rdi hiv resistance
response database initiative

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Multiple refinements improve neural networks accuracy

Small proof-of-principle studies pave way for new high-performance models

Welcome to the fourth issue of RDI e-News. In the past year the RDI has been busy running a number of small 'proof-of-principle' studies. These were designed to test empirically different hypotheses for the improvement of the neural networks methodology. The most important findings are summarised here.

Treatment history improves accuracy across drug classes

In Issue 3 we reported that taking into account previous AZT exposure improved the accuracy with which the RDI's artificial neural networks (ANN) predicted response to d4T, abacavir and tenofovir. This latest study demonstrated that ANN trained to take account of previous exposure to AZT, 3TC any NNRTI and any PI were significantly more accurate than ANN models trained without treatment history variables across a range of treatments.

Two 'committees' of 10 ANN were trained to predict virological response to combination antiretroviral therapy. One was trained using baseline viral load, genotype (55 mutations in RT and protease), drugs and time to follow-up viral load, the other had the four additional binary input variables in their training (i.e. had the patient ever been exposed to drug X, yes/no).

The models were then provided with the baseline data for 51 independent cases including a wide range of combination regimens involving the three major classes of antiretroviral drugs. The models produced predictions of virological responses (ΔVL).

When the predicted ΔVL values were correlated with the actual ΔVL values from the test cases, the r^2 values were 0.30 for the basic models and 0.45 for the treatment history models. The mean absolute difference between the predicted and actual ΔVL values was 0.88 logs for the basic models and 0.78 logs for the treatment history models.

The scatterplots indicate that the improvement was largely due to a reduction in the number of cases where the models predicted a greater virological response than was actually achieved.

"These results suggest that including treatment history in the models can act as a surrogate for minority populations of resistant virus, undetectable by standard genotyping but nonetheless undermining subsequent therapy", commented Dr Brendan Larder, RDI Scientific Chair.
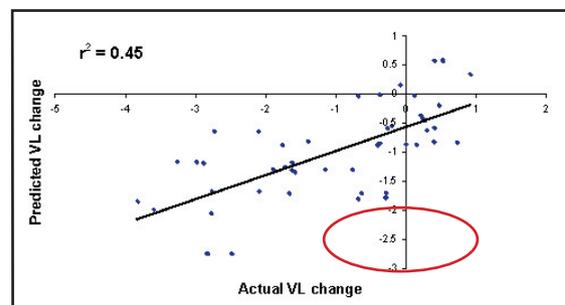
Scatterplot for the ANN models using treatment history. The area where the basic models made over-optimistic predictions is highlighted

Addressing the thorny issue of adherence

ANN models trained using data from highly adherent patients were significantly more accurate ipredictors of virological response than those trained with data from less adherent patients.

This was the unsurprising conclusion of a small study of ANN models developed using data from the BC Centre for Excellence in HIV/AIDS, Vancouver. The data were partitioned according to prescription re-fill data into two groups of 623 treatment change episodes: patients at least 90% adherent over the last six months and those less than 90% adherent.

Correlations between the models' predictions of ΔVL for independent data (from adherent patients) produced r^2 values of 0.11 for the 'non-adherent' models and 0.29 for 'adherent' models. The difference was highly significant (p<0.0001).
Further analysis of the adherence data revealed that the non-adherent patients included two fairly distinct populations; non-adherers (<10% adherence) and partial adherers, the vast majority of whom actually achieved >50% adherence. The contribution of the partially adherent patients data to the training of the models is likely to have reduced the difference in performance of the two ANN committees.

"These results clearly demonstrate the impact that non-adherence can have on response and, as a result, on

the training and performance of the neural networks", commented lead investigator Julio Montaner of the BC Centre. "It is gratifying that the models trained with data from adherent patients gave quite accurate predictions of response, despite the very small training data set."

Global models superior to single clinic models

Global ANN models proved as accurate as single clinic models in predicting virological response to treatment for patients from that single clinic and significantly better at predicting responses for patients from a wholly independent clinic. The results suggest that global models may be the most powerful way to exploit ANN as a generally-applicable aid to treatment decision-making.

This third proof-of-principle study compared global ANN models, trained with data from a large number of clinics, with models trained with data from a single clinic. Performance was compared in terms of the accuracy of their predictions of ΔVL for 'new' patients from the single clinic and for patients from a wholly independent clinic - without data in the training sets for either the global or single clinic models.

Correlations between predicted and actual ΔVL values for patients from the single clinic produced r^2 values of 0.78 and 0.70 for the single-clinic and global models respectively. The mean absolute differences between predicted and actual ΔVL were 0.49 and 0.55 logs respectively. These results were not significantly different.

Correlations for the data from a wholly independent clinic produced r^2 values of 0.07 and 0.23 for the single-clinic and global models respectively. The mean absolute difference scores were 0.97 and 0.66 logs respectively. Both differences in performance were statistically significant.

Models identify potentially effective combinations for treatment failures

Ultimately it is hoped that the ANN models' predictions of virological response will be a useful aid to treatment decision-making, with advantages over conventional, rules-based genotype interpretation. In this stage of the study the ANN models identified potentially effective alternative combinations of drugs for cases of treatment failure.

Nineteen cases of actual treatment failure were identified from the test data set from the single clinic: cases where the patient required a treatment change, the physician obtained a genotype, instituted a new drug regimen (with the genotype information for guidance) and yet the patient experienced virological failure (the viral load increased).

The ANN models were provided with the baseline data from these nineteen cases and were programmed to predict the response to the 100 most common combinations of 3-5 drugs in the RDI database for each case. The combination predicted to most effective was then taken for each case. The predicted and actual ΔVL values are in the following graph.
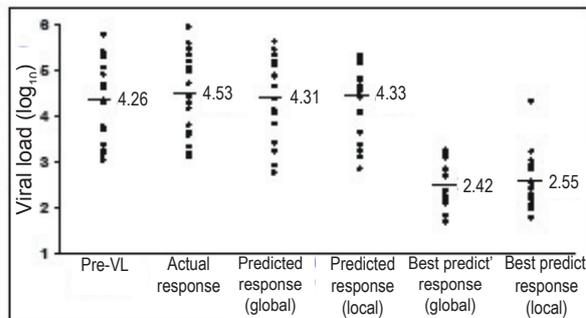
Both sets of ANN models identified alternative regimens that were predicted to result in substantial reductions in viral load. The average predicted reduction in viral load was around 1.75 logs, compared with an increase of around 0.25 logs from the regimens actually used.

"Whilst these are untested predictions, the fact that the models were quite accurate in their predictions of the actual failure and, on average, predicted actual ΔVL to within half a log gives a degree of confidence" commented Andrew Revell, RDI Executive Director.

RDI global family expands

The following institutions are now collaborating with the RDI, contributing data or providing financial support:
- BC Centre, Vancouver, Canada
- Bristol-Myers Squibb, Princeton, USA
- Community Programs for Clinical Research on AIDS (CPCRA), USA
- Fundacion IrsiCaixa, Badelona, Spain
- Hospital Clinic of Barcelona Spain
- ICONA cohort, Italy
- Italian MASTER Cohort c/o University of Brescia
- Italian ARCA Cohort, c/o University of Siena
- National Centre in HIV Epidemiology and Clinical Research, Sydney, Australia
- NIAID, USA
- Northwestern University Hospital, Chicago, USA
- Ramon y Cajal Hospital, Madrid, Spain
- US Military HIV Research Program
- Stanford HIV Database

Our thanks goes to all of you for your support.

The limiting factor for the accuracy of the ANN models is the amount of data we have to train them. In particular we need more data involving the use of atazanavir and tipranavir. If you can contribute.......PLEASE DO!

Coming up

The RDI is currently studying:
- The use of baseline CD4 counts in the ANN models
- The use of different mutation sets
- The use of different follow-up viral load windows
- The comparative accuracy of ANN and rules-based genotype interpretation in predicting virological reponse.

More news of these studies in the next issue.