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A comparison of three computational modelling methods for the prediction of virological response to combination HIV therapy

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Summary

Objective: HIV treatment failure is commonly associated with drug resistance and the selection of a new regimen is often guided by genotypic resistance testing. The interpretation of complex genotypic data poses a major challenge. We have developed artificial neural network (ANN) models that predict virological response to therapy from HIV genotype and other clinical information. Here we compare the accuracy of ANN with

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Random forests;
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alternative modelling methodologies, random forests (RF) and support vector machines (SVM).

Methods: Data from 1204 treatment change episodes (TCEs) were identified from the HIV Resistance Response Database Initiative (RDI) database and partitioned at random into a training set of 1154 and a test set of 50. The training set was then partitioned using an *L*-cross (*L* = 10 in this study) validation scheme for training individual computational models. Seventy six input variables were used for training the models: 55 baseline genotype mutations; the 14 potential drugs in the new treatment regimen; four treatment history variables; baseline viral load; CD4 count and time to follow-up viral load. The output variable was follow-up viral load. Performance was evaluated in terms of the correlations and absolute differences between the individual models' predictions and the actual ΔVL values.

Results: The correlations (r^2) between predicted and actual ΔVL varied from 0.318 to 0.546 for ANN, 0.590 to 0.751 for RF and 0.300 to 0.720 for SVM. The mean absolute differences varied from 0.677 to 0.903 for ANN, 0.494 to 0.644 for RF and 0.500 to 0.790 for SVM. ANN models were significantly inferior to RF and SVM models.

The predictions of the ANN, RF and SVM committees all correlated highly significantly with the actual ΔVL of the independent test TCEs, producing r^2 values of 0.689, 0.707 and 0.620, respectively. The mean absolute differences were 0.543, 0.600 and 0.607 $\log_{10}$ copies/ml for ANN, RF and SVM, respectively. There were no statistically significant differences between the three committees.

Combining the committees' outputs improved correlations between predicted and actual virological responses. The combination of all three committees gave a correlation of $r^2 = 0.728$. The mean absolute differences followed a similar pattern.

Conclusions: RF and SVM models can produce predictions of virological response to HIV treatment that are comparable in accuracy to a committee of ANN models. Combining the predictions of different models improves their accuracy somewhat.

This approach has potential as a future clinical tool and a combination of ANN and RF models is being taken forward for clinical evaluation.

1. Introduction

Despite the approval of more than 20 antiretroviral drugs, HIV treatment failure due to drug resistance still occurs. HIV genotyping is recommended by a range of HIV treatment guidelines and is commonly employed to help the selection of a new regimen to re-establish viral suppression [1—3]. However, the complexity of resistance patterns and the expanding range of therapeutic options available have made the interpretation of genotype results in order to optimise virological treatment response extremely challenging [1]. A number of interpretation systems have been developed that relate HIV genotype to single antiretroviral drug susceptibility using different 'rules' or algorithms [for example, 4—7] and relational databases have been used to predict resistance to specific drugs by matching a test genotype with archived genotypic and phenotypic data [8,9]. There is no recognised standard interpretation system and different systems can produce different results from the same genotype [10—13].

Several groups have explored the use of bioinformatics to address the challenges of genotype interpretation and response prediction [14 for a review]. For example, artificial neural networks (ANN) [15], decision trees [16], support vector machines (SVM) [9] or phenotype matching in relational databases [17] have all been used to predict phenotype from genotype. Other groups have gone further to relate the predicted phenotype of individual drugs to virological response. However, the relationship between phenotype and response to combination therapy is not well characterized and attempting to infer response from genotype via the intermediate step of predicted phenotype has serious limitations [18]. Most of the groups that have attempted this have related predicted phenotype to a categorical prediction of response, with cut-offs in predicted fold-changes in phenotypic sensitivity linked to clinical response [e.g. 19]. However, in terms of potential clinical utility, a strong case can be made for predicting response to combination therapy (rather than individual drugs) as a continuous variable [20], *directly* from genotype. Given the complexity of the drug and genotype permutations the main obstacle facing this approach is the size of the dataset required [21].

The HIV Resistance Response Database Initiative (RDI) is a not-for-profit organization set up to