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PTML Knowledge-Based System for Multi-Output Prediction of Anti-Melanoma Compounds

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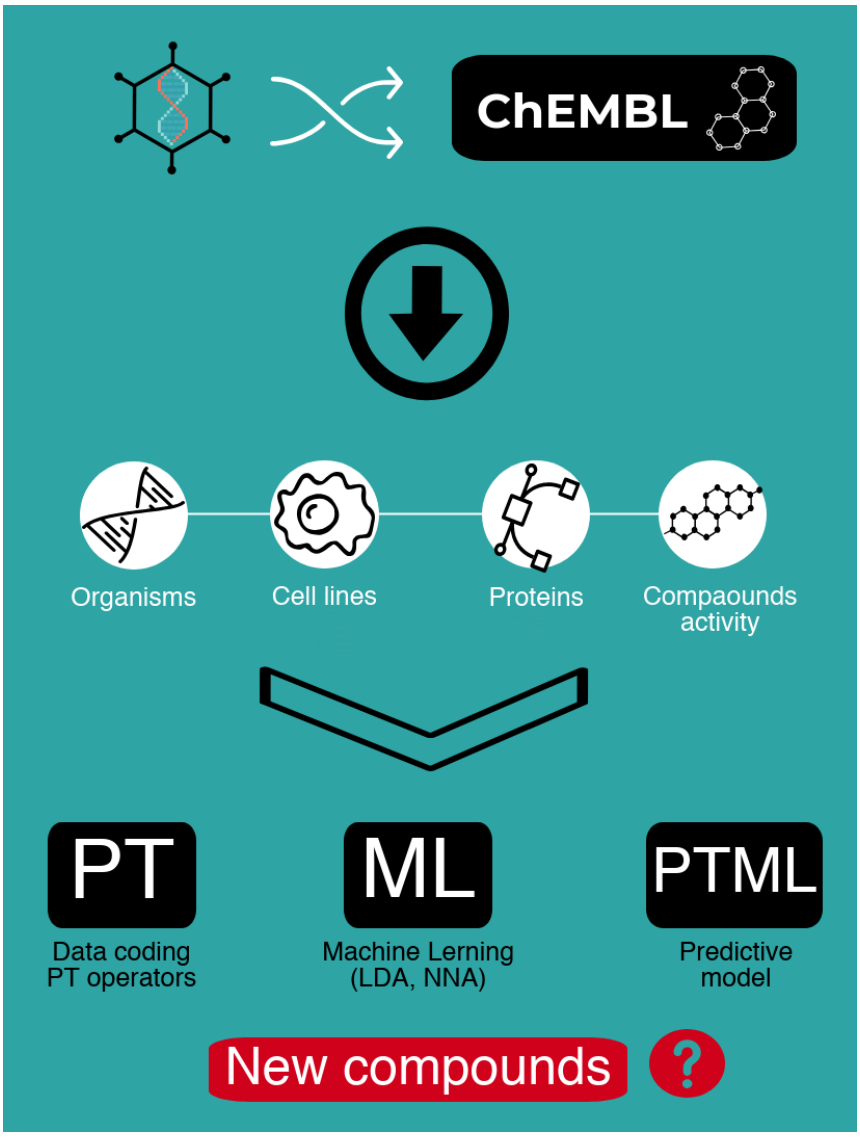
Graphic abstract



Abstract.

Defining the target proteins of new anti-melanoma compounds is a crucial task in Medicinal Chemistry. In this sense, chemists carry out preclinical assays with a high number of combinations of experimental conditions (cj). In fact, ChEMBL database contains outcomes of 327480 different anti-melanoma activity preclinical assays for 1031 different chemical compounds (317,6 assays per compound). These assays cover different combinations of cj formed from >70 different biological activity parameters (c0), >300 protein accessions (c1), >17 different drug targets (c2), >54 different cells (c3) and 5 organisms of assay (c4) and/or organisms of the target (c4), etc. This is a highly complex dataset with multiple Big data features. This data is difficult to be rationalized by researchers in order to extract useful relationships and predict new compounds. In this circumstances, we suggest to associate Perturbation Theory (PT) ideas and Machine Learning (ML) modeling to solve this combinatorial-like problem. In this work, we report a PTML (PT + ML) model

for ChEMBL dataset of preclinical assays of anti-melanoma compounds. This is a simple but very powerful linear model with only three variables, AUROC = 0.872, Specificity = Sp(%) = 90.2, Sensitivity = Sn(%) = 70.6, and overall Accuracy = Ac(%) = 87.7 in training series. The example also have Sp(%) = 90.1, Sn(%) = 71.4, and Ac(%) = 87.8 in external validation series. The model use PT operators based on multi-condition moving averages to capture all the complexity of the dataset. We also related the model with non-linear Artificial Neural Network (ANN) models achieving similar results. This support the hypothesis of a linear association between the PT operators and the classification as anti-melanoma compounds in different combinations of assay conditions. Last, we compared the example with other PTML models reported in the literature concluding that this is the only one PTML model able to predict activity against melanoma. This model is a simple but versatile tool for the prediction of the targets of anti-melanoma compounds taking into consideration multiple combinations of experimental conditions in preclinical assays.

Introduction

The World Health Organization (WHO) pointed out that Cancer is still among the more dangerous diseases nowadays.1 Specifically, Melanoma, wich is one of the most malignant skin tumors with constantly rising incidence worldwide, especially in fair-skinned populations. Melanoma is usually diagnosed at the average age 50, but, nowadays is also diagnosed more frequently in younger adults, and very rarely in childhood. There is no unique or specific clinical presentation of a melanoma. The clinical presentation of melanomas varies depending on the anatomic localization and the type of growth,. There are four major histopathological types of melanoma--superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma. Although dermatoscopy is a very useful tool in early melanoma detection, dermatoscopical features of melanomas are also variable74.

Medicinal chemists may use experimental procedures and/or computational techniques to predict new drugs against different targets 2. Specifically, in Machine Learning (ML) 3-5 techniques we can calculate different molecular descriptors codify the chemical structure of chemical

Materials and Methods

We obtained the outcomes of many preclinical assays from ChEMBL. The result of each assay is expressed by one experimental parameter εij used to quantify the biological activity of the ith molecule (mi) over the j-th target. The values of εij depends on the structure of the drug and also on a series of boundary conditions that delimit the characteristics of the assay cj = (c0, c1, c2, …cn). The first cj is c0 = the biological activity εij (IC50, EC50, etc.) per se. Other conditions are c1 = target protein, c2 = organism of assay, etc. The values εij compiled are not exact numbers in many cases. That is why we used classification techniques instead of regression methods. In so doing, we discretized the values as follow: f(vij)obs = 1 when vij > cutoff and desirability of the biological activity parameter d(c0) = 1 (see Table 1). The value is also f(vij)obs = 1 when vij < cutoff and desirability d(c0) = -1, f(vij)obs = 0 otherwise. The value f(vij)obs = 1 points to and strong effect of the compound over the target. The desirability d(c0) = 1 or -1 indicates that the parameter measured increases or decreases directly with a desired or not desired biological effect.

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