Spread of Viral Plaque

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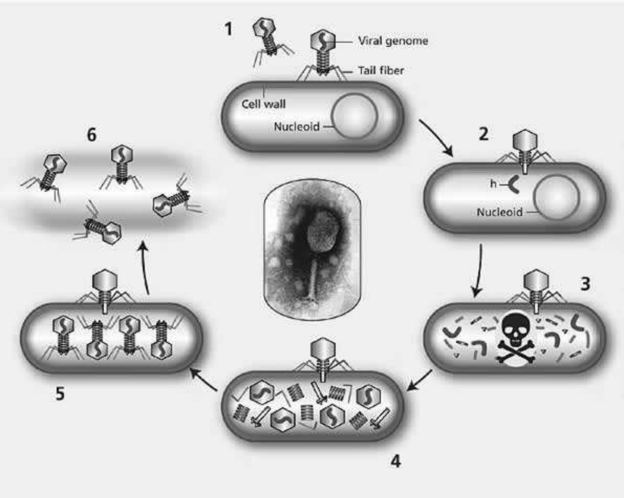
Outline

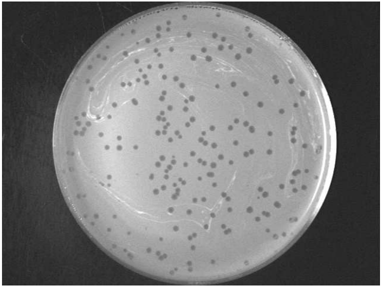
Phage Life Cycle: adsorption to lysis



Latent Period: time from adsorption to burst $\approx 20 - 40$ min.
Burst size: 10-1000 virus.

Plaque Assay

“The plaque technique of virus assay has played an important role in the development of knowledge of the physiology and genetics of viruses. For bacteriophage the technique is quite simple and consists of adding a large number of susceptible bacteria and a few virus particles to a tube containing melted nutrient agar, which is then poured on a Petri plate that already contains a basal layer of nutrient agar. The virus adsorbs to the host bacteria, multiplies, and lyses the bacterial cell; the progeny viruses diffuse to neighboring bacterial cells and multiply further, yielding holes or plaques in the otherwise continuous sheet of bacterial growth." (A.L. Koch: JTB 1964)



Previous Work on Spreading Plaque

Koch (JTB 1964) proposes that

$$\text{speed of plaque spread} \propto \left(\frac{\text{virus diffusion constant}}{\text{latent period}}\right)^{1/2}$$

Yin & McCaskill (BioPhysics 1992) propose the model:
$V =$ virus, $B =$ susceptible bacteria, $I =$ infected bacteria.

$$\begin{aligned} V_t &= d(V_{rr} + \frac{1}{r}V_r) - k_+VB + (k_2\beta + k_-)I \\ B_t &= -k_+BV + k_-I, \\ I_t &= k_+BV - (k_- + k_2)I \end{aligned}$$

in $\mathbb{R}^2$ with initial conditions:

$$V = \begin{pmatrix} V_0, & r \le r_0 \\ 0, & r > r_0 \end{pmatrix}, \; B = \begin{pmatrix} 0, & r \le r_0 \\ B_0, & r > r_0 \end{pmatrix}, \; I = 0$$

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Our First Model

An infected cell remains so for τ time units, then lyses, releasing $\beta > 1$ phage.

First latent period: $0 \leq t \leq \tau$

$$\begin{aligned} V_t &= d\triangle V - kVB \\ B_t &= -kBV, \quad x \in D \\ I_t &= kBV \end{aligned}$$

with initial data: $V(0,x) = V_0(x), \quad B(0,x) = B_0(x), \quad I(0,x) = 0$.

For $t > \tau$:

$$\begin{aligned} V_t &= d\triangle V - kV(t,x)B(t,x) + \beta kB(t-\tau,x)V(t-\tau,x) \\ B_t &= -kB(t,x)V(t,x) \\ I_t &= kB(t,x)V(t,x) - kB(t-\tau,x)V(t-\tau,x) \end{aligned}$$

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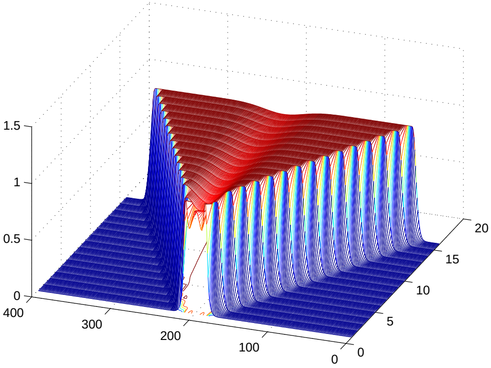
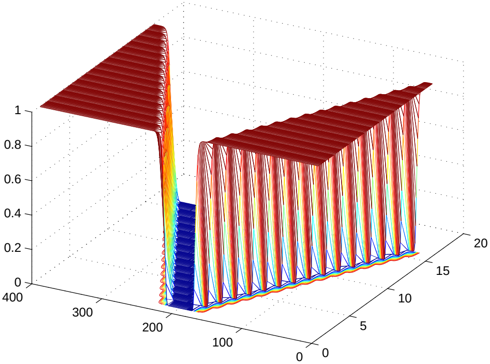
Spreading Phage Plaque: $\beta = 100,\ kB_0\tau = 1$



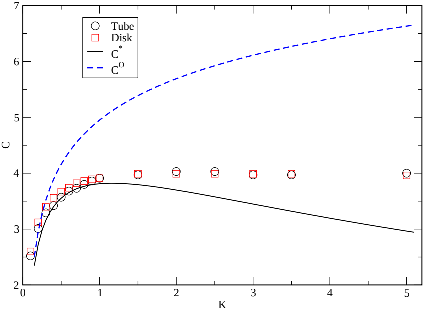
$V(t,x)/B_0(\beta - 1)$ is plotted. $B(0,x) \equiv B_0$ const.

Bacteria are infected and lysed.



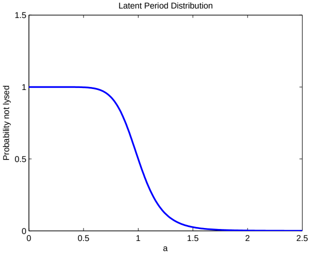
$B(t,x)/B_0$ is plotted.

Theoretical vs Simulated Spread Speed



scaled c^* vs $K = kB_0\tau$ in black

Ingredients of Model II: infection age and virus removal



$\mathfrak{F}(a)$ is the probability that an infected bacterium has not yet lysed a time units after infection.

$b(a)$ is number of virus progeny released when an infected cell lyses a time units after infection.

infected bacteria given by $I(t,x) = \int_0^\infty i(t,a,x)da$ where $i(0,a,x) = i_0(a,x)$ and $i(t,a,x)$ is the infected cell density w.r.t. (a,x).

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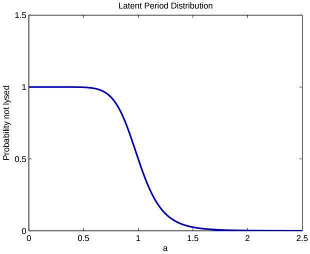

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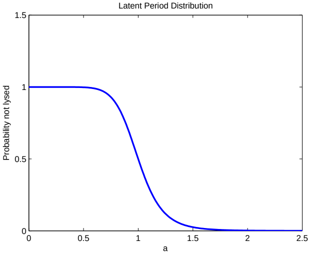

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Model-II: variable latent period, virus removal rate

$$
\begin{aligned}
V_t &= d\Delta V - \alpha V + J(t,x) + k\int_0^t b(a)B(t-a,x)V(t-a,x)(-d\mathfrak{F})(a) \\
B_t &= -kBV, \quad x \in \mathbb{R}^n, \quad t > 0 \\
I &= \int_0^t kB(t-a,x)V(t-a,x)\mathfrak{F}(a)da + \int_t^\infty i_0(a-t,x)\frac{\mathfrak{F}(a)}{\mathfrak{F}(a-t)}da
\end{aligned}
$$

where $-d\mathfrak{F}$ is the Stieltjes measure associated with $1-\mathfrak{F}$,
$\alpha > 0$ is virus removal rate due to adsorption and decay.

$$
J(t,x) = \int_t^\infty b(a)\frac{i_0(a-t,x)}{\mathfrak{F}(a-t)}(-d\mathfrak{F})(a)
$$

is virus released when survivors of the initial infected cell cohort burst.

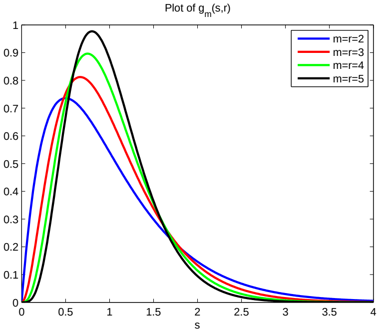
Typically, i_0 is so small that it can be ignored.

Simulations use a Gamma-Distributed Latent Period

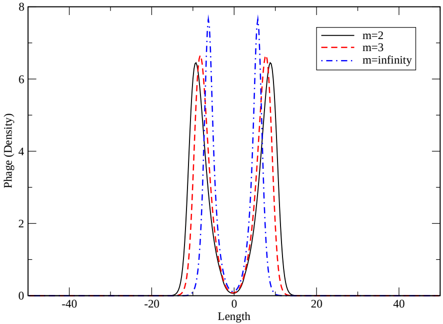
$$\mathfrak{F}(a) = \int_a^\infty g_m(s;r)ds$$

$$g_m(s,r) = \frac{r^m s^{m-1}}{(m-1)!}e^{-rs}.$$

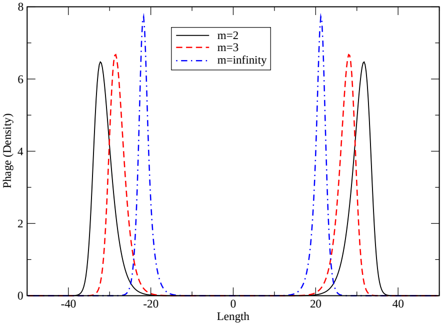
mean latent period m/r
variance m/r^2



Simulations: virus at leading edge of plaque disk



Virus at $T = 5$



Virus at $T = 15$

The mean latent period is 1.0 while its variance is 0.5 (solid lines), 0.33 (dashed lines), and 0 (hashed lines). $k = 1, \ \alpha = 2, \ b = 30$.

Reduction of System to a Single Scalar PDE

Let $u(t,x) = \int_0^t V(s,x)ds$. Then, as $B_t = -kBV$, we have

$$B(t,x) = B_0 e^{-ku(t,x)}.$$

Integrating the V equation w.r.t. t, we find that:

$$u_t = d\Delta u - \alpha u + \hat{V}_0(t,x) + kB_0 \int_0^t b(a) f(u(t-a,x))(-d\mathfrak{F})(a)$$

where

$$\hat{V}_0(t,x) = V_0(x) + \int_0^t J(s,x)ds$$

and where

$$f(u) = \frac{1 - e^{-ku}}{k}.$$

Note that f is bounded and $f(0) = 0$, $f'(0) = 1$, and $f(u) < u$ for all $u > 0$.

Reduction to an Integral Equation

Using the heat kernel $\Gamma(t,x)$ and variation of constants formula

$$u(t,x) = u_0(t,x) + kB_0 \int_0^t \int_{\mathbb{R}^n} \Phi(r,y) f(u(t-r,x-y))drdy$$

where

$$\Phi(r,y) = \int_0^r e^{-\alpha(r-a)} \Gamma(r-a,y) b(a)(-d\mathfrak{F})(a)$$

and

$$u_0(t,x) = \int_0^t \int_{\mathbb{R}^n} e^{-\alpha s} \Gamma(s,y) \hat{V}_0(t-s,x-y)dyds.$$

Virus Spreading Speed & Reproductive Number

Spreading Speed: $c^* = \inf\{c \geq 0 : \exists \lambda > 0, G(c,\lambda) < 1\}$

$$G(c,\lambda) = kB_0 \int_0^\infty \int_{\mathbb{R}^n} e^{-\lambda(cs+y_1)} \Phi(s,y) dyds$$

c^* can be expressed as $c^* = \sqrt{d} c_1$, where (c_1, λ_1) is unique solution of

$$G_1(c,\lambda) = 1, \qquad \frac{d}{d\lambda} G_1(c,\lambda) = 0$$

$$G_1(c,\lambda) = \frac{kB_0}{\lambda c + \alpha - \lambda^2} \int_0^\infty e^{-\lambda ca} b(a) d(-\mathfrak{F}(a)).$$

$c^* > 0 \iff$ Basic Reproductive Number for Virus:

$$R_0 \equiv \frac{kB_0}{\alpha} \int_0^\infty b(a) d(-\mathfrak{F}(a)) > 1.$$

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Spreading Theorem

If $R_0 > 1$ and $\hat{V}_0 \neq 0$ is bounded & continuous, vanishes for $\{(t,x) : |x| \geq \eta,\ t \geq 0\}$, then

$$\lim_{t\to\infty, |x|\geq ct} u(t,x) = 0, \quad c > c^*$$

Further, if u^* is the unique positive solution of

$$u^* = R_0 \left(\frac{1 - e^{-ku^*}}{k} \right).$$

Then, for every $c \in (0, c^*)$,

$$\liminf_{t\to\infty, |x|\leq ct} u(t,x) \geq u^*$$

If $R_0 \leq 1$, then $u(t,x) \to 0, \quad |x| \to \infty,$ uniformly in $t \geq 0$.

Proof uses results of Thieme (JMB 1977,79) for integral equations: sub- & super solutions

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Traveling Wave Solutions

Theorem: Assume that $R_0 > 1$ and $c > c^*$. Then there exists solutions $V(x+ct)$ and $B(x+ct)$ of

$$
\begin{aligned}
V_t &= dV_{xx} - \alpha V + k \int_0^\infty b(a)B(t-a,x)V(t-a,x)d(-\mathfrak{F}(a)) \\
B_t &= -kBV
\end{aligned}
$$

satisfying

$$B(-\infty) = B_0,\ B(+\infty) = B_0 e^{-ku^*},\ V(\pm\infty) = 0.$$

B and V are positive and B is strictly decreasing.

Moreover, the total amount of virus in the wave is given by

$$\int_{\mathbb{R}} V(s)ds = cu^* = cR_0 f(u^*).$$

There is no non-trivial traveling wave with speed $c < c^*$.

Conclusions

1. Formulated a model of phage spread on immobile bacteria where:
    1. length of latent period has prescribed distribution.
    2. burst size depends on length of latency.
2. Identified basic reproductive number, R_0, for virus propagation on uniform "bacterial lawn".
3. Showed that realistic initial data give rise to spreading solutions if $R_0 > 1$.
4. No spreading if $R_0 < 1$.
5. Identified spreading speed c^* of virus.
6. Proved existence of a traveling wave of virus infection for each speed $c \geq c^*$; no wave if $c < c*$.

Thanks For Your Attention

D. Jones, G. Rost, H.S.,H. Thieme, On Spread of Phage Infection of Bacteria in a Petri Dish, SIAM J. Applied Math., (2012) Vol.72, No.2, 670-688.

D. Jones, H.S.,H. Thieme, Spread of Viral Infection of Immobilized Bacteria, to appear, Networks and Heterogeneous Media

Analysis makes use of:

H.R. Thieme, A model for the spatial spread of an epidemic, J. Math. Biology 4, (1977), 337-351.
O. Diekmann, Limiting behavior in an epidemic model, Nonlin. Anal. 1, (1977), 459-470.

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