Modeling multiphage-bacteria kinetics to predict phage therapy outcomes

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Antibiotic resistant bacteria infections result in tens of thousands of deaths each year. Although several alternative therapies are currently under investigation, bacteriophage (phage) cocktail therapy appears poised for long-term success. Here, we investigate potency and longevity of individual *Pseudomonas aeruginosa* phages in cocktail to determine viral co-factors that promote optimal treatment efficacy. We combined both *in vitro* and in silico phage-bacteria interaction models to explore treatment outcomes for various combinations of treatment. Three phages that adsorb symmetrically and asymmetrically were modeled to be administered singly, double simultaneously, or double sequentially. We showed that simultaneously administering two asymmetrically binding phages, each with high cell lysis efficiencies, improved overall cocktail potency. The combined higher lysis potency and reduction in the net probability of independent gene mutations was correlated with prolonged and greater bacterial suppression. Nevertheless, we observe evolution of multiphage resistance in all two-phage cocktails *in vitro*. Our mathematical model framework identified the most sensitive parameters for phage selection when exploring the different treatment regimens. Collectively, our findings attempt to dissect the mechanisms of phage cocktails com-bating *P. aeruginosa* infections and highlight the viral co-factors necessary for treatment efficacy.

Keywords: Differential equation model, bacteriophages, cocktail, phage resistance, sequential, potency, time-kill kinetics, latent period, mutation