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Treatment history, CD4 counts but not previous genotype improve the accuracy with which neural networks predict virologic response to HIV therapy

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Introduction

- Previous exposure to HAART can result in archived resistant virus, undetectable by conventional genotyping, which may undermine the success of new treatment regimens.
- Artificial Neural Networks (ANN) can successfully predict virological response to combination antiretroviral therapy from genotype but undetected minority resistant species might limit their accuracy
- We assessed the influence of previous treatment or genotype history on the accuracy of artificial neural networks (ANN) predicting virologic response to HAART.
- The impact of using baseline CD4 counts as an additional variable in the ANN modelling was assessed in a third study.

Methods

Study 1: Treatment history

- A committee of 10 basic ANN models were trained using 2,559 treatment change episodes (TCEs), i.e. current genotype (55 individual mutations), baseline viral load (VL), new drugs, follow-up time and viral load response.
- 10 treatment history models were trained with 4 additional input variables: previous treatment with any of the following: AZT, 3TC, any NNRTI and any PI.

Study 2: Genotype history

- A committee of 10 basic ANN models were trained as above and 10 'genotype history' models were trained using cumulative data from all available genotypes up to and including baseline.
- 301 TCEs were used in the training of these models

Study 3: CD4 counts

- A committee of 5 basic models were trained as above and 5 'CD4 models' were trained with the additional input variable of baseline CD4 count (within 8 weeks of the treatment change).
- 2,983 TCEs were used in the training of these models.

Testing the ANN models

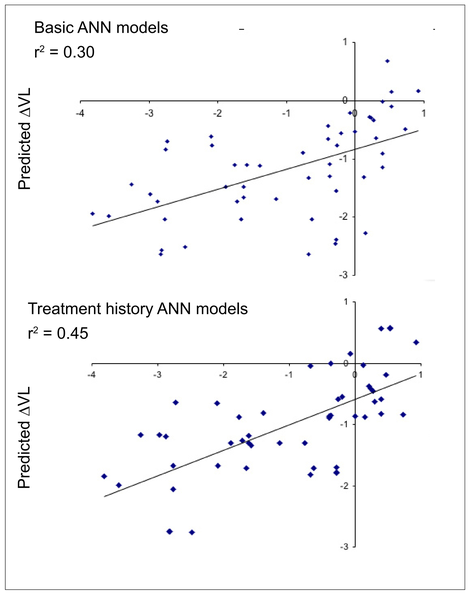
- In all three studies, the ANN models were tested using the input variables of independent test TCEs, which produced a predicted viral load response (ΔVL) that was compared to the actual response.
- The committee average performance of the ANN models was used (the average prediction of ΔVL across all the models in the committee, for each test TCE)
- Comparisons between predicted and actual ΔVL were made in terms of their correlation (Pearson Product-Moment) and the mean absolute difference ($\log_{10}$ copies/ml).

Results

Study 1: Treatment history

- Correlations between predicted and actual ΔVL for basic and treatment history models gave r^2 values of 0.30 *vs* 0.45 respectively ($p<0.01$). The correlations are illustrated in the scatterplots in Figure 1.
- The mean absolute differences between predicted and actual ΔVL were 0.88 and 0.78 logs (ns) for the basic and treatment history models respectively.

Figure 1: Scatterplots of basic and treatment history ANN models



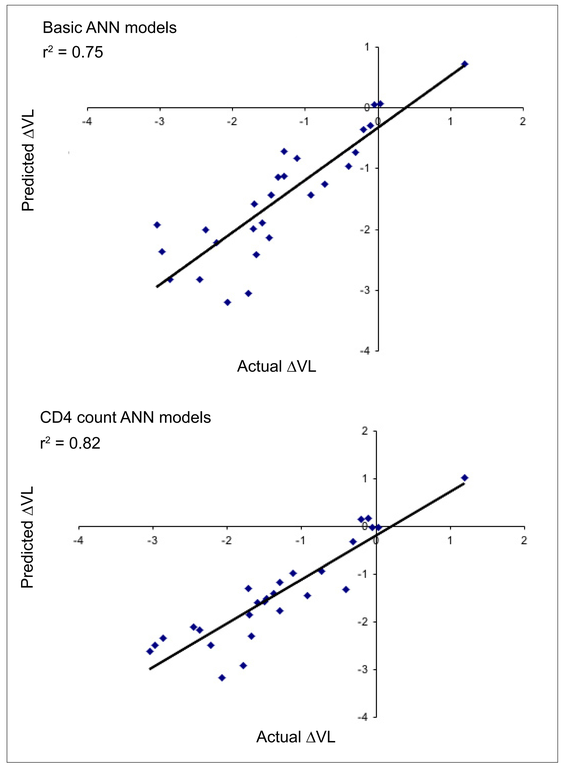
Study 2: Genotype history

- The correlations between predicted and actual ΔVL for the basic and genotypic history models gave r^2 values of 0.39 and 0.31 respectively (ns).
- The mean absolute differences between predicted and actual ΔVL were 0.71 and 0.83 logs (ns) for the basic and genotype history models respectively.

Study 3: CD4 counts

- The correlations between predicted and actual ΔVL for the basic and CD4 count models gave r^2 values of 0.75 vs 0.82 respectively ($p<0.05$). The correlations are illustrated in the scatterplots in Figure 2.
- The mean absolute differences between predicted and actual ΔVL were 0.42 and 0.34 ($p=0.05$) for the basic and CD4 count models respectively.

Figure 2: Scatterplots for basic and CD4 count ANN models



Conclusions

- The addition of treatment history data significantly improved the accuracy of ANN confirming that historical exposure to antiretroviral drugs can influence response to a new regimen.
- This suggests that treatment history may act as a surrogate for minority mutant populations enabling ANN to overcome this shortcoming of current genotyping.
- The use of cumulative historical genotype data did not improve the accuracy of the ANN.
- The addition of CD4 counts to the modelling significantly improved the accuracy with which ANN predicted virological response.
- The performance of the ANN models in these studies suggests that this approach has considerable potential as an aid to treatment decision-making in clinical practice

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