With the dawn of the bioinformatics era comes a profusion of information. The development of innovative tools to extract useful information from this wealth of data points towards a revolutionary way to develop and design drugs. Scientists have high hopes for "in silico" biology techniques that focus on computer modeling and simulation instead of traditional wet laboratory methods of research for pharmicokinetics[1]. This technology promises to expedite the process of developing novel drug compounds by predicting their physiological effects with computers. In fact, several key breakthroughs have resulted from the use of these techniques, and additional discoveries lie within reach.

In silico drug discovery depends on "digital experiments" that utilizes bioinformatics to identify potential drug candidates. The entire process begins with the isolation of a particular human gene under investigation. The next step involves a homology search between the corresponding amino acid sequence and sequences from other model organisms. Then, follows the formation of a prospective three-dimensional model of the human protein based on the known structure of a similar protein. Finally, novel drug compounds are tested for correct binding to the protein to generate the appropriate function of increasing protein activity or disabling the protein[3]. After isolation of a drug candidate, computer simulations enter the picture by facilitating and improving the process in which compounds are tested for toxicity and efficacy.

The movement of experiments away from the bench and onto computers offers a number of advantages. Computer simulations save a great deal of time and labor by circumventing the process of screening thousands of prospective drug compounds by hand and robot to discover

whether they bind to the target protein. Digital experiments also reduce the need for animal testing or preliminary clinical trials. In addition, computer modeling supplants the reliance on biochemical analyses in which human error reduces the precision of the results. Armed with such simulation programs, pharmaceuticals anticipate a faster turnaround rate for marketing new chemical entities at a significantly lower cost, since roughly $500 million is invested into the development of a drug, and a significant $150 million is attributable to failed endeavors[4]. At the same time, the drawbacks of computational biology include the fact that the virtual experiments fail to represent the true environment in which the potential drug functions. Moreover, due to the incredible complexity of the human body, computer models are inevitably imperfect representations, and the numerous reactions and counter-reactions to a particular drug could be overlooked. Therefore, although the dependence on clinical trials on human subjects is greatly diminished, the use of computer simulations does not completely replace them.

The capabilities of computer modeling range from deducing the behavior of proteins in an aqueous environment to predicting the effect a drug candidate induces on the heart. Modeling the interaction between water and proteins is based on intermolecular and intramolecular forces and the role of molecular dynamics in projecting their sequential movements, or timesteps[5]. An atom in the molecule accelerates due to the forces of the other atoms acting upon it, and if the forces are constant, then the new velocity can be calculated, and subsequently, the new position can be calculated in accordance to Newton's Law. The compilation of the calculations for all the timesteps is required for a simulation. The final product is a model demonstrating how water interacts with hydrophilic residues at the protein surface. Simulations of the cell such as E-CELL, a model based on genes from *Mycoplasma genitalium*, allow researchers to manipulate

various metabolic pathways to observe the consequences. E-CELL operates on a rule-based system consisting of three lists: substance, rule, and system lists. The first list defines the components of the cell and the media; the second defines the cellular reactions; while the third defines the spatial and functional organization of the cell and its surroundings[61]. After input of the preceding information, the model calculates the concentrations of all the substances within the cell at every point in time[62]. The system can then be perturbed by the introduction of a potential drug compound to observe the effects on the cell compared to the baseline activity.

Various companies involved in biosimulation have released new technologies assisting in drug development that extend beyond the arena of the cell. For examples, Physiome Sciences, Inc. has developed several three-dimensional conductance models of animal and human hearts based on the electrochemical interactions resulting from the constant flow of potassium, calcium, and sodium ions across the surface of the heart muscle[6]. Scientists can use these models to monitor cardiotoxicity. For example, they can observe the induced effects on the voltage of the heart compared to the normal heart after introducing a drug compound intended to treat congestive heart failure[7]. The Entelos program, PhysioLab™, models the behavior of actual diseases such as asthma or HIV/AIDS. Construction of the models stems from a wide range of data collected from scientific papers that provide insight into the workings of the diseases combined with mathematical algorithms that describe the relationships between the physiological systems involved in the disease[8]. By changing various parameters according to factors such as age, gender, and overall health of the patient, the models facilitate several aspects of the drug development process from identifying drug targets to selecting the most promising candidate. Most importantly, they predict the proper dosage, dose frequency, pharmacologic properties, and

overall success of compounds headed for later clinical trials. Navicyte provides a third option for computer simulation of drug candidates. The IDEA software program aims to identify the most suitable compounds for drug development by "tak[ing] in vitro data and predict[ing] in vivo human pharmacokinetics," focusing on ideal solubility levels for optimal absorption into the body and permeability to the appropriate cells of the body[9].

The future of drug development leans more and more in the direction of in silico biology. Computer simulations offer a quick and easy method to predict optimal binding of drug candidates to target proteins in a physiologically correct environment, possible undesirable reactions induced by the drug, and drug dosage specifications. Although inherently imperfect due to their basis on the limited amount of patchy knowledge, computer models show great promise. With the combined effort of the traditional methods of research and the latest techniques, the prospect of faster and less expensive drug development becomes realistic.