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Computational analysis of viral drug resistance and treatment efficacy: case study for HIV-infection

Tarasova O.*, Ivanov S.M., Poroikov V.V.
Institute of Biomedical Chemistry, Moscow, Russia
** olga.a.tarasova@gmail.com*

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Motivation and Aim: Treatment of most viral diseases may include prescription of several different therapeutic agents for inhibition of a virus replication, immunomodulation, and comorbidities therapy [1–4]. Viral drug resistance and individual patients' response to therapy can significantly decrease the efficacy of antiviral treatment [3–5]. Therefore, to overcome these limitations development of new therapeutic strategies is constantly needed along with the search for new mechanisms of viral infections progression. In our study, we developed a multifaceted computational approach for analysis of viral drug resistance and treatment efficacy. The developed approach can be used for selection of the best therapeutic approaches and implementing new strategies to treat viral infections. We tested this approach on the HIV infection as a case study. Highly active antiretroviral therapy is the gold standard in treatment and cure of HIV-positive patients [4]. HIV drug resistance decreases the outcome of antiretroviral therapy. The methods designed for predicting treatment efficacy and novel therapeutic strategies are helpful for these purposes.
Methods and Algorithms: The approach is based on the computational analysis of (i) HIV drug resistance, (ii) HIV drug exposure using treatment history, and (iii) the transcriptomic data of human blood samples obtained from HIV-positive patients. Data on drug resistance including HIV proteins sequences associated with drug resistance and HIV treatment history were obtained from the Stanford HIV drug resistance (StDB) [6] and RHIVDB databases [7, 8]. The transcriptomic data were obtained from the key transcriptomic repositories (GEO, ArrayExpress).
Results: We implemented a web-interface of RHIVDB [8] that include the sequences of HIV-l proteins (reverse transcriptase (RT), protease (PR), and integrase (IN)) with the data on the drug treatment schemas for the patients carrying a particular viral variant. Using the data available from RHIVDB combined with the data from StDB, we created models for predicting the drug exposure and therapy efficacy based on the Bayesian approach and the set of machine learning methods including random forest, deep learning, support vector machines (Fig. 1). The features for the models were built based on the amino acid and nucleotide sequences of HIV RT, PR and IN.
Additionally, we considered the prediction of treatment efficacy based on the transcriptomic data of patients with HIV infection. We identified the feature importance for the models using amino acid and nucleotide sequences and based on the transcriptomic data. In particular, we determined the level of transcription of particular genes that contributed to the antiretroviral therapy outcome.

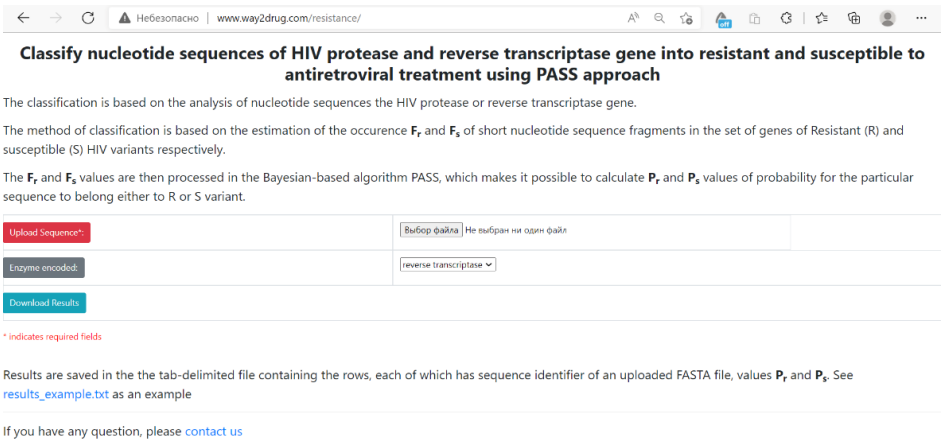

Fig. 1. A part of web-platform developed for predicting HIV drug resistance and treatment efficacy in application of highly active antiretroviral therapy: web-interface of naïve-Bayes viral drug resistance predictor

The average balanced accuracy of prediction for drug resistance and drug exposure ranged from 0.85 to 0.96 for different drugs and drug combinations, the balanced accuracy of therapeutic efficacy prediction ranges from 0.83 to 0.91. All our models are freely available on the Internet [9].

Conclusion: We developed a computational approach for predicting drug resistance and therapy efficacy and tested it in the case study of HIV infection. The average balanced accuracy of therapy efficacy prediction reaches 0.96 for particular drugs and drug combinations. Therefore, the developed approach can be used for drug therapy regimen optimization and search for new treatment strategies.

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References

1. Nguyen M.H. et al. Hepatitis B virus: Advances in prevention, diagnosis, and therapy. *Clin Microbiol Rev.* 2021;33(2):e00046-19.
2. McFee R.B. COVID-19: Therapeutics and interventions currently under consideration. *Dis Mon.* 2020;66(9);101058.
3. Naggie S., Lok A.S. New therapeutics for Hepatitis B: the road to cure. *Ann Rev Med.* 2021;72:93-105.
4. Masters M.C. et al. Beyond one pill, once daily: current challenges of antiretroviral therapy management in the United States. *Expert Rev Clin Pharmacol.* 2020;12(12):1129-1143.
5. Lu D.-Y. et al. HAART in HIV/AIDS treatments: future trends. *Infect Disord Drug Targets.* 2018;18(1):15-22.
6. Shafer R.W. Rationale and uses of a public HIV drug-resistance database. *J Infect Dis.* 2006;194(Suppl. 1):S51-S58.
7. Tarasova O. et al. RHIVDB: A freely accessible database of HIV amino acid sequences and clinical data of infected patients. *Front Genet.* 2021;12:679029.
8. RHIVDB URL: [http://www.way2drug.com/rhivdb/]. Accessed on 24.04.2022.
9. Naïve Bayes HIV viral drug resistance predictor URL: [http://www.way2drug.com/resistance/]. Accessed on 24.04.2022.