Prediction of higher order drug combinations to treat cancer

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Prediction of higher-order drug combinations to treat cancer

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Finding a treatment for cancer is a major challenge of our time. In the ongoing research, combination therapies (the use of several drugs together) are of high interest. In comparison with the use of a single drug, combinations of synergistic drugs (*i.e.* drugs that are more effective together than alone) can be as effective while allowing to overcome the drug resistance, to reduce the doses at which the drugs are used, and consequently decrease their toxic effect and multiply their targets.
However, the space of all potentially effective combinations is too large to experimentally test all of them and assess their effectiveness, this is known as the combinatorial explosion problem. To overcome that, the identification of interesting combinations requires the help of computational tools. In recent years, machine learning models have been successfully used in biomedical applications. They are typically used in order to determine which combinations would be interesting to be experimentally tested. Since some models aiming at predicting the responses of *pairwise* combinations already exist, there are only a few machine learning models able to predict responses of *higher order* drug combinations (the order of a drug combination is defined as the number of drugs in the combination). In addition to the response of a drug combination (typically expressed as a growth percentage), the synergy score of this combination is of high interest. The synergy score allow to answer the question: how much are those drugs more effective together than individually?

This work is a step towards the use of machine learning to predict the effect of *higher order* (order larger than two) cancer drug combinations. It has been made in collaboration with Aalto University (Finland), where a machine learning tool called ComboFM has been developed. ComboFM is able to efficiently predict pairwise responses of cancer drugs. The goal of this work is to extend the use of ComboFM to the predictions of *higher order* drug combinations. To that end, we propose to combine ComboFM with another model, called the Dose model. The Dose model computes the responses of *any* order drug combinations, based on all the pairwise responses existing in the combination.

This work investigates how those two models can be combined together (Figure 1) in order to predict responses of *higher order* drug combinations (Figure 2) while decreasing the amount of required experimental data (pairwise responses). This combination of models gives rise to several issues that are tackled and investigated (Figure 3).
The experiments made in this thesis showed that ComboFM and the Dose model can efficiently be combined, as long as the parameters of both models are optimized specifically for this application.

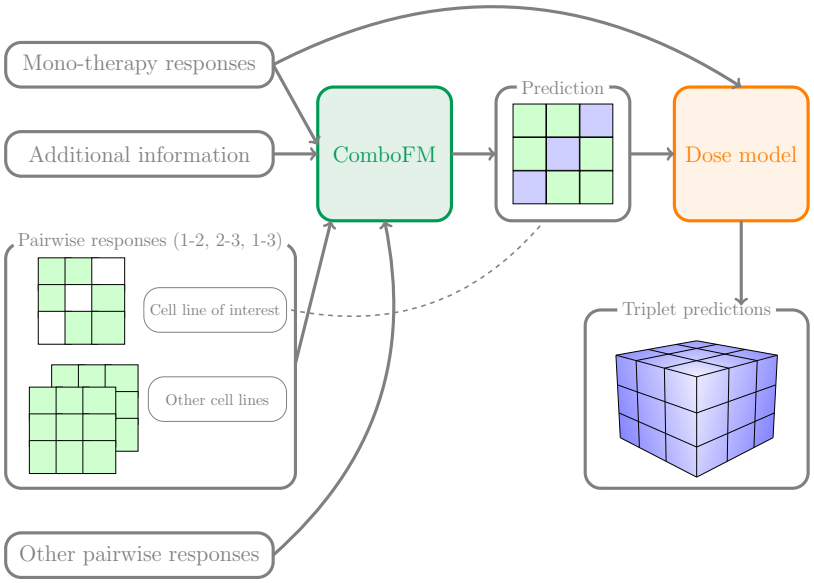

Figure 1: Schematics of the combination of ComboFM and the Dose model. This example corresponds to a combination of three drugs and corresponds to the scenario two of the experiments. ComboFM predicts some entries of the matrices of interest (depending on the chosen scenario) and the Dose model uses those predictions as input. Color representation: white = unknown; green = known; blue = predicted.

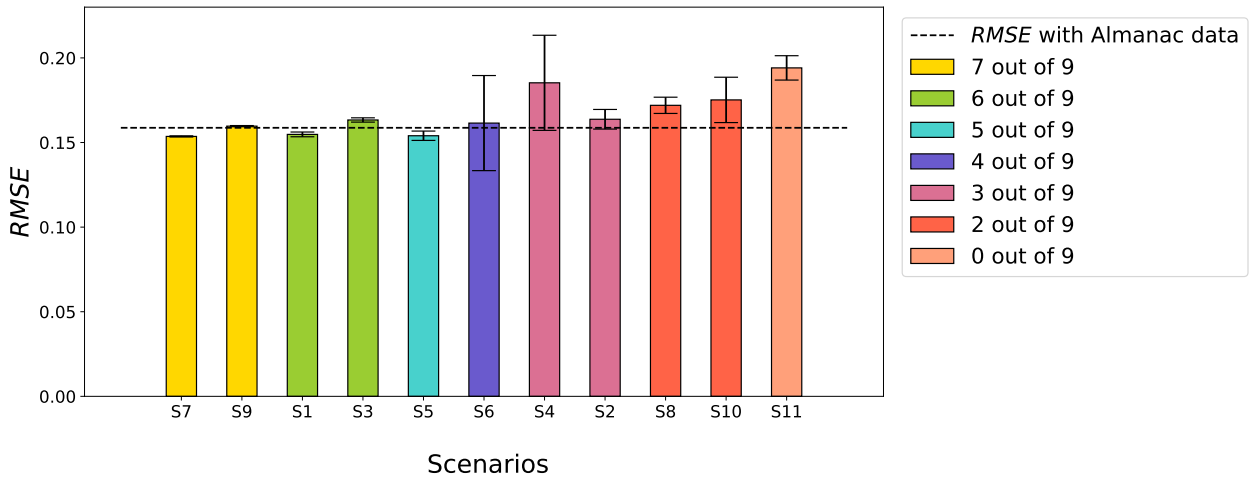

Figure 2: Performance of the combined model ComboFM and Dose model in terms of $RMSE$, for 11 different scenarios. The mean and standard deviation across the results corresponding to 5 different random seeds of ComboFM have been computed.

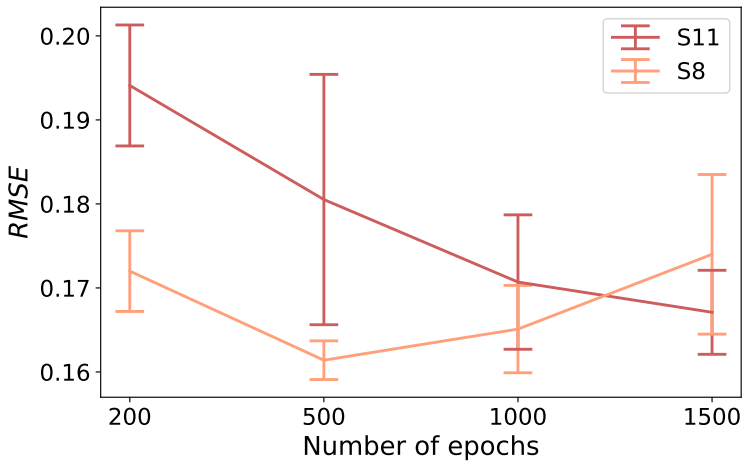

Figure 3: Evolution of the mean and the standard deviation of the performance in terms of $RMSE$ of the combined model ComboFM and Dose model across the 5 random seeds when the number of epochs in the training step of ComboFM increases.