**Abstract**

Developing students’ understanding of cells and the microscopic scale is an important goal of biology education. Cells are the building blocks of multicellular organisms, and most of Earth’s biodiversity is found at the microscopic scale. Developing an understanding of the microscopic scale requires that students use their quantitative reasoning skills. Here, resources are presented that help students develop their quantitative reasoning skills and improve their understanding of the small scale of microscopic life. The crosscutting concept, Scale, Proportion, and Quantity, and the science and engineering practice, Using Mathematics and Computational Thinking, are highlighted. The development of students’ quantitative reasoning skills in biology is universally recognized as an important outcome of biology education.

**Key Words:** measurement; microorganisms; modeling; proportion; quantitative reasoning; scale.

**Introduction**

Biologists investigate phenomena that encompass a wide range of scales from molecules and cells up to the entire biosphere. It can be challenging for students to comprehend phenomena at the extremes of this range (Rutherford & Ahlgren, 1990). How do we help students understand phenomena at the microscopic scale when the size of cells seems beyond the level of their intuitive comprehension? “To understand a phenomenon, a scientist must first describe it, to describe it objectively, he must first measure it” (Mukherjee, 2010, p. 19). Students need opportunities to make measurements of cells, work with magnitudes at the cellular level in mathematical terms, compare the size of cells to objects at more familiar scales, and compare the sizes of cells to one another. Here, two resources designed to engage students with quantities at the microscopic scale are discussed, and a sample worksheet is presented that is designed to extend and enhance these resources by guiding students through the comparison of the sizes of prokaryotic and eukaryotic cells to each other and to more familiar objects. Recommendations are provided for modifying the worksheet, assessing student mastery, and incorporating more quantitative reasoning in introductory biology courses. Activities like those described here can help students begin to develop the quantitative reasoning skills that are universally recognized as essential for understanding biology (National Research Council, 2003, 2012; American Association for the Advancement of Science, 2011; NGSS Lead States, 2013; College Board, 2019).

**Engaging with the Microscopic Scale**

Before engaging with the activities described here, all students should have the opportunity to examine and measure microorganisms under a microscope. Pure cultures are available at modest prices from scientific suppliers. Alternatively, pond water collected locally can serve up a smorgasbord of different types of microorganisms. Resources like Rainis and Russell’s *Guide to MicroLife* (1996) can be kept on hand for students to identify the organisms found in pond water. Techniques for restricting the movements of microorganisms so they can be measured are described by Morholt and Brandwein (1986). Viewing microorganisms as they go about their business can be the springboard to a deeper understanding of this Lilliputian world (Cudmore, 1977; Cooper, 2019).

Students can begin to develop an intuitive sense of the microscopic scale by exploring the *Cell Size and Scale* interactive (Genetic Science Learning Center, 2010). But in order to achieve a deeper understanding, students must develop some familiarity with the micrometer (μm), the unit typically used to express the sizes of microorganisms. Among the larger microorganisms students can view under a microscope, just barely visible to the naked eye, are rotifers (*Philodina* sp.), which are approximately 0.5 millimeters (mm) long (Rainis & Russell, 1996). But a great many microorganisms are much smaller, ranging in size from 0.002 mm to 0.2 mm. To avoid working with such small numbers, we convert the units to micrometers. A micrometer is one-millionth of a meter, or one-thousandth of a millimeter (mm). Using micrometers, rotifers measure 500 μm, and the typical size range for many other microorganisms is from 2 μm to 200 μm.
What van Leeuwenhoek Saw

An excellent activity for introducing students to measurements at the microscopic scale is *What van Leeuwenhoek Saw*, a classroom-tested, hands-on activity that teaches and reinforces students’ skills working with metric units, ratios, and conversions (HHMI BioInteractive, 2017). Using these skills, students construct scale models of a variety of microorganisms. While engaged in this activity, students are also introduced to a small sampling of the vast biodiversity of the earth, most of which exists at the microscopic scale. In a short film related to this activity, biologist Bonnie Bassler explains, “Everything that you can actually see with your eye is just the smallest sliver of life on this earth. Most of life is invisible. We still have this idea that we’re the most central feature of Earth, and it’s the humans that are the bystanders. The microbes are doing the work” (*Animated Life: Seeing the Invisible*, HHMI BioInteractive, 2014). To impress upon students the importance of microorganisms, we may well ask, “What would the world be like without them?” In another short film, science writer Ed Yong and Biologist Jack Gilbert answer this question as they imagine *A World Without Microbes* (HHMI Tangled Bank Studios, 2018).

In the activity *What van Leeuwenhoek Saw*, students are introduced to the necessary measurements and calculations for determining the actual size of a microorganism from a scaled image. Here, all students work with *Daphnia ambigua* (class Branchiopoda, order Cladocera), a microscopic crustacean better known as the “water flea” that is found throughout much of North America (Herbert et al., 2003; http://tolweb.org/Branchiopoda/6243). Students make measurements on the scaled image and then calculate the actual size of *Daphnia* in micrometers using the conversion factor derived from the scale bar on the image. Students then draw a scale model of *Daphnia* on paper that is magnified 1000x. Finally, students work in small groups to determine the actual size of a second organism or cell from the cards and then construct a second scale model that is magnified 1000x (see Figure 1). [Note: Additional teaching tips are provided in the Educator Materials available at HHMI BioInteractive, 2017.]

Extending and Reinforcing the Concepts and Skills

To provide additional practice, further reinforce students’ understanding of the relative sizes of prokaryotes and eukaryotes, and emphasize just how small cells are, the *What van Leeuwenhoek Saw* activity should be followed up with the “Cell Size and Scale” worksheet, which guides students through comparisons of different cell types. (The worksheet is available as Supplemental Material with the online version of this article.) Students model the cells of microorganisms as regular geometric shapes (spheres, cylinders, etc.) so they can use simple mathematical formulas to approximate the volumes of the cells. Students can then get a sense of how much larger one cell is than another by calculating how many of the smaller cells would fit inside the larger cells.

Students search in the *Cell Size and Scale* interactive (Genetic Science Learning Center, 2010) to find the diameter of a skin cell and the dimensions of an *Escherichia coli* cell. Using a sphere to model the shape of a skin cell and a cylinder to model the shape of an *E. coli* cell, students insert data from the interactive into the mathematical formulas for these regular geometric shapes to calculate an estimated volume for each. The two volumes can then be compared to determine how many *E. coli* cells would fit within a skin cell. Students find that the volume of the skin cell is more than 16,000 times greater than the volume of an *E. coli* cell, so more than 16,000 *E. coli* cells would fit within one skin cell, assuming that the skin cell was spherical. To compare cell sizes to something at a scale within the students’ realm of experience, they also calculate how many skin cells and *E. coli* cells could fit within the volume of one drop of water. The numbers are surprising.

Students then make a similar comparison between the sizes of human egg and sperm cells. Egg cells are among the largest cells in a multicellular organism, while sperm cells are among the smallest (Alberts et al., 2002). A mature egg cell contains all the material necessary for beginning the growth and development of a new organism except a second copy of the genome (Gilbert, 2006).

Sperm cells, in contrast, are very small and have very little cytoplasm. They are optimized for speedily and efficiently...
delivering their genome to the egg, so they are “stripped down,” lacking unnecessary organelles like endoplasmic reticulum, Golgi bodies, and ribosomes. Sperm do have one organelle in relative abundance—mitochondria, wrapped around the base of the flagellum.

The final problem in the worksheet asks students to compare the size of a zygote, a fertilized egg cell, to the size of a period at the end of a sentence. Students began their lives as a zygote. It should excite their sense of wonder to learn that as a zygote, with a diameter of around 130 μm or 0.130 mm, they could have hidden under the period at the end of this sentence (Cudmore, 1977). Yet that one tiny cell contained two meters of DNA and produced all the trillions of cells that now compose their bodies, with their many different structures and functions.

The Cell Size and Scale interactive (Genetic Science Learning Center, 2010) can be used as a source of additional comparisons that can be made so instructors can develop additional worksheets or questions for assessment. For example, students could determine how many HIV virus particles could fit within an E. coli cell or a skin cell. An interesting and topical formative assessment could challenge students to determine the number of SARS-CoV-2 virus particles it would take, with a diameter of 100 nanometers (Bar-On et al., 2020), to equal the size of a respiratory droplet with a diameter of 40 μm (the number is about 67 million). A 40-μm respiratory droplet is about one-millionth the size of a drop of water.

Comparisons of the sizes of molecules can also be made using information from Cell Size and Scale or from other sources, such as The Machinery of Life (Goodsell, 2009). For example, how many HIV virus particles could fit within an E. coli cell or a skin cell. An interesting and topical formative assessment could challenge students to determine the number of SARS-CoV-2 virus particles it would take, with a diameter of 100 nanometers (Bar-On et al., 2020), to equal the size of a respiratory droplet with a diameter of 40 μm (the number is about 67 million). A 40-μm respiratory droplet is about one-millionth the size of a drop of water.

The book Cell Biology by the Numbers (Milo & Phillips, 2016) provides a rich source of quantitative information about structures and processes related to cells. Using this resource, quantitative comparisons of the sort described here could conceivably become a theme that runs throughout an introductory course. The book provides data for making quantitative comparisons between cells and organelles, quantities and concentrations of molecules within cells, quantities of energy, rates and duration of processes, quantities of information, and error rates.

I have found that many of my students have the impression that math is used in chemistry and physics, and biology is about memorizing the definitions of a lot of words. Some students have said to me, “This is biology. Why are we doing math?” Activities like those described here have demonstrated for my students the value of quantitative reasoning in biology and helped them begin to develop a sense of the vast scale of biological phenomena ranging from molecular interactions to the effects of global climate change on ecosystems.

Conclusion

Most students become very excited when looking at the microorganisms you can find in pond water. But viewing organisms under the microscope, while awe-inspiring, is not sufficient in and of itself to lead students to a deeper understanding of the scale of the microscopic world. “Understanding scale requires some insight into measurement and an ability to think in terms of orders of magnitude … At a basic level, in order to identify something as bigger or smaller than something else—and how much bigger or smaller—a student must appreciate the units used to measure it and develop a feel for quantity” (National Research Council, 2012, p. 90). The activities described here lay a foundation for developing an understanding of the scale of the microscopic world and help students develop the quantitative reasoning skills that are universally recognized as essential for understanding biology.

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References

Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K. & Walter, P. (2002). Molecular Biology of the Cell, 4th ed. New York: Garland Science.

American Association for the Advancement of Science (AAAS, 2011). Vision and change in undergraduate biology education: A call to action. Washington, D.C.: AAAS.

Bar-On, Y.M., Flamholz, A., Phillips, R. & Milo, R. (2020). SARS-CoV-2 (COVID-19) by the numbers. eLife, 9: e57309.

College Board (2019). AP Biology Course and Exam Description, rev. ed. New York: College Board.

Cooper, R. (2019). Using mathematical reasoning to quantify the microscopic scale. HHMI BioInteractive Educator Voices [Web log post], August 19. https://www.biointeractive.org/professional/educator-voices/using-mathematical-reasoning-quantify-microscopic-scale.

Cudmore, L.L. (1977). The Center of Life: A Natural History of the Cell. New York: Quadrangle/The New York Times Book Co.

Genetic Science Learning Center (2010). Cell size and scale [interactive]. https://learn.genetics.utah.edu/content/cells/scale/.

Gilbert, S.F. (2006). Developmental Biology, 8th ed. Sunderland, MA: Sinauer.

Goodsell, D.S. (2009). The Machinery of Life. New York: Springer.

Herbert, P.D.N., Witt, J.D.S. & Adamowicz, S.J. (2003). Phylogeographical patterning in Daphnia ambigua: Regional divergence and intercontinental cohesion. Limnology and Oceanography, 48(1), 261–268. https://aslo-pubs.onlinelibrary.wiley.com/doi/abs/10.4319/lo.2003.48.1.0261.

HHMI BioInteractive (2004). Animated life: Seeing the invisible [video file]. https://www.hhmi.org/biointeractive/seeing-the-invisible.

HHMI BioInteractive (2017). What van Leeuwenhoek Saw [classroom activity]. https://www.hhmi.org/biointeractive/what-van-leeuwenhoek-saw.

HHMI Tangled Bank Studios (2018). A world without microbes [video file]. Chevy Chase, MD: Howard Hughes Medical Institute.

Ley, B. (1999). Diameter of a human hair. In G. Elert, (Ed.). The Physics Factbook. https://hypertextbook.com/facts/1999/BrianLey.shtml.

Milo, R. & Phillips, R. (2016). Cell Biology by the Numbers. New York: Garland Science. http://book.bionumbers.org/.

Morholt, E. & Brandwein, P.F. (1986). A Sourcebook for the Biological Sciences, 3rd ed. New York: Saunders College Publishing.

Mukherjee, S. (2010). The Emperor of All Maladies: A Biography of Cancer. New York: Scribner.
National Research Council (2003). *BIO2010: Transforming undergraduate education for future research biologists*. Washington, DC: National Academies Press.

National Research Council (2012). *A Framework for K–12 Science Education*. https://www.nap.edu/read/13165/chapter/8#90.

NGSS Lead States (2013). *Next generation science standards: For states, by states*. Washington, DC: National Academies Press.

Rainis, K.G. & Russell, B.J. (1996). *Guide to Microlife*. New York: Franklin Watts.

Rutherford, F.J. & Ahlgren, A. (1990). *Science for All Americans*. New York: Oxford University Press.

ROBERT A. COOPER is a retired Biology Teacher living in Warminster, PA; e-mail: bcooper721@gmail.com.

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