Proposal of an Integrated Machine Learning Model for the Rapid Development and Analysis of New Drugs and Drug delivery Systems

Riley Kinsella, Titiana Tambi, Camila Cersosimo, Betsi Santos, and Chamudi Kashmila

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Overview

Traditional drug delivery methods come with many challenges, and can hinder the desired effects of treatments. Due to their ability to provide high bioavailability, the lungs offer a great alternative to these methods for systemic administration. Nanocarriers are a promising area of biotechnology, as they provide increased target ability, dosage control, bioavailability, and sustained release in the delivery of therapeutics. Inhalable nanocarriers are currently being studied as a method for delivery to the deep lung, allowing for a more targeted and sustained release of therapeutics. Nanoparticle-based drug delivery systems are often composed of a therapeutic encapsulated in a polymer to allow for the sustained release of the drug over a period of time. Due to the role they play in detecting and removing debris, macrophages are being studied as possible targets for drug delivery, and are based in receptor-ligand interactions. These interactions will be influenced by many factors in the formulation process, including choice of polymer and nanoparticle size, thus presenting a need for a detailed understanding. Through mathematical and computational methods, we suggest using various models of the mechanics and drug, substrate and tissue interactions that make nanoparticles a unique delivery system, and combine these computational models into a program that will allow a researcher to model many pharmacological aspects of a compound and delivery system at once.

Background

Traditional drug delivery methods, when injected, undergo metabolic processes through the spleen and the liver, where they accumulate in high levels. This presents an issue because, in cases where the site of disease is not located in the liver or the spleen, the therapeutics are not able to reach the target organ.[1] Currently, the lungs are being studied as possible routes of systemic administration of various therapeutic agents, due to their ability to provide high bioavailability in comparison to other non-invasive forms of administration. The large surface area, thin liquid layer over the alveoli, many capillary vessels, and relatively low enzymatic activity of the alveolar region of the lung allow for a direct and unhindered pathway to drug absorption.[2]

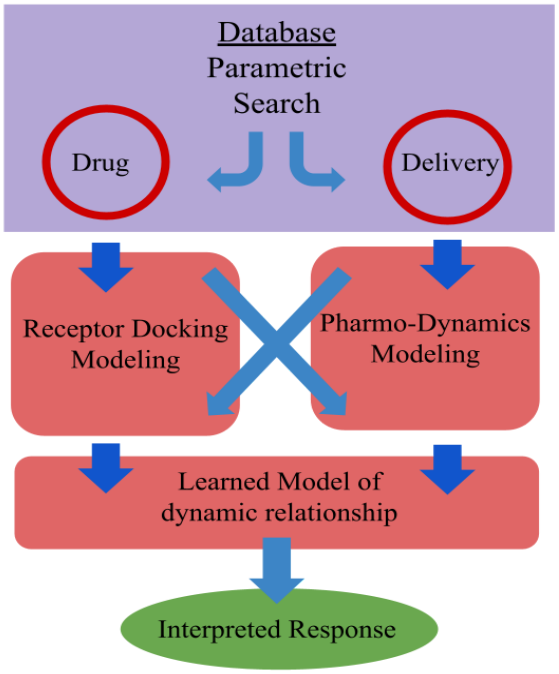
Nanoparticles have emerged as “intelligent” drug delivery systems due to their ability to overcome the challenges associated with traditional formulations, including wide systemic side effects, high toxicity, and rapid decay of therapeutics once in the target site. For pulmonary delivery, inhalable nanocarriers offer the ability to target specific sites within the lung, as well as provide a sustained release of the therapeutics.[2] Macrophages have recently been an area of interest for enhanced drug delivery due to the role they play in detection, phagocytosis, and removal of foreign bodies. These macrophage targeting systems are based in receptor-ligand interactions, and form the basis for the determination of size and chemical composition of nanoparticle formulations.[3]

To obtain desired sustained release, nano- and micro- carriers are encapsulated in a polymer, which allows for the sustained release of the drug over a period of time. Additionally, polymers often used for these applications offer high biodegradability,

tunability, and processability.[4] The interaction between the nanoparticles and macrophages will be strongly influenced by the chosen encapsulating polymer, as there are many factors that could affect the desired absorption of the drug. Thus, there is a need to develop an understanding of these ligand-receptors interactions at a detailed level, and this can be carried out using mathematical and computational methods in machine learning.

Our Proposed Application

We suggest using various models of the mechanics and drug, substrate and tissue interactions that make nanoparticles a unique delivery system, and combine these computational models into a program that will allow a researcher to model many pharmacological aspects of a compound and delivery system at once. Thus, the researcher could compare the dynamics of different drugs and deliveries and create a simulation that may predict dose response. We plan to use a variety of methods for optimizing the search and analysis of novel compounds and substrates.



Each pink box denotes a MLP net and blue arrows show information flow.

An overview can be seen in the figure database search and curation, along with dynamic modeling are computationally expensive tasks which could prohibit a proposal such as this from producing useful models. An ensemble of Multi-Layer Perceptron (MLP) classification networks model different parameters which contribute to an interpretation of these models into a prediction of the pharmacodynamics of a drug and its delivery system.

Deliverables

We aim to produce the following resources at the close of this project.

1. A program submitted as a script file (on Git) which can interface common molecule libraries.
2. Progress report, tracking the evolution of our methods, along with improvements that have been made
3. Documentation of the program to allow for researchers to implement their own models.
4. A final report which illustrates our results from applying our program to predict the dynamics of real compounds and delivery systems which are of present interest to researchers at URI.

Overall Goals

- Develop an understanding of ligand receptors to deliver drug products into the lungs, utilizing an appropriate database for research
- Create an efficient way to deliver drugs.
- Use machine learning to create a model for drug delivery.
- Explain and optimize current limitations of nanoparticles and macrophages interactions.
- Combine computational models into a program that will aid researchers in the modeling, comparison, and prediction of many pharmacological aspects of any particular compound.
- The computational model should be able to predict and optimize the pharmacodynamic model for nanoparticle utilization.

Project Description and Specific Goals
Semester Goals

- Identify a target receptor and therapeutic and determine their ligand-receptor interactions
    - Ideas: macrophages
- Utilize statistical programming for predictive modeling of ligand-receptor interactions
- Develop predictive models for the pharmacokinetic properties of our target drug
- Develop a database for bacteriological data in Dr. Martin's lab
- Clean necessary datasets for accurate analysis of this database

Long-Term Goals:

- Develop a streamlined, open-source program that will allow any researcher to model many pharmacological aspects of a compound and delivery system at once
- Build in a drug delivery optimization component to the program

Project Team Management Plan

- **Coding, machine learning, databases:** **Riley Kinsella**, Chamudi Kashmila
- Statistical analysis: Chamudi Kashmila, Titiana Tambi, Camila Cersosimo
- Writing and document gathering: Camila Cersosimo
- Manager: Titiana Tambi (task manager), Betsi Santos (scheduling)
- Biological expertise: Betsi Santos
- Pharmacy and nanoparticle background: Titiana Tambi, Camila Cersosimo

Milestones/Timeline

- February 16th, 2022 – Final proposal
    - Details about biological targets, drug, start looking for databases
    - Contact professors for machine learning expertise
- February 16th - March 2nd, 2022
    - Determine which database to use, clean up data
    - Select platform to use for programming (most likely R)
- March 2nd - Mid April
    - Statistical analysis/predictive modeling
- Mid April - May 11th
    - Write paper, work on presentation
    - Finalize the program
    - Create documentation for program use
    - Work on deliverables

Resources Needed

- Find an adequate database
- Find machine learning resources

Team Information

- **Riley Kinsella:** Philosophy major, Math minor. Interested in CS research and applications in biology and pharmacology. Email: riley_kinsella@uri.edu cell: 401-465-3339.
- **Camila Cersosimo:** Chemical Engineering major with concentration in pharmaceutical engineering, Statistics minor. Experience with nanoparticle drug delivery for pulmonary applications. Email: _ccersosimo@uri.edu, cell: 401-662-3409.
- **Betsi Santos:** Cell and Molecular Biology with concentration in Bioinformatics. Previous experiences in General Biology, Chemistry. Internship research with focus in Biocontrol. Basic classes in computer sciences, in specific Python and basic understanding of C/C++. Email: brsantos@uri.edu cell: 401-696-4349.
- **Titiana Tambi:** Pharmaceutical Sciences Major. Economics Minor. Previous Experience: SQL, R, Microsoft Excel. Currently working in a neuroscience lab, studying cerebral palsy and Alzheimer's disease. titiana_tambi@uri.edu
- **Chamudi Kashmila:** Graduate student in computer Science. Interested in Data Science and Machine Learning. Email: abeysck@uri.edu, cell: 401-212-7410

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