression was clear, evolving from an inability to see cells (Fig. 1C,H), to seeing cells as simple lines (Fig. 1D,I), to recognizing and capturing subtle differences between cell morphologies (Fig 1G,K).

Upon considering her first drawing, our other student felt quite pleased with her work (Fig 2A,B). However, replicating the drawing 3 more times for the atlas, she realized that her 4 attempts were different from one another and from the reference image (Fig. 2B-D). To fix her perception issue, she began to study the shape of the box in which her sample should fit, and to pay attention to the amount of space *surrounding* her drawings in the box (the negative space). She next encountered a new challenge: the images she was reproducing became three-dimensional and/or exponentially more detailed (Fig 2F,G) and frustrating to draw. Similarly to the first student intern, she began to break the image into smaller sections, focusing all her visual attention on a single, very limited section of the reference image. Her drawings improved by becoming more representational and showing solid shading that resulted in the elimination of dark lines around her samples. (Fig. 2H-J). She also could reproduce images (Fig. 2A,E and Fig. 2H,J) much faster than she had been able to at the start of the internship.

Overall, both interns displayed growth in observation as assessed through their representational drawing skills (Fig. 1H-K and Fig. 2A-J). Meeting each new drawing challenge presented a unique learning opportunity where students became aware of the rift between reality and their perception; as a result, their drawings became more accurate.

Using Art to Engage Students in Quantifying Cellular Forms in Microscopic Images

In this section, we describe two activities in which using art was used to engage and instruct TU-CA students in analyzing microscopic images of cells, tissues and organisms.

Quantitative Analysis of Artistic Biological Microscopic Images

The first exercise involved a group of 65 Masters students in Medical Health Sciences students at TU-CA in a Molecular Cell Biology course. In one module in the middle of the semester, the instructor presented a lecture introducing the students to microscopy and then directed an activity on image analysis. In this exercise, each student was asked to select an image from the Nikon Small World Competition (https://www.nikonsmallworld.com), which shows the winning images of an annual artistic competition of photomicrography of cells, tissues, embryos and organisms. The students were then instructed to closely observe their microscopic images and to focus on a structural feature of the cell, tissue or organism that could be mathematically decomposed. They then proceeded to make a measurement on their selected biological features (either using ImageJ or manually). The students wrote a one page paper (including an introduction, methods, results and discussion), which framed the significance of their feature/measurement in a narrative about physiology, health and/or disease.

As the students worked on this activity they encountered several challenges, such as deciding what feature of their image to observe and measure, and how to develop a narrative based on what they had measured. The students quickly surmounted the challenge of deciding what to measure, when examples of mathematical shape descriptors, such as length/width ratio, circularity, density and area were introduced. In addition, one concept that helped the students develop their narrative was the instruction to compare the features and measured parameters between two regions of the structure or organism in their images, or between their image and a related image. For example, one student selected an image of a fetus with a placenta from the Nikon Small World website, and chose to measure the area of both the fetus and placenta (Fig. 3). They then developed a narrative based on a comparison of the areas of these two structures, and extrapolated to other types of placentas. The students enjoyed this activity, with one student stating: "Nikon's bright, colorful, and detailed artistic images were a blank canvas that they could use to come up with a hypothesis and then put that hypothesis to test".

Pairing Paintings and Photographs with Microscopic Images of Cellular Forms

A second activity involved medical students at TU-CA pursuing independent research projects in which they made morphometric measurements on paired artistic and biological images. These students selected abstract paintings or photographs that resembled microscopic images of biological tissues, and then made morphometric measurements on the paired art and biology images.

In one project, students paired three paintings by the Abstract Expressionist painter Sam Francis (www.samfrancis.com) with three microscopic images of biological tissues (neural ectoderm cells, nuclei of white blood cells and a kidney corpuscle) (Fig. 4; Lakhani et al, 2016). The students then measured two shape parameters - aspect ratio and circularity - on forms in the paintings and cells in the micrographs. Their results showed statistical similarities in these parameters between the painted and cellular forms, which mathematically specified the biomorphic nature of the forms in Sam Francis' abstract paintings (Lakhani et al, 2016). In another project, students paired aerial photographs of man-made landscapes captured by the environmental artist Edward Burtynsky (www.edwardburtynsky.com) with microscopic images of biological tissues (kidney corpuscle, mesenteric duct and peripheral nerve). Using fractal dimension and fractional concavity measurements, the students showed that the patterns in the Burtynsky photographs and micrographs were similar in complexity, thereby specifying similar scaling in patterns in Burtynsky's photographs of man-created environments and natural, organic tissues.

In both activities, using art enhanced the students' learning of morphometrics to analyze and decompose the microscopic images. A student interested in pursuing pathology as a career wrote that "searching for biological images that resembled the Burtynsky photographs refined their observational and pattern recognition skills" and that the art made them "appreciate the beauty within the histopathological images."

Discussion

Two seminal skills for making new discoveries in biological science are observation and analysis of microscopic images of cells, tissues and organs. However, because art education in grade- and high schools has been suffering major cutbacks for decades (Simmons, 2019), students enter higher education biology courses with little training in art and, therefore, in observation skills. In addition, although clinicians increasingly use mathematical metrics on images to identify health or disease, introducing undergraduate and graduate students to quantitative skills in biological courses is a pedagogical challenge (Aikens and Dolan, 2014; Feser et al., 2013; Bru et al., 2007). Here, we present activities rooted in visual art to train diverse groups of undergraduate, masters and medical students in how to observe and analyse microscopic images of cells and tissues.

Significance of drawing in improving observation skills in Developmental Biology

Using art as a platform, Biology undergraduates at LMU representationally drew a variety of embryos. Through this activity, they became aware of the brain's interpretation of reality into patterns disconnected from reality. Students built a foundation of observation and increased their ability to see cellular details, lighter and darker values, and relative proportions in embryos. Because drawings place what students see in their mind onto an external paper media, representational drawing is a practical tool that facilitates effective self-critique and feedback (Ridley and Rogers, 2010). As a result of the Art exercises detailed here, students in the Developmental Biology class gained expertise in the comparative anatomy of embryos. Similarly, undergraduate interns learned the gross anatomy, tissue structures and nomenclature related to head and heart cells.

Impact of doing quantitative analysis of artistic images on understanding biological images

In quantitatively analyzing artistic images that resemble microscopic biological images, medical and masters students at TU-CA became aware of the relationship between images (and patterns in images) from two very different contexts. This will help students that seek to pursue biological research and clinical practice in fields such as pathology and radiology, which require recognition of similarities and differences in images of healthy and diseased biological cells, tissues and organs (Bru et al., 2007). In addition, incorporating aesthetically appealing artistic images helped engage the students in learning how to apply mathematics to analyze features and patterns in microscopic images. They learned about specific morphometric measurements and how to translate their observations of biological forms and patterns into numerical values. With the increasing importance of mathematics in decomposing images in research and clinical practice, these skills are correspondingly important for premedical and medical students to learn.

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Figures

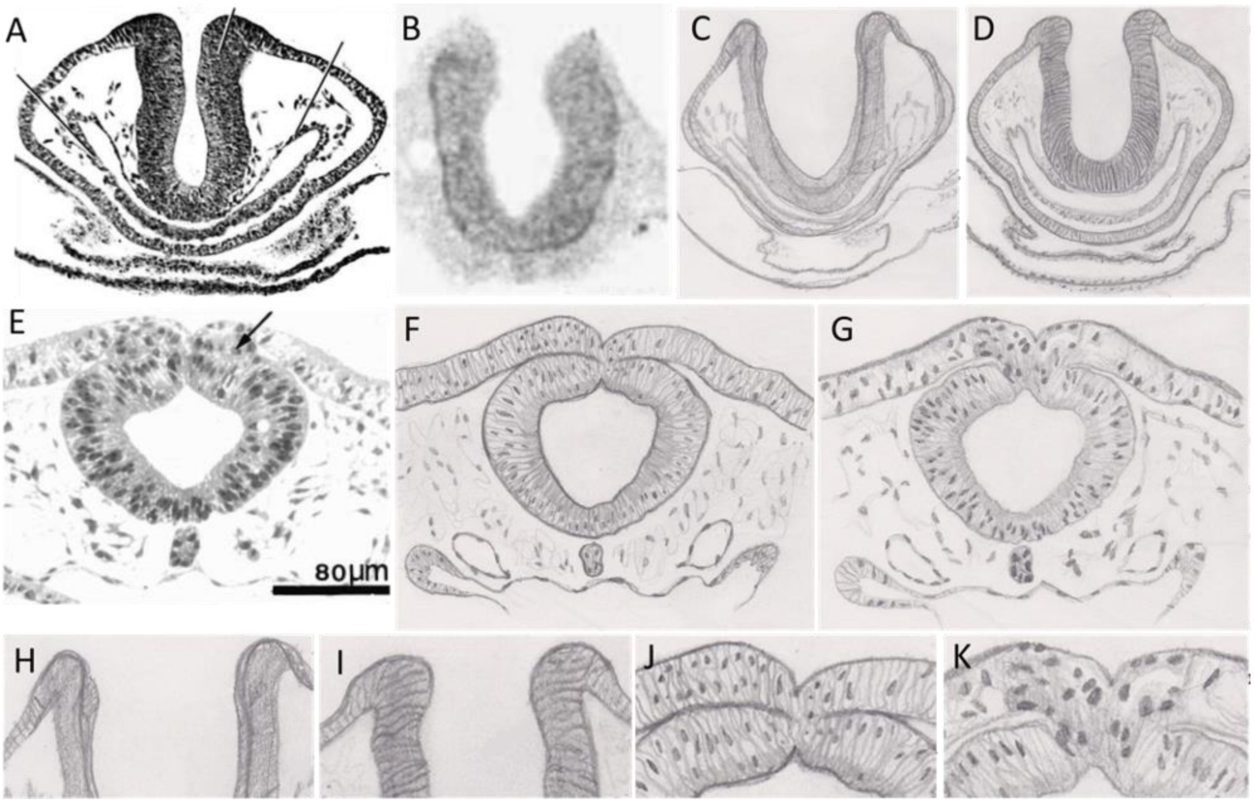

Figure 1. A student's increasing perception of cellular details through drawing. A, B. These reference figures show cell nuclei **(A)**, and cross sections of the neural tube (Bellairs and Osmond, 2005; Dady et al., 2012). **C.** The student's first drawing attempts to capture the shape of the neural tube in 'B' and the cell details from 'A'. **D.** After feedback, the student showed a horizontal arrangement of cells (A) and the asymmetric shape of the neural tube (B). **E.** This reference figure, from Mayordoma and colleagues (1998), features neural crest cells (arrow) extracting themselves from the neural tube. **F.** This stylized rendition of 'E' shows cells as uniform, organized, and spanning the apicobasal extent of the neural tube - characteristics not present in the reference image. **G.** This redrawn image better captures the characteristics of all cell types shown in E. **H-K.** Higher magnification images of drawings shown in C,D, F, G. Panel 'H' displays an absence of cells, panel 'I' shows cells as simple nuclei-free linear compartments. In 'J', the student is beginning to see cell nuclei and their varying positions. In Panel 'J', the student also captures areas of cellular organization and chaos, replicating the disorganized neural crest (in the middle) and the far more organized neural tube cells.

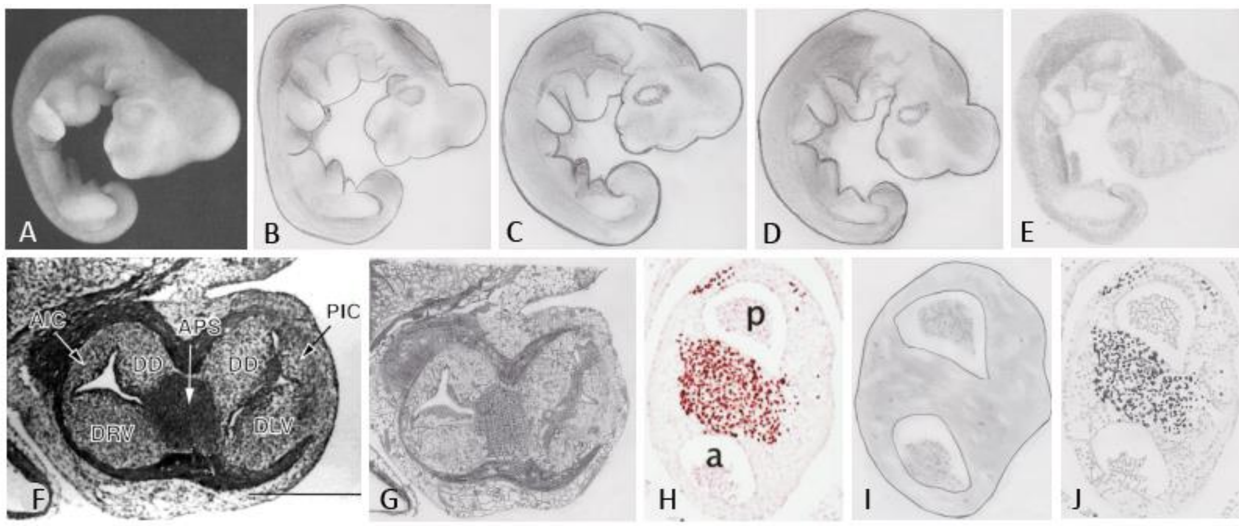

Figure 2. A student's improvement in visualizing proportions and capturing values. A. Reference image of a Day 4 chicken embryo, from Hamburger and Hamilton's series of chicken development (1953). **B-D.** First attempts at drawing, showing incorrect proportions with the three representations being noticeably different from one another and from the original image. **E.** Day 4 embryo, redrawn after the internship. **F.** Reference image of the heart's septated outflow tract (Qayyum et al, 2001). **G.** Student's drawing successfully captures a plethora of details, cell positions and areas of condensed nuclei seen in 'F'. However, proportions remain inaccurate. **H.** Reference image showing cardiac crest cells (brown) condensed in the heart's outflow tract (Waldo et al, 1998). **I.** First rendition of the reference image: all details are eliminated and the prominence on the right is too pronounced. **J.** After feedback, the student represented the outflow prominence accurately and captured the concentric characteristic of the rings of condensed nuclei (brown dots from 'H').

	Area
Fetus (Red)	**695,951 pixels**
Placenta (Green)	**335,688 pixels**

Fig. 3: Example of analysis of a Nikon Small World Microscopic Image.
This artistic image from the Nikon Small World Competition of a fetus and a placenta was analyzed by a masters student at TU-CA. They chose to measure the area of the fetus (red) and placenta (green) (Table). Though the students could only make their measurements in pixels, a comparison of relative sizes of fetus and placenta was possible from their analysis (Table).

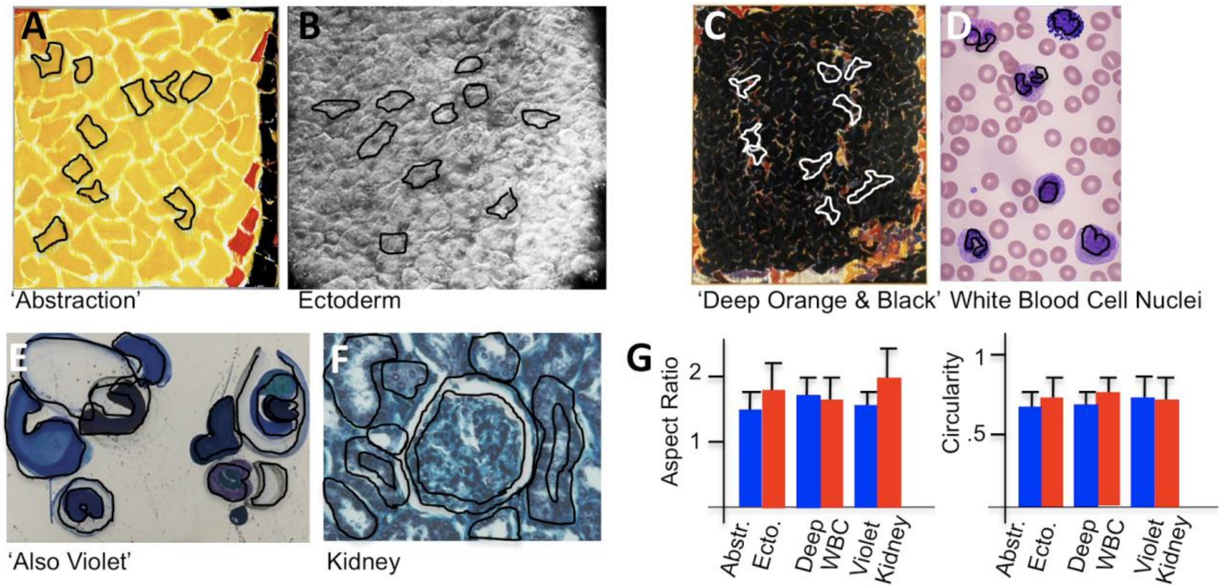

Fig. 4: Pairing abstract paintings with microscopic biological 'look alike' images. Forms in Sam Francis' abstract lyrical paintings **(A, C, E)** and in microscopic images of biological tissues **(B, D, F)** visually resemble one another. Measurement of two mathematical shape parameters - aspect ratio and circularity - show statistical similarity between the forms outlined in the paintings and images **(G)**. Figure reproduced from Lakhani et al., 2016.