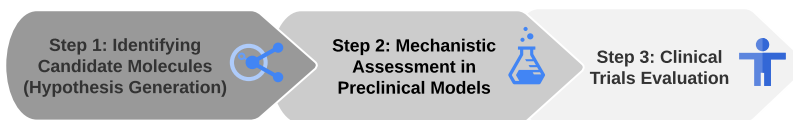


Learning Deep Representations of Drug Combination Mechanics

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Motivation Drug discovery is a challenging endeavour hampered by high attrition rates in the pharmaceutical industry [1], problem complexity in certain therapeutic areas (e.g., several types of cancers), and changing regulatory requirements [2]. Drug repurposing (also known as repositioning, reprofiling or re-tasking) has emerged as a time and cost-efficient viable alternative towards identifying existing approved drugs for uses outside their original medical indication [2, 3]. The use of already approved drugs involves a lower risk (as the compounds have an acceptable safety profile), and lower research and development costs (US\$300 million for a repurposed drug v/s US\$2-3 billion for a new chemical entity on average [4]).



The steps involved in the drug repurposing pipeline can be seen in the figure above. The first step wherein candidate drug compounds of interest are identified, is of critical importance. There exist both computational and experimental approaches to the candidate identification problem [2]. Computational approaches typically involve leveraging different properties of the drug compounds and target genes/proteins from existing databases and electronic health records (EHRs) in order to identify synergistic drug combinations.

In contrast to single compounds, combinations of drugs are more effective since they are able to target multiple biological mechanisms. However, it is important to note that the search space is combinatorial, and efficient candidate combination identification is vital towards realising drug repurposing within practical timeframes. Existing computational approaches either require heavy manual intervention [2], or do not consider a comprehensive holistic view of information-driven combination generation [5].

Goal The project will address the three most important barriers in practical drug repurposing - automation, computational efficiency and effectiveness. The framework will manifest as a deep neural network driven adaptive sampling algorithm, that iteratively generates promising candidate drug combinations, and interfaces with an automatic cell profiling laboratory to experimentally evaluate the corresponding efficacy. The adaptive sampling process proceeds until a pseudo-optimal combination is found. The project is therefore highly interdisciplinary, and involves basic research in model-based sampling, design of experiments and deep learning.

Current State-of-the-Art A recent promising approach involves the use of machine learning (ML) regression models to learn the relationship between a pair of drug molecular signatures as input, and drug synergy as output [5]. Two drugs are said to be synergistic if the combined therapeutic treatment effect of the two drugs is greater than the sum of their individual effects. The regression model used in [5] is a combination multi-layer perceptron (MLP) network, which is composed of two individual MLPs - one for learning embeddings or features from single drugs, and the second for combining and mapping the features to a synergy score. There exist opportunities to improve the current state-of-the-art at multiple levels.

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- In addition to drug signatures, information about drug-target interactions, drug adverse effect profile, etc. can also be used as input to the regression model, and can potentially accelerate the search for pseudo-optimal drug candidates. Such information has not been utilised previously as part of an automated model-based sampling approach to the best of our knowledge. It is also important to consider combinations of size >2 so that the treatment efficacy can be maximised.
- Given the large combinatorial search space, it is imperative to consider the (epistemic) uncertainty associated with unexplored/insufficiently explored candidates in a principled manner. Existing work uses deterministic regression models, and even when a probability distribution has been considered over the predicted synergy, it has been aleatoric in nature [5] rather than epistemic.
- Adaptive sampling combines space-filling *exploration* of the variable space (drug/dosage combinations) with *exploitation* of potentially promising combinations. The interpretation of these two entities has been relatively narrow and limited in literature, and there exist several possibilities to explore in terms of defining exploration and exploitation with a view to minimize the number of preclinical experiments needed to arrive at pseudo-optimal drug/dosage combinations.
- Given access to co-PI Spjuth’s automatic robotized cell profiling laboratory, the project entails a very unique opportunity to develop a highly integrative and symbiotic pipeline, harmonizing the computational and experimental aspects of the drug repurposing.

Aims With a view of the motivation and opportunities outlined above, we define the following project aims.

- **Aim 1:** Systematically investigate and design a wider, more comprehensive and informative collection of inputs to the regressor (e.g., information about drug-target interactions, adverse effect profiles, other genotypic data).
- **Aim 2:** Design a bespoke deep Bayesian neural network (BNN) [6] architecture optimized to extract expressive features from the input collection outlined in Aim 1. The exact characteristics of the architecture will be dictated by the nature of inputs obtained from Aim 1.
- **Aim 3:** Develop a balanced adaptive sampling strategy that can leverage the prediction uncertainty provided by the BNN. Different interpretations of exploration and exploitation will need to be evaluated and considered herein.

Figure 1 presents an overview of the workflow corresponding to the proposed approach. Note that the deep learning driven adaptive sampling process will make use of existing data available in databases, in conjunction with live *in-vitro* experimental results. The feedback loop from the experiments will also iteratively enhance the accuracy of the neural network regressor.

The Interdisciplinary Aspect The project is highly interdisciplinary in nature, combining statistics (design of experiments, statistical sampling), machine learning (deep learning, Bayesian methods, active learning), computational science (surrogate modeling), optimization, bioinformatics and pharmaceutical biosciences. PI Singh brings extensive experience in the areas of design of experiments [7], adaptive sampling [8, 9] and deep learning [6, 10], while co-PI Spjuth has made substantial contributions in AI-driven high-throughput and high-content cell profiling, particularly in the field of drug development, and pharmacology in general.

Host Institution and Supervision Duties The PhD student will be hosted by the Division of Scientific Computing (TDB), Department of Information Technology, Uppsala University (UU). Assistant Professor Prashant Singh (TDB, UU) will be the main supervisor, and Prof. Ola Spjuth at the Department of Pharmaceutical Bioinformatics (Pharmbio, UU) will be the co-supervisor of the doctoral student. Both supervisors will be involved in all stages of the project, with PI Singh leading activities on the machine learning and

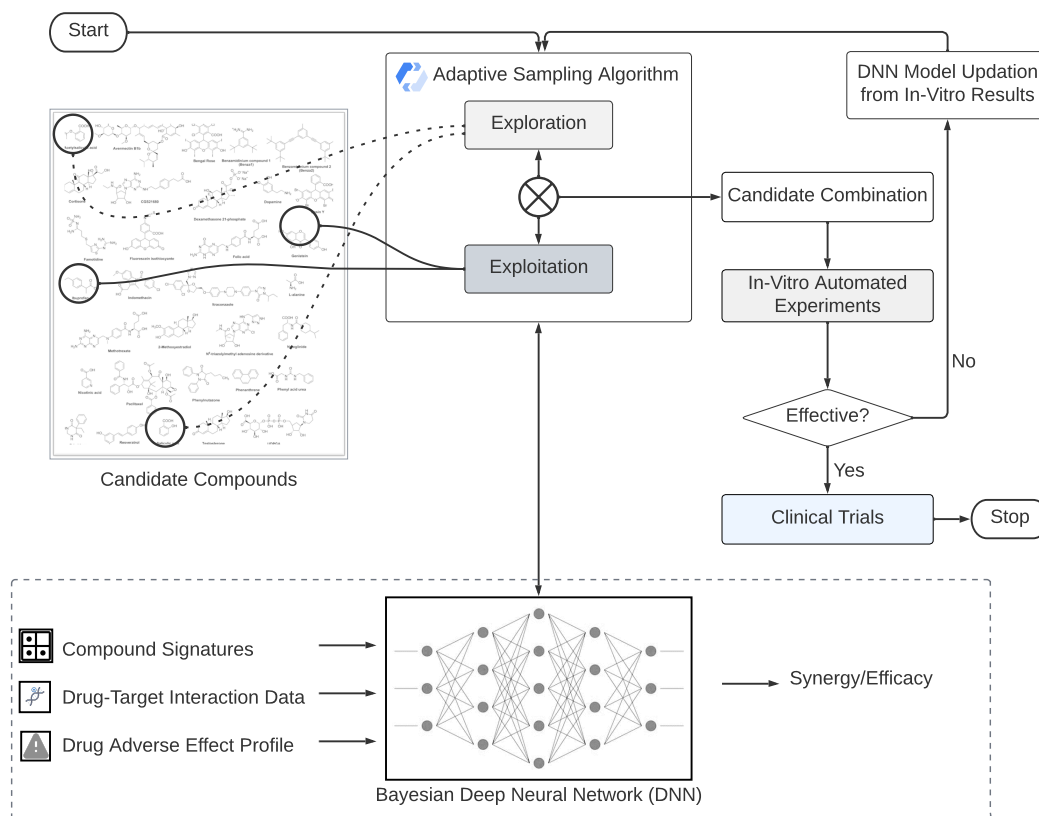


Figure 1: A high-level overview of the proposed approach.

statistical sampling side, and co-PI Ola Spjuth leading the activities in the bioinformatics, pharmacological and experimental areas.

Research Environment The student will be a part of the Integrative Scalable Computing Laboratory (ISCL) at TDB, with supportive colleagues from diverse research backgrounds including distributed computing, machine learning, optimization, stochastic modeling, and cybersecurity. There will be free-flowing and fluid contact with co-PI Spjuth’s Pharmbio lab with colleagues working in AI, cell biology and automation. PI Singh is a fellow, and co-PI Spjuth a group leader at the Science for Life Laboratory (SciLifeLab). The student will therefore also have the opportunity to take part in career development activities, seminars and research visits organized by SciLifeLab. The student is also encouraged to participate in leading conferences and research visits abroad. Project collaborators also include Wallenberg Advanced Bioinformatics Infrastructure (WABI), who will provide their expertise on the computational aspects of drug repurposing. Dr. Ivo Couckuyt at the surrogate modeling (SUMO) lab at Ghent University, Belgium will also be involved in the design of the uncertainty-based sampling component.

Financing CIM (50%), Division of Scientific Computing, Department of Information Technology (25%), Pharmaceutical Bioinformatics Research Group, Department of Pharmaceutical Biosciences (25%)

Data We will study both Sarcoma cancer cell lines available in the Spjuth lab, and primary Soft Tissue Sarcoma (STS) cells from patients available via collaborators at the National Sarcoma Center at the Karolinska University Hospital. The cell lines will be used for methods development and for building an STS-specific knowledgebase, and the primary cells will be used in the later phase of the project when applying the developed methodologies to individual patient samples.

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