

Kinetics of Asian and African Zika Virus Lineages over Single-cycle and Multi-cycle Growth in Culture: gene expression, cell killing, virus production, and mathematical modeling

Huicheng Shi¹ and John Yin¹

¹University of Wisconsin-Madison

May 1, 2021

Abstract

Since 2014, an Asian lineage of Zika virus has caused outbreaks, and it has been associated with neurological disorders in adults and congenital defects in newborns. The resulting threat of the Zika virus to human health has prompted the development of new vaccines, which have yet to be approved for human use. Vaccines based on the attenuated or chemically inactivated virus will require large-scale production of the intact virus to meet potential global demands. Intact viruses are produced by infecting cultures of susceptible cells, a dynamic process that spans from hours to days and has yet to be optimized. Here, we infected Vero cells adhesively cultured in well-plates with two Zika virus strains: a recently isolated strain from the Asian lineage, and a cell-culture-adapted strain from the African lineage. At different time points post-infection, virus particles in the supernatant were quantified; further, microscopy images were used to quantify cell density and the proportion of cells expressing viral protein. These measurements were performed across multiple replicate samples of one-step infections every four hours over 60 hours and for multi-step infections every four to 24 hours over 144 hours, generating a rich dataset. For each set of data, mathematical models were developed to estimate parameters associated with cell infection and virus production. The African-lineage strain was found to produce a 14-fold higher yield than the Asian-lineage strain in one-step growth and a 7-fold higher titer in multi-step growth, suggesting a benefit of cell-culture adaptation for developing a vaccine strain. We found that image-based measurements were critical for discriminating among different models, and different parameters for the two strains could account for the experimentally observed differences. An exponential-distributed delay model performed best in accounting for multi-step infection of the Asian strain, and it highlighted the significant sensitivity of virus titer to the rate of viral degradation, with implications for optimization of vaccine production. More broadly, this work highlights how image-based measurements can contribute to discrimination of virus-culture models for the optimal production of inactivated and attenuated whole-virus vaccines.

Hosted file

ShiandYinMainDocumentUpdated.pdf available at <https://authorea.com/users/411340/articles/520405-kinetics-of-asian-and-african-zika-virus-lineages-over-single-cycle-and-multi-cycle-growth-in-culture-gene-expression-cell-killing-virus-production-and-mathematical-modeling>

Hosted file

Table.pdf available at <https://authorea.com/users/411340/articles/520405-kinetics-of-asian-and-african-zika-virus-lineages-over-single-cycle-and-multi-cycle-growth-in-culture-gene-expression-cell-killing-virus-production-and-mathematical-modeling>









