19. Effective antiviral combination therapies against drug-resistant HIV mutants

Niko Beerenwinkel, Thomas Lengauer, [1] Martin Däumer, Rolf Kaiser, [2] Hauke Walter, Klaus Korn, [3] Daniel Hoffmann, [4] Joachim Selbig [5]

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1 Introduction

There are currently 16 antiretroviral agents for treatment of patients infected with human immunodeficiency virus type 1 (HIV-1), including inhibitors of the viral protease and reverse transcriptase. Despite the introduction of combination thearpies of three to six different drugs, therapeutic success in the management of HIV-infected patients is limited. The evolution of drug-resistant genetic variants plays a key role in treatment failure [1]. Persistent replication at a high mutation rate produces escape mutants that become dominant in the viral population resulting in therapy failure. Finding a new potent drug combination after therapy failure is considered challenging [2]. Resistance can be detected either by growing the isolated virus in cell culture in the presence of drug (phenotypic resistance testing, [3]) or by sequencing the viral genes coding for the drug targets (genotypic resistance testing, [1]). The latter method, while faster and cheaper, relies on the ability of interpreting sequence information. Matched genotype-phenotype pairs have previously been used to derive models that allow for predicting phenotype from genotype [4, 5]. Here we extend this sequence based classification approach to quantitative predictions and use these predictions for identifying effective drug combinations against a given viral mutant.

2 Scoring function

Support vector machine (SVM) regression is used to predict the fold-change in susceptibility to each drug compared with a wild type virus. Since these resistance factors scale differently across drugs (Figure 1), we model their distribution as a two component Gaussian mixture of wich one component accounts for the susceptible and the other for the resistant subset and define the activity of a drug against a viral strain as the conditional class probability of a susceptible virus given the (predicted) phenotype. Combinations with drugs targeting different molecules benefit from a synergistic effect which is less pronounced for inhibitors with the same drug target and mechanism of action, because in this case inhibitors are competing. Since phenotypic resistance test results are not available for combinations of

[1]Max Planck Institute for Informatics, Stuhlsatzenhausweg 85, 66123 Saarbrücken, Germany. E-mail: {beerenwinkel, lengauer}@mpi-sb.mpg.de

[2]Institute of Virology, University of Cologne, Fürst-Pückler-Str. 56, 50935 Köln, Germany. E-mail: {martin.daeumer, rolf.kaiser}@medizin.uni-koeln.de

[3]Institute of Clinical and Molecular Virology, German National Reference Center for Retroviruses, University of Erlangen–Nürnberg, Schloßgarten 4, 91054 Erlangen, Germany. E-mail: {hauke.walter, klaus.korn}@viro.med.uni-erlangen.de

[4]Center of Advanced European Studies and Research, Friedensplatz 16, 53111 Bonn, Germany. E-mail: daniel.hoffmann@caesar.de

[5]Max Planck Institute of Molecular Plant Physiology, Am Mühlenberg 1, 14476 Golm, Germany. E-mail: selbig@mpimp-golm.mpg.de

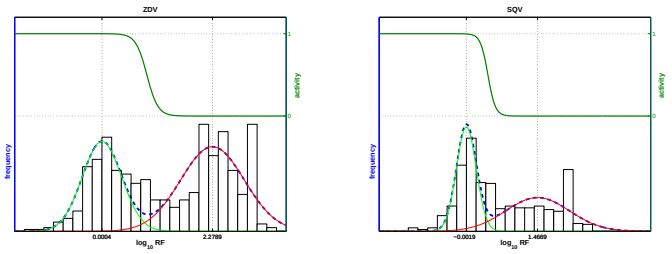

Figure 1: Frequency distributions of resistance factors for the two antiretroviral drugs zidovudine (ZDV, left) and saquinavir (SQV, right). Dashed lines represent the Gaussian mixture model that was fitted to histogram data. Solid lines show single Gaussian component densities and the solid logistic curve on the top depicts activity scores.

more than one drug, we model the activity of a combination therapy as the sum over all drug classes of the maximum of activities of drugs in the combination from that class. Since the viral population has a quasi-species structure consisting of a dominant strain and many closely related variants and because we expect new mutants to emerge under therapy, we estimate activity not only on the dominant strain, but also on nearby mutants. We use a heuristic beam search strategy to explore the mutational neighborhood of a sequence. Activity scores are generated in each search depth, i.e. for each number of point substitutions, up to a certain maximal depth.

3 Evaluation on clinical data

To illustrate the utility of these activity scores, we analyze a clinical data set of 96 viral sequences and therapies labeled as either succesful therapy changes or failures. Linear decision models were constructed from activity scores up to search depth ten. The expected prediction error decreased significantly for search depth greater or equal to one stressing the utility of searching sequence space. Different estimates for the expected prediction error argue for an optimal search depth of three for this data set.

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