Cellular metabolism is an extensively complex network of enzymes, metabolites, and other biomolecules required to both maintain homeostasis and appropriately react to stimuli and studying of it became recently possible after introduction of precise mass spectrometry. However, those measurements provide just snapshots of the concentrations and cannot fully capture the dynamics of changes (fluxes) caused by perturbations in concentrations in the substrates, enzymes, drugs introduced into a cell for therapeutic purposes, or foreign substances internalized into the cell. Even though, increased technological methods have enabled the investigation of biology at nanoscale levels, investigation of dynamics of such systems require the use of computational methods to fully comprehend the complex interactions that occur. An ability to use computers to simulate metabolic fluxes in response to external stimuli, and/or changes in the cellular environment would be extremely beneficial in preparing and planning laboratory and animal experiments, as it would allow researchers to predict the impact of those changes on the cell metabolism. As a result, the number of laboratory or animal experiments could be limited, and time for development of new therapeutic drugs reduced.

In general, dynamic systems have been modeled using sets of ordinary differential equations since Isaac Newton and Gottfried Wilhelm Leibniz developed calculus in the 17th century. However, this standard approach becomes rather tedious when the dynamic relationships among system variables involve randomness. In 1906, Andrey Markov first described dynamic relationships of random but dependent quantities, and such systems are now commonly referred to as Markov chains. With the proliferation of telephone services at the beginning of the 20th century, it became apparent that to predict and describe the operation of telephone networks, a technique to model random but dependent quantities must be applied. That idea led a Danish engineer, Agner Krarup Erlang, to model the number of telephone calls arriving at an exchange by a Poisson process, which was the first introduction and application of the queueing theory.

An overall goal of the project is to develop a computer simulation framework to model metabolism of a human cell using interconnected queueing networks. In such a model, each queue represents a different type of molecule of interest. Because of the relative ease of interconnecting queueing networks, such a model would be modular in nature, and allow for addition of new building blocks representing separate metabolic pathways once modules representing them are developed. It is expected, based on the preliminary results that the developed model would allow for computer simulation of complex interconnected metabolic pathways together with the controlling them intracellular signaling network. Use of queueing networks instead of ordinary differential equations or direct Markov chain description will allow for much greater scalability of the model both in terms of the number of involved molecule types and dynamic ranges of chemical reactions. There are many thousands metabolites and other small molecules in each human cell, making the intuitive aspect of understanding metabolite dynamics nearly inconceivable. In addition, as shown in our preliminary work, the queueing network approach allows for easy inclusion of random variations among different cells and an intracellular molecular noise, as well as conditional reaction triggers, the aspects not easy to capture through conventional biochemical modeling.

The proposed project will develop a computer simulation model for glucose metabolism combined with an associated signaling network. The model will include a signaling cascade from the insulin detectors at the cell membrane to glucose intake and all steps of converting glucose to cellular energy carrying molecules. Additionally, the final simulation model will include metabolic pathways for conversion of lipids and amino acids to the cellular energy carrying molecules together with the signaling pathways controlling the metabolic processes involved, including conditional triggers. All the developed simulation tools will be made available in a form of an interactive website for online simulation of metabolic fluxes. The tool will provide researchers and drug developers with a method to predict the metabolic fluxes crucial in development of new drugs and would show drug developers how cells react to a particular compound. This will significantly reduce time to conduct experiments, as computer simulation experiments will be much easier to prepare than cell culture or animal experiments. Number of sacrificed laboratory animals could then be significantly reduced, as computer experiments would be able to limit the number of animal experiments needed to be conducted by eliminating those that lead to failures. It will also enable researchers to consider many more possibilities, sometimes those looking like ‘out-of-box’ or farfetched approaches, and finally significantly reduce costs of developing new drugs, which in turn mean lowering costs of them.