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Detecting and understanding combinatorial mutation patterns responsible for HIV drug resistance

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Abstract

We propose a systematic approach for a better understanding of how HIV viruses employ various combinations of mutations to resist drug treatments, which is critical to developing new drugs and optimizing the use of existing drugs. By probabilistically modeling mutations in the HIV-1 protease or reverse transcriptase (RT) isolated from drug-treated patients, we present a statistical procedure that first detects mutation combinations associated with drug resistance and then infers detailed interaction structures of these mutations. The molecular basis of our statistical predictions is further studied by using molecular dynamics simulations and free energy calculations. We have demonstrated the usefulness of this systematic procedure on three HIV drugs, (Indinavir, Zidovudine, and Nevirapine), discovered unique interaction features between viral mutations induced by these drugs, and revealed the structural basis of such interactions. More advanced Bayesian models are also developed for transmitted drug resistance and cross-resistance for multiple drugs.

Biography

Jing Zhang has completed her Ph.D in 2009 from Harvard University and postdoctoral studies from Harvard University. She is an assistant professor of Yale University, Department of Statistics. She has published about 20 papers in reputed journals and serving as an editorial board member of repute.