

Modeling infectivity rates and attack windows for two viruses

Jian Wu, A. John Bailer and Stephen E. Wright

Department of Mathematics and Statistics

Miami University

Oxford, Ohio 45056

T: 513.529.3538

F: 513.529.1493

Email: baileraj@muohio.edu

(ENAR 2008 Crystal City talk – Session 54: Monday 4:45 p.m.)

OUTLINE

1. Motivation and project goal
2. Problem Structure
3. Inference
4. Illustration
5. Future work

1. Motivation

Dr. Xiao-Wen Cheng (MBI @ Miami) found an interesting phenomenon that happened in animal cells when they simultaneously exposed them to two viruses, **AcRed** and **AcGFP**.

If AcRed infects a cell, the cell stains **red**

If AcGFP infects a cell, the cell stain **green**

Usually, the infection by one virus precludes the infection by the other virus.

However . . .

if both AcRed and AcGFP virus arrive at a cell within a very small time window, then the cell could be **infected by both viruses**

When both viruses infect a cell, the cell will stain **yellow**.

The cell will not stain any color if not infected by either virus, i.e., censored data will be observed in this case.

Project Goals

- Estimate the infectivity rates along with of the window during which in a cell might be susceptible to infection by multiple viruses.
- Test if the rate of infection by the **AcRed** virus is same as that of the **AcGFP** virus.

2. Problem Structure

Time until a viral infection occurs (survival time) will be modeled using an exponential distribution for both AcRed and AcGFP viruses, i.e.

$$T_i \sim \exp(\lambda_i)$$

$i=R$ (AcRed virus), G (AcGFP virus),

$$f(t_i) = \lambda_i \exp(-\lambda_i t_i) \text{ for } \lambda_i > 0 \text{ and } i=R, G.$$

Assuming that T_R and T_G are independent, the joint density function of the two random variables T_R and T_G is easily constructed.

Suppose that the investigator decides to terminate the study after a specific duration of exposure to the two viruses, e.g. two hours.

DATA: a cell exhibits one of the four possible outcomes

RED

GREEN

YELLOW

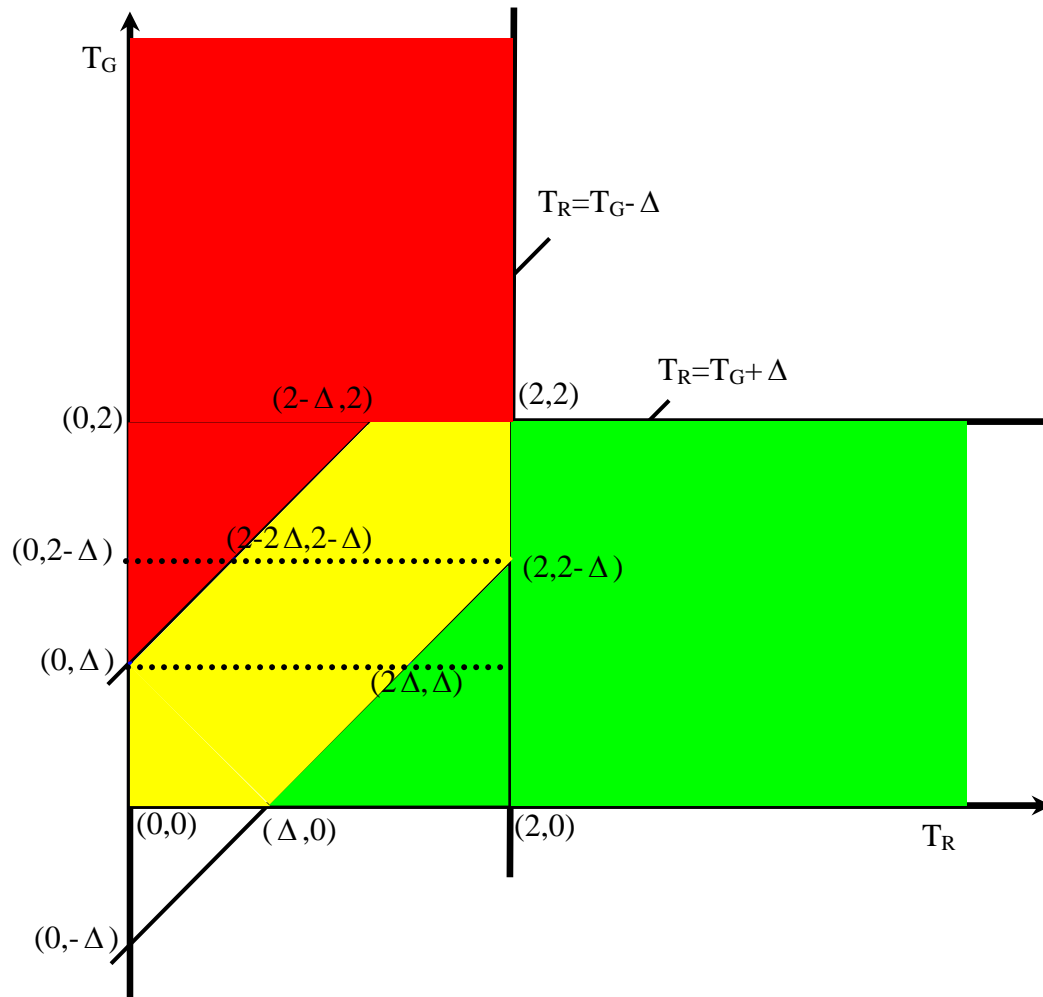
BLANK

(multinomial outcome)

Table: Schematic table to the results of simultaneously exposing cells to two viruses.

Time Interval index	Intervals	Number of cells at risk of infectious at stratum	Number of cells staining Red	Number of cells staining Green	Number of cells staining Yellow	Number of cells shown in Blank
1	[0,2]	$n_1 = n$	n_{R_1}	n_{G_1}	n_{Y_1}	$n_{B_1} = n - n_{R_1} - n_{G_1} - n_{Y_1}$
...

Figure: Illustration of color characteristics of a cell will present during virus infection where T_R (T_G) is the time until infection by the red (green) virus and Δ is the window in which a cell might be infected by both viruses.



Multinomial Probabilities

Case 1: Pr(cell stains RED) = Pr(Infection by RED virus only)

$$\begin{aligned}\pi_R &= \Pr[(T_R < 2) \cap (T_G > 0) \cap (T_R < T_G - \Delta)] + \\ &\quad \Pr[(T_R < 2) \cap (T_G > 2) \cap (T_R > T_G - \Delta)] \\ &= \frac{\lambda_G e^{\lambda_R \Delta} e^{-2(\lambda_R + \lambda_G)}}{\lambda_R + \lambda_G} + \frac{\lambda_R e^{-\lambda_G \Delta}}{\lambda_R + \lambda_G} - e^{-2(\lambda_R + \lambda_G)}\end{aligned}$$

Case 2: Pr(cell stains GREEN)=Pr(Infection by GREEN virus only)

$$\begin{aligned}\pi_G &= \Pr[(T_G < 2) \cap (T_R > 0) \cap (T_R > T_G - \Delta)] + \\ &\quad \Pr[(T_R > 2) \cap (T_G < 2) \cap (T_R < T_G + \Delta)]\end{aligned}$$

Case 3: Pr(cell stains YELLOW)=Pr(Infection by both viruses)

$$\begin{aligned}\pi_Y &= \Pr[(|T_R - T_G| \leq \Delta) \cap (T_R \leq 2) \cap (T_G \leq 2)] \\ &= \frac{\lambda_G e^{-\lambda_R \Delta}}{\lambda_R + \lambda_G} \left[e^{-(\lambda_R + \lambda_G)(2 - \Delta)} - 1 \right]_+ \\ &= \frac{\lambda_G e^{\lambda_R \Delta}}{\lambda_R + \lambda_G} \left[e^{-(\lambda_R + \lambda_G)\Delta} - e^{-2(\lambda_R + \lambda_G)} \right]_+ \\ &\quad \left[1 - e^{-\lambda_G \Delta} \right] \left[1 + e^{-2(\lambda_R + \lambda_G)} \right]\end{aligned}$$

Case 4: Pr(unstained)=Pr(Not infected by either virus)

$$\pi_B = e^{-2(\lambda_R + \lambda_G)}$$

3. Inference - Estimation of parameters $\lambda_R, \lambda_G, \Delta$

multinomial likelihood:

$$L(\lambda_R, \lambda_G, \Delta) = \binom{n}{n_R \ n_G \ n_Y \ n_B} \pi_R^{n_R} \pi_G^{n_G} \pi_Y^{n_Y} \pi_B^{n-n_R-n_G-n_Y}$$

$$\begin{aligned} L(\lambda_R, \lambda_G, \Delta) &= \binom{n}{n_R \ n_G \ n_Y \ n-n_R-n_G-n_Y} (\pi_R)^{n_R} (\pi_G)^{n_G} (\pi_Y)^{n_Y} (\pi_B)^{n-n_R-n_G-n_Y} \\ &= \binom{n}{n_R \ n_G \ n_Y \ n-n_R-n_G-n_Y} \cdot \left(\frac{\lambda_G e^{\lambda_R \Delta} e^{-2(\lambda_R+\lambda_G)}}{\lambda_R + \lambda_G} + \frac{\lambda_R e^{-\lambda_G \Delta}}{\lambda_R + \lambda_G} - e^{-2(\lambda_R+\lambda_G)} \right)^{n_R} \\ &\quad \cdot \left(\frac{\lambda_R e^{\lambda_G \Delta} e^{-2(\lambda_R+\lambda_G)}}{\lambda_R + \lambda_G} + \frac{\lambda_G e^{-\lambda_R \Delta}}{\lambda_R + \lambda_G} - e^{-2(\lambda_R+\lambda_G)} \right)^{n_G} \\ &\quad \cdot \left\{ \frac{\lambda_G e^{-\lambda_R \Delta}}{\lambda_R + \lambda_G} \left[e^{-(\lambda_R+\lambda_G)(2-\Delta)} - 1 \right] + \frac{\lambda_R e^{\lambda_G \Delta}}{\lambda_R + \lambda_G} \left[e^{-(\lambda_R+\lambda_G)\Delta} - e^{-2(\lambda_R+\lambda_G)} \right] + \left[1 - e^{-\lambda_G \Delta} \right] \left[1 + e^{-2(\lambda_R+\lambda_G)} \right] \right\}^{n_Y} \\ &\quad \cdot \left(e^{-2(\lambda_R+\lambda_G)} \right)^{n-n_R-n_G-n_Y} \end{aligned}$$

Testing for equal infectivity ...

$$H_0 : \lambda_R = \lambda_G = \lambda$$

$$G^2 = -2 \ln \left(\frac{L_0(\hat{\lambda}, \hat{\lambda}, \Delta_0)}{L_1(\hat{\lambda}_R, \hat{\lambda}_G, \Delta_1)} \right)$$

Interval estimates of attack window ...

Wald-based CI: $\hat{\Delta} \pm z_{\alpha/2} se(\hat{\Delta})$

Likelihood-based CI: $\left\{ \Delta_0 \mid -2 \ln \left(\frac{L(\hat{\lambda}_R^*, \hat{\lambda}_G^*, \Delta_0)}{L(\hat{\lambda}_R, \hat{\lambda}_G, \hat{\Delta})} \right) \leq \chi_1^2 \right\}$

4. Illustration

We generated a toy data set with 1000 cells tested for one time interval $[0,2]$ with $\lambda_R=0.05$, $\lambda_G =0.95$ and $\Delta=0.005$

Table: A hypothetical multinomial outcome for the number of infectious cells

	Red	Green	Yellow	Blank	Total
Observed Number	44	825	1	130	1000

Table: Estimates for parameters λ_R , λ_G and Δ :

Parameter	Estimate	SE	Lower	Upper
λ_R	0.0512	0.00782	0.0295	0.0729
λ_G	0.9660	0.03946	0.8565	1.0756
Δ	0.0118	0.01186	-0.0211	0.0447

$\lambda_R=0.05$, $\lambda_G=0.95$ and $\Delta=0.005$

$H_0 : \lambda_R = \lambda_G = \lambda$ (equal infectivity)

$$\begin{aligned}
 G^2 &= -2 \ln[L_0(\hat{\lambda}, \hat{\lambda}, \hat{\Delta}_0)] - \{-2 \ln[L_1(\hat{\lambda}_R, \hat{\lambda}_G, \hat{\Delta}_1)]\} \\
 &= -2 \ln[L_0(\hat{\lambda}, \hat{\lambda}, \hat{\Delta}_0)] + 2 \ln[L_1(\hat{\lambda}_R, \hat{\lambda}_G, \hat{\Delta}_1)] \\
 &= 1992.5 - 1133.8 = 858.7
 \end{aligned}$$

$G^2 > \chi_1^2(0.05) = 3.841 \Rightarrow$ two infectivity rates differ.

5. Future Work

- simulation study of operating characteristics of equal infectivity tests
- simulation study of coverage of the interval estimation procedures
- natural extension to multiple time period data

References

- [1] “The influence of dilution on the probability of Multiple infection of cells by Virus particles of different types”, M. Pring, *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 58, No. 2. (Aug. 15, 1967), pp. 607-611.
- [2] “A Generalized One-Hit Model for Bioassays of Insect Viruses”, M. S. Ridout; J. S. Fenlon; P. R. Hughes, *Biometrics*, Vol. 49, No. 4. (Dec., 1993), pp. 1136-1141.
- [3] “Application of Exponential Models to Problems in Cancer Research” M. Zelen, *Journal of the Royal Statistical Society. Series A (General)*, Vol. 129, No. 3. (1966), pp. 368-398.
- [4] “Mathematical characterization of insect cell (Sf-9) death in suspended culture”, *Biotechnology Letters*, N.G. Dalal¹ and W.E. Bentley¹, Publisher: Springer Netherlands, Volume 21, Number 4, (April 1999), pp325 – 329.
- [5] “Independent-Action and Birth-Death Models in Experimental Microbiology”, *Bacteriol Rev.*, 1965 March; 29(1): 102. George Shortley and Judd R. Wilkins¹
- [6] Unpublished data from Dr. Cheng at Dept. of Microbiology, Miami University, Oxford, Ohio.

Abstract

Cells exist in an environment in which they are simultaneously exposed to a number of viral challenges. Infection by one virus may preclude infection by other viruses. Under the assumption that the times until infection by two viruses are independent, a likelihood-based procedure is presented to estimate the infectivity rates and the size of the window during which a cell might be susceptible to infection by multiple viruses. A test for equal infectivity rates is proposed, along with interval estimates of parameters. The performance of this test and estimation procedure is explored in a small simulation study.