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Concise language promotes clear thinking about cell shape and locomotion

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The lack of a concise and consistently applied vocabulary to describe dynamic membrane protrusions has become an impediment to the study of cell motility. Specialized protrusions are used by many unicellular eukaryotes for feeding, mating, and evading predators, activities that are central to carbon cycling through global food webs. Human cells also produce dynamic extensions that mediate physical interactions with the environment, including: nerve growth cones, the leading edges of migrating immune cells, and filamentous protrusions with a variety of functions including cell-to-cell signaling, and cell protrusions that support migration of individual cells as well as the coordinated movement of cell sheets during development.

Unfortunately, most of the words we use for protrusions were coined based on morphology without regard to function or the molecular mechanism. We now know that similar-looking structures can be formed by different molecular mechanisms and, conversely, that protrusions with distinct morphologies may be produced by the same molecular machinery. Some words, therefore, can mean more to readers and listeners than we intend. Here, we define some words commonly used to describe cell protrusions, and discuss how their shifting definitions cloud our thinking and can impede interpretation and comparison of experimental results. We suggest that a new and more concise vocabulary, based on function and assembly mechanism as well as gross morphology, would decrease confusion among researchers just entering the field and streamline communication among those who have been around for a while.

What kinds of protrusions do eukaryotic cells build?

In addition to microtubule-based flagella, whose stereotyped structure is easily verified by electron microscopy, cells also assemble cellular projections whose identity can be difficult to ascertain. Here we focus on transient structures that extend from the cell body, surrounded by plasma membrane.

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Pseudopod/pseudopodium {see Footnote 1}

Morphological origin: This is probably the oldest word used to describe a biological protrusion, dating back at least to the 1840s.^[1] This generic term for a protrusive membrane structure is interchangeable with the word “protrusion” itself, and has been applied to all of the structures described below at one time or another.

Functional connotations: From the earliest uses of the word, pseudopods have been thought of as “instruments of motion”,^[1] but not all pseudopods contribute to cell locomotion. Even for pseudopods that are associated with cell motility the connections between protrusion and locomotion are complicated and/or unclear.

Mechanistic connotations: As the most generic term for protrusion, “pseudopod” also has the least mechanistic baggage. Some pseudopods are supported by actin filament networks; others are created by non-canonical cytoskeletal polymers such as the Major Sperm Protein of nematode sperm;^[2] and some pseudopods, such as blebs (see below), are defined by the absence of cytoskeletal elements.

Filose pseudopod

Morphological origin: This term refers to thin, often tapered or needle-like pseudopods of protozoa and occasional metazoan cells, and has been used to describe cell protrusions built by microtubules as well as by bundled actin filaments. The latter is also often referred to as a filopod or filopodium (see below).

Mechanistic connotations: The term “filose pseudopod” is a more generic term than “filopod,” and in many cases is used to describe structures of unknown molecular composition.

Filopod/Filopodium

Morphological origin: Descriptions of “fine” or “delicate” pseudopods can be found as early as the middle of the 19th century, but the word “filopod” (or “filopodium”) appears to have been coined by Kinnander and Gustafson in 1960.^[3] These authors described linear protrusions, 60–80 um long that appear during gastrulation of sea urchin embryos. Many other words have since been coined to describe similar structures, including “cytonemes” and “nano-tubes.” These cellular structures likely arise by a variety of mechanisms and carry out a range of biological functions. Structures described as “filopods” in the literature range in scale from micron-sized spikes at the leading edge of some mammalian cells to huge spikes that are several tens of microns long protruding from neurons.

Functional connotations: The filopods described by Kinnander and Gustafson help drive gastrulation during sea urchin development. Filopods are often described as having a

{Footnote 1}: Many of the words on our list are derived from Greek roots (pseudopod) or are Greek-Latin mixtures (lamellipod). Some writers append the latin suffix “-ium” to these words while others do not. Both forms are acceptable but we generally prefer to omit the suffix.

role in cell signaling and/or probing the properties of the extracellular environment. In some cases (e.g. nerve growth cones) filopods are described as having a pathfinding function.

Mechanistic connotations: Most filopodia are supported by thin bundles of linear actin polymers. It remains possible that these membrane-bound actin bundles may not be initiated by a single molecular event, and current efforts aim to define molecular assembly mechanism(s).

Lobose pseudopod/lobopod

Morphological origin: The term “lobose pseudopod” describes blunt, or “finger-like” pseudopods that are less tapered or pointed than those described as filose.

Functional connotations: Lobose pseudopods are associated with the migration of a wide variety of free-living amoebae, but the term has also been applied to some human cells. [4]

Mechanistic connotations: Petrie et al. adopted the term “lobopodia,” to refer specifically to cylindrical protrusions that rely on contractility and which are associated with blebbing. [4] However, lobose pseudopods from other species appear to be filled with actin polymer.

Lamellipod/lamellipodium

Morphological origin: “Lamellipodium” was coined by Abercrombie in 1970 to describe thin, flat, veil-like pseudopods produced by slow-moving mesenchymal cells adhering to glass surfaces. [5]

Functional connotations: In strongly adherent animal cells, the lamellipod is thought to extend in order to promote creation of focal adhesions to the extracellular substrate, which then pull the cell body forward. In addition to the highly adherent lamellipods of mesenchymal cells, however, many fast-moving cells create lamellar pseudopods that are not supported or templated by a flat surface. [6] These free-standing lamellar pseudopods appear to have a different function from the classical lamellipods, and so applying the term “lamellipod” to any thin, flat protrusion has the potential to create confusion.

Mechanistic connotations: This term has developed a strong association with branched-actin networks built by the Arp2/3 complex, but has also been used to describe thin, flat pseudopods that contain no actin filaments at all (e.g. nematode sperm [21]).

Bleb

Morphological origin: The word “bleb” to describe a blister dates to the 17th century, but its use in biology to describe a protuberance on the surface of a cell can be traced to the early 1960s. [7] Similar to blisters, blebs represent regions where the plasma membrane has detached from the underlying cortex. A bleb, therefore, generally contains little or no cytoskeletal polymer and is mainly filled with cytoplasm.

Functional connotations: Dying cells often generate many blebs and for years blebbing was strongly associated with cell stress and/or death, and more recently with crawling motility (see below).

Mechanistic connotations: A bleb forms when the plasma membrane delaminates from the actin cortex and inflates with cytosol to create a spherical bubble protruding from the cell. Actin enters the bleb, new cortex forms, and the cell then creates another bleb to continue the process.

Language used to describe protrusion-associated cell movement.

Cell motility refers to all types of active cell movement, including both cell crawling and flagellar-based swimming. Cell migration is more often used to describe crawling of individual cells, but is also sometimes applied to the collective movement of groups of cells (such as during development). There have been efforts to categorize modes of crawling by environment (surface vs 3D), adhesion strength, degree of cortical contractility, and rates of actin polymerization, but to date no systematic nomenclature has taken hold. Here, we briefly discuss various terms used to describe cell movement, beginning with the most generic.

Mesenchymal motility:

The most exhaustively studied form is the adhesion-dependent movement of some animal cells, especially fibroblasts, which attach tightly to the extracellular matrix using the cell-surface protein integrin. While this type of movement has been explored in detail, many of the mechanistic insights from this work do not apply to other cell types and organisms that migrate without making specific adhesions. Cancer biology literature generally categorizes tumor-cell movement as “mesenchymal” vs. “amoeboid.” Mesenchymal, or fibroblast-like, motility is characterized by strong integrin adhesion, actin stress fibers, and elongated and spindle-like cell shape. Amoeboid cancer cells exhibit low adhesion, strong cortical actin contractility, and rounder morphologies.

Amoeboid motility:

In classical Greek, the word *ἀμοιβή* means “change” or “transformation” and in the 19th century it was applied to microorganisms whose shape appeared to change continually. “Amoeboid motility” now describes a mode of locomotion that is associated with dramatic cell shape change. Irregularly-shaped cells, however, are often called “amoeboid” regardless of whether they are known to be motile at all. Amoeboid motility has also acquired more specialist uses. Recently some cell biologists have begun to use amoeboid motility to describe a specific form of bleb-based cell migration (e.g. Lämmermann et. al^[8]). Because of the multiple meanings it has acquired, we suggest caution in the use and interpretation of the term amoeboid motility.

Blebbing motility:

Blebbing results from detachment of the plasma membrane from the underlying actin cortex and generally occurs when cortical contractility is high.^[8] Many different cells can crawl by

serial blebbing. *Entamoeba histolytica*, for example, crawls exclusively with a bleb-based pseudopod at the leading edge.^[9] Other cells, such as *Dictyostelium discoideum*^[10], and primordial germ cells in several species, cancer cells, and a number of other mammalian cell lines^[8] can switch between bleb- and actin-based pseudopods. How cells choose whether to form a leading edge pseudopod by blebbing or by creating a branched-actin remains an active area of research.

These terms are just the tip of the iceberg; the cell migration literature is rife with terms for new modes of motility (A1/A2 motility, α -motility), and old terms that are used consistently such as lamellum, and others that need clear definition, like “uropod”—which was originally defined as an actin-filled protrusion at the back of migrating cells, and is now used to describe any rearward protrusion.

Words matter.

For trainees and colleagues from other disciplines, the major barrier to understanding the biomedical research literature is linguistic. Biological macromolecules, biochemical activities, and complex cellular processes are often described by words that give us no clues to their meaning. When the meanings themselves begin to drift and bifurcate, even experts have a hard time keeping them straight. More importantly, when the meaning of a word drifts, it is often a sign that our understanding of a cellular process has changed; and when a word acquires more than one meaning it can reflect the fact that multiple, distinct processes have been inelegantly lumped together. The study of cell migration has now reached an inflection point where lumping cellular structures and processes together based on morphology has the potential to mask underlying differences in mechanism, causing confusion and misunderstanding.

We recognize that a coherent lexicon requires not just one or two research labs but an entire community. We are assembling a working group to address the situation, and if you are interested participating, please contact either RDM or LKFL.

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Three examples of a single morphological terms used for similar-looking protrusions built by distinct molecular mechanisms.

“Lamellipod” can refer to branch-actin filled protrusions build by fibroblasts as well as thin sheets build by polymers of the unrelated Major Sperm Protein. “Lobose pseudopods” can result from either actin polymer assembly or membrane delaminations (“blebs”). “Filose pseudopods” can be built by either linear actin bundles or by microtubules. We chose these particularly obvious examples to highlight the issue; many organisms have had these and other terms applied without *any* knowledge of underlying molecular mechanisms.