Enhanced Decision Support for HIV Drug Resistance Interpretation

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1 Background

When made available in September 2000, the Stanford HIVdb expert system represented a landmark in genotypic drug resistance interpretation for HIV. It is consulted by clinicians, researchers and even patients throughout the world.

However, perhaps more important than the expert system itself was the establishment of a semi-formal language in which knowledge about HIV drug resistance could be expressed in order to be interpreted by an expert system. This language is called the Algorithm Specification Interface (ASI). ASI is rule-based, providing an appropriate level of abstraction for the encoding of rules relating mutations to inferred drug resistance. It is independent of the language and computing environment used to program an interpretation system. Knowledge gleaned from the published literature by virologists can be encoded in ASI rules and incorporated into the expert system without the assistance of computer programmers.

The establishment of a standard language for encoding such knowledge allowed for other interpretation systems to be similarly expressed. This makes it possible to compare other publicly available interpretation systems. Other interpretation systems which have published their rule sets in ASI include the Agence Nationale de Recherches sur le SIDA in France and the Rega Institute in Belgium.

2 Methods

We have identified several limitations and shortcomings of ASI and propose an improved language to address them. We outline these limitations and shortcomings, describe how our improved language obviates them and outline some additional advantages of our approach. Among them are:

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- ASI is specified as a DTD schema language for XML. DTD was developed at a time of great flux in the development of Web standards and has since been superseded by more mature schema languages.
- The ASI syntax specification is incomplete. The supplied BNF grammar does not even provide coverage for the examples given.
- The ASI specification lacks any semantics whatsoever.
- In the course of time, newer rule set versions published by Stanford and others have implicitly introduced deviations and extensions to ASI without amending the specification of the language itself. This kind of "implementation creep" has led to the ASI specification becoming effectively deprecated; the de facto specification, being the latest version of the ASI compiler, which is not published, has floated from the de jure specification.
- ASI is limited to expressing additive resistance effects. Multiplicative effects and other more intricate interactions cannot be readily expressed.

3 Results

In the context of the Virolab project, we have defined a formal language DRIL (Drug Resistance Interpretation Language) which improves on ASI and enhances it in the following ways:

- DRIL has a fully specified, formal semantics. This ensures that every expression of DRIL has a unique, unambiguous meaning.
- Equipping DRIL with formal semantics allows us to perform inference on rule sets. We can check a rule set encoded in DRIL using automated reasoning tools for important properties such as internal consistency, coverage and parsimony. It further allows us to compare rule sets automatedly for equivalence, subsumption and discordance.
- We provide a reimplementation of the ASI compiler in a more suitable programming language for expressing rule-based systems. (The HIVdb used Perl; we use Prolog.) This provides additional validation for **all** systems using ASI.
- We provide a cross-compiler from ASI to DRIL; an interpreter for the current version of ASI. This gives cross-validation between both compilers.
- DRIL allows for the expression of multiplicative and more complex drug resistance effects.
- It lays a foundation for integrating evidence from experiments, simulations and other sources withing the context of the Virolab project.

4 Conclusions

Formally specifying a language for drug resistance interpretation and enhancing it with semantics opens the door to making rigorous judgements and comparisions of HIV drug resistance interpretation systems.