# Strength Comes from Numbers for Zippers and Cadherin

Hans Pope
Living Architecture Research Project Report
Cell Biology 219, Professor Robert Morris
Wheaton College, Norton, MA, USA
December 4, 2012
Click here for HeLa cell report

**Rule to build by:** To build strong junctions, use small identical units that distribute mechanical load.

**What:** A microscopic structure that upholds this principle are Cadherin, which is a cell-cell adhesion molecule (CAM). The macroscopic structure that upholds this principle is a zipper.

**How:** Before we can begin exploring our understanding of Cadherins, we must first examine cell-cell adhesion. This begins with forming two main groups of cell-cell junctions: *Adherens junctions,* and *desmosomes* (Alberts et al., 2009). These two types of junctions provide mechanical strength to cell-cell adhesion by similar mechanisms. They both employ homophilic binding interactions that use proteins to span the membrane of one cell and chemically bind with an identical protein of a neighboring cell (Oda & Takeichi, 2011). These proteins originate in the intracellular space in order to attach to cytoskeletal filament; most commonly adhesion junctions bind to actin, while desmosomes bind to intermediate filaments such as keratin (Alberts et al., 2009). By doing so they obtain a mechanical backbone that will provide tensile strength to the binding proteins in the extracellular space, thus the junction as a whole. When multiple cells bind to each other in this way they create an *epithelium,* which can be simply defined as a sheet of cells (Alberts et al., 2009). Now that the basic foundation of joining two epithelium together has been explained, we can now examine in detail cadherin and the key elements that make them work.

The protein mentioned above that binds homophilically in the extracellular space is a *cadherin,* a family of transmembrane proteins that typically bind monotypic cells together (Truong, 2002). A cadherin protein consists of three main domains, the first being a cytoplasmic (Truong, 2002). Here the cadherin's C-terminal end attaches to a *linker protein* that mediates the connection between the cadherin protein and a cytoskeletal filament (Alberts et al., 2009). Next a hydrophobic membrane spanning region allows for the protein to cross form the intracellular lumen of the cell to the extracellular matrix. Finally a cadherin has an extracellular region that will hold most of our attention. For a visual to help illustrate this section please see Figure 2.

The extracellular region possess a unique domain repeat know as the cadherin motif, also called the EC domain, which contains negatively charged peptide sequences (Yagi & Takeichi, 2000). Typically the EC domain consists of 5 repeats that occur in tandem, although recently variations have been discovered (Oda & Takeichi 2011). These sequences interact with calcium ($Ca^{2+}$) ions (Yagi & Takeichi, 2000). Cadherin function is $Ca^{2+}$ dependent thus it is

critical that $Ca^{2+}$ is present in the extracellular matrix. Without $Ca^{2+}$ cadherins cannot bind with identical cadherins, and are susceptible to proteolysis (Troung, 2002). It is from this $Ca^{2+}$ dependency that ***Ca***dherins earn their name (Alberts et al., 2009).

It is crucial to and any living creature that cells can congregate and organize properly. It is also just as important for cells to remain adjacent to the correct neighboring cells. It is our current understanding that cadherins play a crucial role in accomplishing these three feats, starting as early as development (Takeichi, 1988). Takeichi suggests that cadherin posses the ability to selectively associate through homophilic binding (Takeishi, 1988). Experimental evidence of dissociated animal tissues consisting of multiple cell types were able to not only regain confluence with one another when $Ca^{2+}$ was re- introduced, but were able to associate in their original, correct formation (Takeishi, 1988).

Now that we understand what cadherin are and how cell-cell binding occurs, we can place this in context with the rule to build by. The rule states that: “to build strong junctions, use small identical units that distribute mechanical load,” upheld by cell junctions. Their strength comes from the hemophilic binding between identical cadherin, which are attached to cytoskeletal filaments that have incredible tensile strength (Alberts et al., 2009). Many cells make up a typical epithelium, and even more cadherin connections between them yields an immensely strong system of junctions.

A zipper is a simple man made machine that is used to seal virtually all types of materials that must be able to exist in an open or closed conformation, such as a jacket or tent. The traditional zipper is composed of four essential components: a box, pin, teeth, and a slider. A box, multiple, identical teeth spaced evenly, and a slider compose one track, or side of the zipper. A pin and teeth evenly spaced (staggered with the opposite track) create the opposing track. To zip, the pin is placed in the box at the bottom of the zipper to begin the initial alignment. The slider then connects the teeth by matching one tooth’s “hook” with the opposing tooth’s “hollow”. This “hook to hollow” relation continues the length of the zipper (Harris, 2002). The “hook to hollow” mechanism that zippers employ to bind hemophilic teeth is the molecular equivalent to the hemophilic binding interactions of cadherin. By using hemophilic binding with many identical teeth, load is distributed over the length of the zipper, decreasing the load on each individual “hook and hollow” pair.

**Why:** It is a distinct advantage for an organism to have strong junctions to help cope with all of the stress imposed upon its body. Junctions mediated by cadherin allow for epithelia to remain confluent when the system (such as skin) is placed in tension. As mentioned earlier, an epithelium is a sheet of cells. The principle dictated in the rule to build is upheld by stating strong junctions are created by binding small identical units. An event where tension is induced to, lets say skin epithelia, the tension force would be distributed over a great number of cells, effectively inducing minimal fractions of the total load to each cell junction.

Another way to understand how the distribution of load is advantageous to an organism, we can apply principles of physics to explain. The phenomenon known as pressure, most basically stated as the amount of force exerted over some unit of area (Serway & Jewett, 2012). The following equation is used to mathematically represent this theory:

**P**ressure = **F**orce/**A**rea or **P = F/A**

This equation demonstrates that with a constant **F**orce value, the pressure depends on the area over which the force is

applied. Note that as the value of **A**rea increase, the pressure will decrees so long as the load remains constant. For the purpose of cellular biology, we can manipulate this equation to specifically represent the rule to build by as it applies to cadherin. To do so, we can simple replace the **P** variable to show average **L**oad. Next we can change our **A** variable to **# of Cells**, and we can simply place the word *tension* in front of our **F** variable. The equation now reads:

$$\mathbf{L}\text{oad}_{avg} = \mathbf{T}\text{ension } \mathbf{F}\text{orce/\# of } \mathbf{C}\text{ells or } \mathbf{L_{avg} = TF/\#C}$$

Now we can see that the load cells of an epithelium experience is related to the **T**ension **F**orce applied divided by the **#** of **C**ells in that system. Note that for every cell-cell interaction, there are multiple cadherin binding events, each having its own strength value. Cells must be connected via cadherin or our **#C** value, no matter how large, is meaningless. Also note that as the number of cells increases, the **L**oad$_{avg}$ decreases assuming a constant **T**ension **F**orce. To see this mathematical expression put into practice, let's look at human skin.

Human skin on average contains roughly $1.1x10^{11}$ skin cells (Milo et al., 2010). If all of the skin could be pulled simultaneously with a force of let's say 300 Newtons (roughly a force that a human could apply by pulling). We would see our **L**oad$_{avg}$ distribution would look like this:

$$\mathbf{L_{avg}} = 300N/1.1x10^{11}$$

$$\mathbf{L_{avg}} = 2.7x10^{-9}$$

This demonstrates that the average load experience by each junction mediated in part by cadherin is incredibly small.

Zippers also uphold the rule to build by just as well as cadherin because their strength comes from the same basic mechanism. As can be seen in Figure 1, each track is made up of simple repeating units (teeth). This allows for the system to seamlessly tie together in a way that is strong due to the numerous identical teeth homophically binding to each other. It is possible to imagine a zipper with only a few teeth connecting, the zipper seal would not be very strong. This principle can be mathematically expressed by further deriving out **L**oad$_{avg}$ equation. By simply changing the variable (**#** of **C**ells) to **#** of **t**eeth, we can demonstrate the same **L**oad$_{avg}$ distribution pattern seen with our cellular example. For zipper strength always remember: "one zip, a zipper does not make (Morris, 2012)."

## Figures:

**Figure 1:** The zipper is a man made structure that is used for numerous products worldwide products. Notice the

repeating “teeth” that lock together as they are joined. Also note that this zipper does not have a slider (Rabensteiner,n.d).

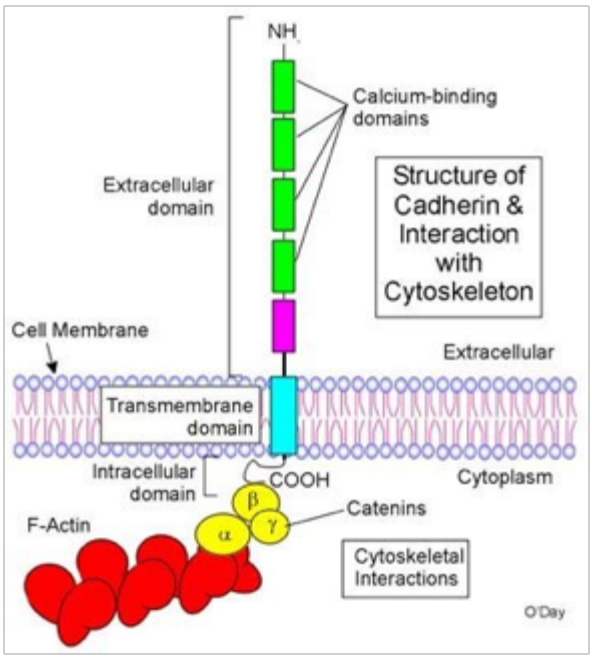


**Figure 2:** A cartoon that shows the basic molecular components that interact together to make a cadherin protein. Note that that this shows only one cadherin, to bind via hemophilic interaction, an identical cadherin would bind to the $Ca^{2+}$ binding domain near the N-terminus (Inserillo, 2011).

## References:


Alberts, B., Bray, D., Hopkin, K., Jonhson, A., Lewis, J., Raff, M., et al. (2009). *Essential cell biology* (3rd ed.). New York: Garland Science.

Inserillo, Elena. (2011). Cadherin. Vesicle recycling and Cell Migration. Web. 3 Dec, 2012.

Harris, Tom. (2002). "HowStuffWorks "How Zippers Work"." *HowStuffWorks "Science"*. N.p., 14 Apr. 2002. Web. 1 Dec. 2012. <http://science.howstuffworks.com/innovation/everyday-innovations/zipper2.htm>.

Milo et al. Nuci. Acids Res. (2010). Number of Human Skin Cells. *B10NUMB3R5*. Retrieved December 3, 2012, from bionumbers.hms.harvard.edu/bionumber.aspx?&id=101734&ver=7&trm=human%20skin

Morris, R.L. (2012). In person Discussion.

Oda, Hiroki, and Masatoshi Takeichi. (2011). "Evolution: Structural and functional diversity of cadherin at the adherens junction." *National Center for Biotechnology Information*. N.p., n.d. Web. 1 Dec. 2012. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3216324/>.

Rabensteiner. (n.d). *Zipper*. Zippers, N/A. *Wikipedia*. Web. 3 Dec. 2012.

Serway, R. A., & Jewett, J. W. (2012). *Principles of physics: a calculus-based text* (5th ed.). Boston, MA: Brooks/Cole, Cengage Learning.

Takeichi, Masatoshi. (1988). "The Cadherins: Cell-cell adhesion molecules controlling animal morphogenesis." *Biologist.org*. N.p., 1 Jan. 1988. Web. 1 Dec. 2012. <dev.biologists.org/content/102/4/639.full.pdf>.

Truong , K. (2002). "The Cadherin Resource - Introduction to Cadherins." *Cellular Calcium Information Server*. N.p., n.d. Web. 1 Dec. 2012. <http://calcium.uhnres.utoronto.ca/cadherin/pub_pages/general/intro_cadherins.htm>.

Yagi, Takeshi, and Masatoshi Takeichi. (2000). "Cadherin superfamily genes: functions, genomic organization, and neurologic diversity." *Genes & Development* . N.p., n.d. Web. 1 Dec. 2012. <http://genesdev.cshlp.org/content/14/10/1169.full>.