卒業論文
宿主内での突然変異ウイルスの確率的絶滅：薬剤耐性出現の時間変動パターン

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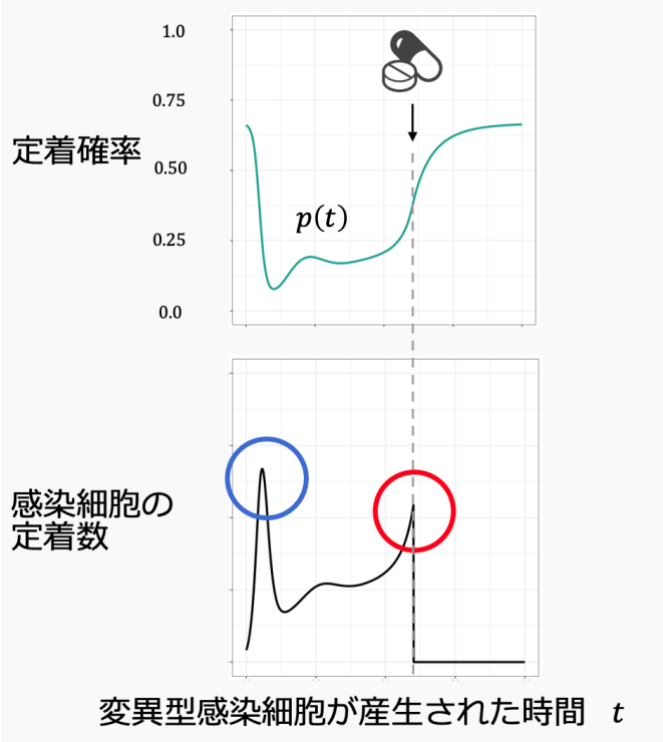
ウイルスは、宿主体内で、標的細胞に感染してその分子機構をもちいてコピー数を増やし、その後、他の標的細胞に感染して増殖する。ゲノムの複製ミスにより、増殖ステップのいずれかが元の株より効率よく起きる変異株が出現すると、それは、急速に増殖し宿主を乗っ取る。しかし、スタートするときの変異株の感染細胞数が少ないため、変異体の多くは高い確率で消滅する。加えて、元の株の増殖により、感染できる標的細胞数が減少するため、変異株の増殖速度は急速に低下する。

私は、時刻tで出現した変異株が、確率的絶滅をまぬがれて生き残れる割合、定着確率$p(t)$を、成長率に時間依存性のある連続時間分岐過程に基づいて計算した。ウイルスの感染経路について、[1]感染した細胞が感受性標的細胞と接触してウイルスを感染させる場合，[2]感染した細胞が多数の遊離ウイルス粒子を放出して，感受性標的細胞に感染する場合、の 2 つを分析した。$p(t)$が従う微分方程式をみちびき、それを解き、数学の予測を数値シミュレーションで確認した。その結果、変異株は、元の株の感染初期につくられたものは高い確率で生き残れるが、（図、青丸参照）その後、生存確率が急速に減少する、最終的な値に収束する前に振動する、最終の定常値は変異株と元の株との感染力の比率によって大きく影響されることがわかった。抗ウイルス薬を投与され、元の株が排除される場合に、薬剤に耐性をもつ変異株の定着確率を調べると、投与の直前に出現した変異株が高い確率で定着できることがわかった。（図、赤丸参照）



修士論文要旨

An Epidemic Dynamics Model in a Community With Vaccinated Visitors During a Season

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1. INTRODUCTION

In our work, we focus on the effects of visitors on the epidemic dynamics of a community with ongoing vaccination during a season, if a proportion of the visitors are vaccinated. When visitors are allowed into a community during an infectious disease outbreak, there may be a presumption that there would be a resultant increase in the disease spread. However, since vaccination helps in breaking the spread of an infectious disease, what happens when a proportion of the visitors are vaccinated, becomes an interesting puzzle.

2. ASSUMPTIONS

- The disease is transmissible, but not fatal.
- The total population size of the residents is assumed to be a constant independent of time in the epidemic dynamics.
- The community accepts a constant number of visitors per unit time.
- The frequency of vaccinated visitors is given by a constant.
- Only susceptible residents are allowed to take part in the ongoing vaccination program of the community.
- Recovery from the disease, by either infected visitors or residents, has same effect as the vaccination.
- Vaccination or recovery does not offer total immunity to the disease hence, vaccinated or recovered individuals have a likelihood of being reinfected.
- A visitor must not necessarily stay throughout the season, and can also leave the community irrespective of the infectious state.

3. MODEL

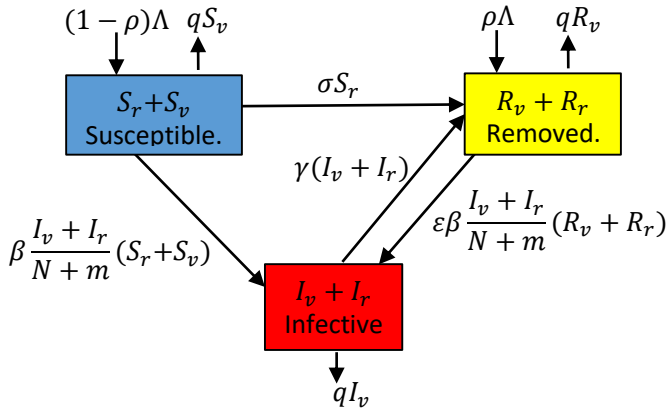

Fig. 1. The schematic diagram of the model for the epidemic dynamics of the community with visitors.

$$\text{Dynamics for the visitor:}\begin{cases}\frac{dS_v}{dt}=(1-\rho)\Lambda-\beta\frac{I_v+I_r}{N+m}S_v-qS_v;\\ \frac{dI_v}{dt}=\beta\frac{I_v+I_r}{N+m}S_v+\varepsilon\beta\frac{I_v+I_r}{N+m}R_v-\gamma I_v-qI_v;\\ \frac{dR_v}{dt}=\rho\Lambda+\gamma I_v-\varepsilon\beta\frac{I_v+I_r}{N+m}R_v-qR_v;\end{cases}$$

$$\text{Dynamics for the resident:}\begin{cases}\frac{dS_r}{dt}=-\beta\frac{I_v+I_r}{N+m}S_r-\sigma S_r;\\ \frac{dI_r}{dt}=\beta\frac{I_v+I_r}{N+m}S_r+\varepsilon\beta\frac{I_v+I_r}{N+m}R_r-\gamma I_r;\\ \frac{dR_r}{dt}=\sigma S_r+\gamma I_r-\varepsilon\beta\frac{I_v+I_r}{N+m}R_r.\end{cases} \quad (1)$$

$S_r(t)$: Susceptible residents at time t,

$S_v(t)$: Susceptible visitors at time t,

$I_r(t)$: Infective residents at time t,

$I_v(t)$: Infective visitors at time t,

$R_r(t)$:Removed residents at time t,

$R_v(t)$: Removed visitors at time t,

ρ : Frequency of vaccinated visitors,

q : Per capita emigration rate of visitors,

β : Infection rate,

γ : Recovery rate,

σ : Vaccination rate of the residents,

$\varepsilon\beta$: Reinfection coefficient for the recovered or vaccinated individuals, $0 \le \varepsilon \le 1$.

Λ : Net immigration rate.

$m = S_v(t) + I_v(t) + R_v(t)$: Total visitors' population density.

$N = S_r(t) + I_r(t) + R_r(t)$: Total residents' population density.

The initial condition:
$\big(S_v(0), I_v(0), R_v(0), S_r(0), I_r(0), R_r(0)\big) = \big((1-\rho)m, 0, \rho m, S_{r0}, I_{r0}, 0\big)$.

Non-dimensional transformation of variables and parameters:
$\tau := qt\,; \quad x_v(t) := \frac{S_v(t)}{m}; \quad y_v(t) := \frac{I_v(t)}{m}; \quad x_r(t) := \frac{S_r(t)}{N}; \quad z(t) := \frac{I(t)}{N+m}; \quad \mu := \frac{m}{N}(< 1); \quad b := \frac{\beta}{q}; \quad c := \frac{\gamma}{q}; \quad \omega := \frac{\sigma}{q}.$

The non-dimensionalized system:

$$\frac{dx_v}{d\tau} = (1-\rho) - bzx_v - x_v$$
$$\frac{dy_v}{d\tau} = (1-\varepsilon)bzx_v - \varepsilon bzy_v - (c+1)y_v + \varepsilon bz\,;$$
$$\frac{dx_r}{d\tau} = -bzx_r - \omega x_r; \qquad (2)$$
$$\frac{dz}{d\tau} = \frac{1-\varepsilon}{1+\mu}bz(\mu x_v + x_r) - \varepsilon bz^2 - (c-\varepsilon b)z - \frac{\mu}{1+\mu}y_v.$$

4. DYNAMICS WITHOUT VISITORS

$$\frac{dx_r}{d\tau} = -by_r x_r - \omega x_r;$$
$$\frac{dy_r}{d\tau} = (1-\varepsilon)by_r x_r - \varepsilon b{y_r}^2 - (c-\varepsilon b)y_r\,.$$

The endemic equilibrium exists if and only if $R_{00} := \frac{\varepsilon b}{c} > 1$.

Theorem 1

i. *The disease-eliminated equilibrium $E_0(0,0)$ is globally asymptotically stable if and only if $R_{00} \le 1$.*

ii. *If and only if $R_{00} > 1$, the endemic equilibrium $E_+({x_r}^*, {y_r}^*)$ is globally asymptotically stable, while the disease-eliminated equilibrium is unstable.*

5. LOCAL STABILITY OF THE DISEASE-ELIMINATED EQUILIBRIUM FOR THE DYNAMICS WITH VISITORS

Theorem 2

If

the condition $1 - \rho < \frac{1+(1+\mu)c}{\mu(1-\varepsilon)b}\left\{\frac{1+c}{1/(1+\mu)+c} - \frac{\varepsilon b}{c}\right\}$ *(3)*

is satisfied, the disease-eliminated equilibrium is locally asymptotically stable. If the inverse inequality for (3) is satisfied, it is unstable.

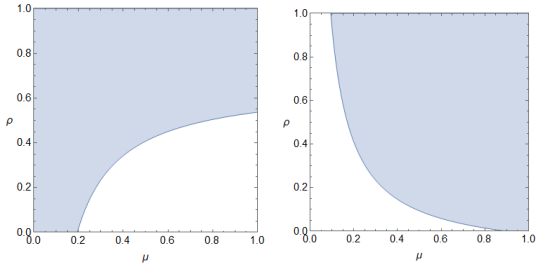

Fig. 2. Numerically drawn parameter region for ρ and μ according to (3.7). The shaded region is such that the condition (3) is satisfied. (a) $(b, \varepsilon, c) = (10, 0.55, 6.0)$, $R_{00} = 0.916667$, (b) $(b, \varepsilon, c) = (1.9, 0.55, 1.0)$, $R_{00} = 1.045$..

6. CONCLUDING REMARK

- When there is already an epidemic outbreak in the community without visitors, even with a sufficiently large proportion of vaccinated individuals, if the number of visitors allowed into the community is not above a certain threshold value, the disease might remain endemic in the community.

- When there is already an epidemic outbreak in the community without visitors, a large number of visitors with sufficiently high proportion of vaccination may suppress the outbreak.

- When the epidemic is suppressed in the community without visitors, if the number of visitors accepted into the community is sufficiently large, the epidemic might outbreak if the proportion of vaccinated visitors is not sufficiently large.

- When the epidemic is suppressed in the community without visitors, a sufficiently small number of visitors is best to keep the disease suppressed, even with the acceptance of visitors.