

295d Engineering Virus Growth by Gene-Order Permutation

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How does the growth of an organism depend on the linear arrangement of its genes? For viruses, changes in gene order may inhibit or enhance growth, advancing their use as live attenuated vaccines, gene-therapy vectors or anti-tumor therapeutics. We have developed a kinetic model for the intracellular growth of vesicular stomatitis virus (VSV), an RNA virus that encodes five genes: 3'-N-P-M-G-L-5'. Our model accounts for the 120 possible permutations of these five genes and correctly predicts the growth ranking of virus strains having four of those permutations, NPMGL (N1, wild-type), PNMGL (N2), PMNGL (N3), and PMGNL (N4), confirmed by single-cycle growth experiments in the laboratory. Simulated growth yields for virus strains that carry the 120 permuted genomes span a factor of more than 1000, and wild-type VSV is predicted to grow with the third highest yield. By ranking the effects of gene position on growth we found that VSV growth is most enhanced by permutations that reduce the expression of protein L, the least abundant protein in wild-type VSV infections, or increase the expression of protein N, the most abundant protein in wild-type infections. This study shows how altering the expression profiles of the same set of five genes can dramatically affect the yield of progeny viruses.