Introduction
Metabolism is the set of chemical reactions that happen in living organisms to maintain life. Metabolism is divided into two categories, anabolism and catabolism. In anabolism, small and simple precursors are built up into larger and more complex molecules, including lipids, polysaccharides, proteins, and nucleic acids. Energy is required for these syntheses.

So where does the energy coming from? Catabolism is the set of pathways that break down molecules into smaller units and release energy. This decomposition is an oxidative process involving a release of chemical free energy, most of which is used to drive the synthesis of adenosine triphosphate (ATP). ATP transports chemical energy within cells for metabolism. This energy is primarily stored in the addition of the third and final phosphate to the molecule and released by hydrolysis of ATP to ADP and a phosphate. ATP is usually produced in intracellular processes, and various mechanisms (such as the citric acid, a proton gradient created by an electron transport chain, and the enzyme ATP synthase) store the energy from breaking down glucose or another energy molecule in ATP. Glucose is a ubiquitous fuel in biology. It is used as an energy source in most organisms from bacteria to humans. Eukaryotic cells have specialized organelles, mitochondria, which are especially efficient in producing ATP from glucose. While ATP is well suited to its role as an energy carrier within the cell, it cannot be used as an effective energy storage molecule, as it is designed to store a much smaller amount of energy. Breaking down an entire glucose molecule to water and carbon dioxide releases enough energy for the cell to phosphorylate quite a few ADP molecules to ATP (38 in mitochondria).

For large scale organisms, glucose and other more complicated energy sources are actively transported in the body, for example, through the circulatory and digestive systems. Diffusion is simply too slow to move molecules at large scales. However, a single cell alone usually does not have the ability to actively transport glucose into the cell. Therefore, many single celled organisms rely on diffusion of these outside molecules into the cell, and rely on diffusion within the cell to perfuse the glucose throughout it. Even within larger scale organisms, diffusion plays a very significant role at the scale of a single cell, and glucose will diffuse from the blood into the individual cells where it can get broken down.

However, glucose in solution does not have free access to diffuse into a cell. All cell membranes are made of a phospholipid bilayer with the polar-water soluble phosphate groups on the outside of the both layers and the non-polar-water insoluble lipid groups on the inside. In cells with cell walls, for example plant cells with walls made of cellulose, fungi cells with walls made of chitin, or bacterial cells with walls made of peptidoglycan, the cell membrane is located just inside the cell wall, with the wall on the outside. In animal cells, the cell membrane forms the outside boundary that separates the cell from its environment. The cell membrane controls what substances come into and out of a cell. Everything the cell needs, from food to oxygen, enters the cell through the cell membrane while waste exits through the cell membrane. For a cell to survive, the cell membrane must be permeable to these molecules. The movement of molecules
like air through a screen can be passive or active. Passive transport does not require energy supplied, but might require a membrane-bounded protein. Active transport requires a membrane bound protein and cellular energy (ATP). Diffusion is the process by which the collisions between molecules cause them to continually spread apart from each other. Molecules are constantly moving. They move in straight lines unless they are deflected by other molecules or obstacles in the membrane. Their overall movement can therefore be described as movement from an area of larger concentration to another area of lower concentration. Diffusion continues until the molecules are equally distributed, that is, their concentration is equal throughout the area that contains them. At this point, the molecules continue to move and collide, but their concentration remains the same throughout the area of containment. Diffusion is an example of passive transport, which moves from high concentration to low concentration, as is osmosis, which is the diffusion of water molecules across a semi-permeable membrane.

However, molecules like glucose cannot freely diffuse through the membrane. Transporting glucose through membranes requires specific transport proteins from the GLUT family. These transport proteins mediate facilitated transport, that is, they can only transport glucose (or fructose) from areas of high concentration to areas of lower concentration. The glucose (or fructose) is bound by the protein, a flip-flop mechanism that reverses the membrane direction of the glucose (or fructose)-protein complex. The molecule is released and the protein flips around once more to initiate a new cycle. Transport activity is dependent upon the glucose concentrations and the number of transport proteins in the outer cell membrane. Principally, the GLUT family can transport glucose both into and out of cells. In most tissues the internal glucose concentration is quite low; transport can only proceed from the extracellular area into the cell. In the gluconeogenesis tissues (like liver and kidney), however, intracellular glucose concentration can exceed blood glucose concentration in the post-absorptive or fasting states. Export of glucose from liver and kidney occurs through GLUT2.

Many organisms, especially microorganisms, reside in habitats where nutrient concentrations are very different from the intracellular concentration that is required to maintain the optimum operation of the metabolic machinery. Evolution has provided mechanisms for coupling energy to the transport process so that nutrients can be captured from the environment and concentrated to optimum levels within the cells. These transport processes are tightly coupled to intracellular metabolism. Thus, they are subject to regulation by metabolic processes; in turn, the transport machinery itself is, in a number of cases, the primary site of intracellular metabolic regulation. It is clear that when considering the overall physiology of a cell, its transport systems cannot be ignored. As a corollary, a significant part of the biotechnology endeavor involves the use of microorganisms to produce economically useful products, any strategy for the optimum development of a microbiological process should consider the trans-membrane activities of raw material uptake and product secretion. In addition, the consumption and diffusion dynamics seen in a cell put physical limits on the maximum size of growth. The concentration profile of glucose within a cell will give us insight into the structuring and development of the cell.

**Set-up**
In this study, we model the diffusion and consumption of glucose in a cell with the diffusion
equation set in cylindrical coordinates. Because of the geometry of the cell, which we assumed to be a very long cylinder for this example, glucose diffuses in radially through the membrane and diffusion at the ends are minimal. Some cells (such as neurons and E. coli) are rod-shaped, and therefore well suited to be modeled as cylinders. This assumption allows us to neglect changes in the $\varnothing$ and Z directions, reducing the diffusion equation to a one dimensional partial differential equation. We recognize that many cell are not cylindrical but rather spherical; however, we use this assumption for the sake of simplicity in our analytical solution. A spherical cell can be modeled similarly with the assumption that the diffusion of glucose only depends on the radial component with no dependence on the $\Theta$ and $\varnothing$ directions. We have calculated the solutions for the spherical cell numerically.

To model consumption throughout the cell, an additional reaction term is added to the diffusion equation. We treat the consumption of glucose as a first order reaction in which the rate of glucose consumption is proportional to the concentration within the cell by a factor of $K$, the reaction rate constant. With this premise, the majority of the metabolic activity occurs in the outer shells of the cells where high concentrations of glucose occur and slowly tapers off as you approach the central axis of the cell.

Of course, it should be noted that uniform metabolic activity is unrealistic. The distribution of mitochondria, or metabolic enzymes in the case of prokaryotes, is not necessarily even throughout the cell. Therefore, our addition of the consumption reaction in the diffusion equation is not ideal. Simulations of alternative distributions of the metabolic activity are presented in the numerical solutions. In these cases, metabolic activity is confined to specific shells within the cell and appropriately scaled. While not considered in our simulations, the reaction rate constant $K$ could also depend on the angular positioning within the cells or length along the cell, thus potentially reintroducing $\varnothing$ and Z components to the equation. The addition of these two dimensions further complicates this problem, especially because the 1-D MATLAB pdepe solver can no longer be utilized.

To solve this partial differential equation, boundary and initial conditions must be applied. For the initial condition, we assume that the cell is at homeostasis and the concentration of glucose is constant everywhere. As for the boundary conditions, the center of the cylinder is assumed to be finite. This condition is obvious for physical reasons but also necessary when evaluating the Bessel function of the second kind, $Y$, because in this problem, $Yo$ functions are not allowed as they go to minus infinity as $r$ approaches 0; only the $Jo$ functions are permitted as they are finite at the center. When numerically simulating this boundary condition, we instead used the no-flux boundary condition at the center. For the second boundary condition, the concentration of glucose is equal to the concentration of glucose outside of the cell, which we call $C_0$. In addition, we evaluated the effect that a sudden change in the environmental glucose concentration would have on the cell using numerical simulations.

The accuracy of our numerical simulations are greatly dependent on the constants used. For consistency, we tried to find values for the diffusion coefficient, reaction rate constant and initial
glucose concentration from a single source. In a study conducted by E. Pollard, the diffusion constant, D, of sucrose in a cell was found to be approximately $1.0 \times 10^6$ cm$^2$/s. Although this value is for sucrose, we believe that the physical and chemical differences between sucrose and glucose are negligible in terms of their effect on diffusion, thus allowing us to utilize this diffusion coefficient for our analysis. The same paper reported values of the overall rate of glucose consumption, the approximate cell volume and the average glucose concentration within a cell to be $7.9 \times 10^5$ molecules/s, $2 \times 10^{-12}$ cm$^3$ and $2.6 \times 10^{14}$ molecules/cm$^3$, respectively (Pollard 1963). Unfortunately, values for the reaction rate constant, K, could not be found in the literature. Instead, we used the values of D, V and C$_i$ to estimate the value of K to be approximately 1500 s$^{-1}$.

Solution
The analytical solution obtained was (consult Addenda for derivation of analytical solution):

$$ u(\rho, t) = C_0 + \sum_{n=0}^{\infty} \frac{2}{L^2} \int_{0}^{L} (u(\rho, 0) - C_0) J_0 \left( \frac{j_n \rho}{L} \right) \rho d\rho \frac{e^{-\left( \frac{j_n^2}{L^2} + k \right) t}}{J_1(j_n)^2} J_0 \left( \frac{j_n \rho}{L} \right) $$

The analytical solution is essentially a linear combination of zeroth order Bessel functions of the first kind. The contribution of each term is derived from a Bessel-Fourier series of the difference between the initial conditions and the right boundary condition.

We also simulated these problems in MATLAB. Our code and all of the plots it generated are included in the addenda. Additionally, some of the plots are included below, and analyzed in our conclusion section.
comparison for shell

- t = 1ms
- t = 0.25 ms
- red: cylinder
- blue: sphere

[Glucose] (umol)

Radius (cm)

x 10^2
Conclusions
In this study, we utilized MATLAB’s pdepe solver to numerically simulate four different situations: the system described by the analytical solution; the case in which all metabolic activity is constrained to a shell within the cell; the case in which a different diffusion coefficient is applied within the cell membrane region; and the case where the boundary conditions drop over time (simulating moving from a high to low environment).

In the first graph presented, we displayed the first and simplest case in which glucose diffusion and consumption occur throughout the cell with constant diffusion and reaction rate constants. As expected, the concentration is much greater near the membrane and rapidly falls as it nears the center. The geometry of the cell also plays a significant role. Diffusion of glucose is greater in the sphere, indicated by the blue line. The transition from the dotted to solid line shows how the diffusion of glucose progresses with time. The dotted line represents the state after a quarter of a millisecond, when the system is still changing. However, after 1ms, the system has more or less reached steady state (solid lines).

Next, we look at the example in which the consumption of glucose is constrained to a shell. The shell ends at one quarter of the total radius, and this appears to set the concentration at the end of the shell to close to zero. It appears that consumption is so rapid that confining it to a shell is similar to setting a boundary condition at the outer part of the shell that the concentration is a
very small value. Once again, however, the trend of faster diffusion in a sphere is observed, and there are slightly higher concentrations of glucose throughout in both the transient and steady state plots.

We also simulated the cell with a membrane that had a lower diffusion constant than the rest of the cell, to model the fact that transporters are required to assist passage of the molecules through the hydrophobic interior of the membrane. In this simulation, we observed a very steep drop across the membrane, representing the lag due to the slower diffusion constant. This graph gets smaller as time progresses.

Lastly, we evaluate the case in which the external glucose concentration quickly falls. There are many different places where this phenomena can be observed, including the case in which a cell migrates from a glucose rich to glucose starved region. As expected, the initial glucose concentration profile approaches what we observe in the first case. However, when the drop in concentration occurs, the positive concentration difference between the inside and outside of the cell no longer exists. Thus, without this driving force for glucose diffusion, the cell returns back it its original state. Unfortunately, this simulation does not accurately describe what would happen in a real cell under these conditions. Because glucose cannot passively diffusion in or out of the cell, we would not see such a dramatic drop in glucose concentration near the cell membrane if a cell were to experience a sudden decrease in extracellular glucose. Instead, the cell would continue to actively pump whatever extracellular glucose it can against the concentration gradient but at a lower rate. In addition, the control mechanisms within the cell would try to stabilize the intracellular glucose levels by regulating the metabolic rate (decreasing the reaction rate constant) or using other forms of energy storage for food.

**Future Work**
The boundary condition at the cell membrane, while convenient for solving this problem, does not accurately describe the real process by which glucose is transported into the cell. As mentioned previously, glucose enters the cell through specific transport proteins rather than through standard diffusion. A more complete solution of this problem would model the diffusion through the membrane as a reaction process in which glucose “reacts” with the transport proteins when being transported into the cell. This requires investigating the distribution and concentration of membrane bound proteins which facilitate the flip-flop mechanism and their reaction rate constants.

For simplicity, one of the initial assumptions we made was that there were no end effects which allowed us to neglect the Z direction. This assumption, however, is only valid for cells in which the length of the cell is much greater than its diameter. Thus, in the future we should consider the effects of diffusion through the ends of the cylindrical cells as may significantly change the concentration profile along the Z axis. Additionally, we assumed that diffusion is radially symmetric. While this is a somewhat valid assumption for a cell in liquid culture, different conditions may hold for a cell on a solid surface. In these cases, the diffusion may not be radially symmetric, and $\varnothing$ and Z components must be considered and reintroduced to the
equation.

This diffusion/consumption dynamic within the cell can also be modeled as a control system. In response to a change in extracellular glucose, the cell may alter its diffusion through the membrane by regulating the membrane bound proteins. In addition, the cell can alter its metabolic activities by up or down regulating the enzymes necessary. Thus, the cell can maintain a reasonably stable level of glucose, making it less vulnerable to changes in the environment. Treating this system as a control system introduces many more variables and constants that we cannot account for without further research.

Lastly, more accurate diffusion and reaction rate constants could be found. As mentioned earlier, these greatly impact the performance of our simulations. Our estimates for K are not validated by any experimental evidence, rather it is a crude estimation using the available data.

Works cited: