Introduction (cont'd)

- There were very few studies to link within-host and epidemiological dynamics of parasites.
- The previous study by the authors showed a trade-off between transmission and virulence emerges from within-host dynamics.
  - The shape of trade-off curve depends on model parameters; it means the existence of "Evolutional Stable Virulence" (=optimal virulence).

Evolution of optimal virulence in single parasite species infection

- Using $R_0$ (basic reproduction number; generally speaking, indicates the number of infected hosts regenerated by the single infectious host), $\mu$ (mortality of uninfected host), $\sigma$ (virulence; excess mortality caused by infection), $\nu \alpha$ (recovery rate), $\beta$ (transmission rates), and $S$ (density of susceptible hosts), the equation $R_0 = \beta S / (\mu + \nu \alpha + \sigma)$ generally stands (Anderson and May, 1991)

R codes for the previous slide

```r
alpha <- seq(0, 0.1, length=101)
v1 <- exp(-alpha*10)/10
v2 <- exp(-alpha*20)/10
beta <- rep(0.4, 101)
S <- rep(1, 101)
mu <- rep(0.1, 101)
R0v1 <- beta*S/(mu+alpha+v1)
R0v2 <- beta*S/(mu+alpha+v2)
layout(t(1:2))
par(mar=c(4, 4, 0.5, 0.5), cex=2)
plot(alpha, v1, ylim=c(0, 0.1), xlab=expression(alpha), ylab=expression(v1))
points(alpha, v1, pch=18)
pplot(alpha, R0v1, ylim=c(0, 1), xlab=expression(alpha), ylab=expression(R0v1))
points(alpha, R0v1, pch=18)
```

Features of P. falciparum

- P.f. kills about 2 million people each year, shares 3.1% of world mortality.
- Not very virulent, because most adults in endemic area can survive. Majority of malaria death occurs in children due to naive immune system.
- Gametocytes can invade mosquito hosts but it constitutes only a few percent of circulating parasites.

Model

- New features
  - Distinguish two within-host stages (replicate=merozoites=asexual; density $x_1$ / transmit=gametocytes=sexual; density $x_2$)
  - Lymphocytes (density $y$) kills parasites of both stages
- Equations (see, Table 1)
  - $dx_1/dt = (\phi(1-m)\cdot y)\cdot x_1$
  - $dx_2/dt = \phi x_1 \cdot 2 y x_2$
- This framework is applicable to persistent infection (steady state).
  - Old experimental data showed rapid reach to stable state (Boyd, 1949).
Epidemiological dynamics (cont’d)

• Transmission from human to vector can be linked with stable density of sexual stage parasites ($\tilde{x}_2$).
• Since mosquitoes have immune system, minimum number of sexual parasites is needed to infect.
• Assume a mosquito ingests 4 microliter out of 5 litter human blood pool, mean number of sexual parasites within it ($M$) is, using stable density, $M=8 \times 10^7\times 2$.
• Probability of having exactly $n$ sexual parasites ($p_n(M)$) obeys Poisson distribution, thus $p_n(M) = M^n e^{-M} / n!$
• $\beta$ is the products of $p_n(M)$ and a transmission constant, and assume the parasite virulence as, $\beta'(M) = u_1 x_1\phi_1 + u_2 x_2\phi_2$.

Results (cont’d)

• Sensitivity analysis for host natural mortality changes (Fig.3); A for linear, B for sigmoid transmission function; $\mu$’s effects are larger in B than in A.
• Effect of parasite conversion rate (m) and within-host growth rate ($\gamma$) on $R_0$ (Fig.4)

Implication to health policy

• Effect of a treatment targeting either the asexual (A; $\tau_1$) or sexual (B; $\tau_2$) life stage of parasites (Fig.5)
-- Increasing $\tau_2$ has clear impact.

Change of dominant plasmodia in Solomon Islands

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Implications for my study

• In Solomon Islands, dominant parasites changed from P.f. to P.v. for recent 10 years.
• Parasite rates of P.f. decreased under chloroquine treatment and wide-use of bednets.
• Instead, asymptomatic P.v. infection increased.
• Replication of plasmodia is restricted by the existence of other species/strains (Bruce et al., 2000).
• Switching of dominant plasmodium species in Solomon Islands could be modeled as application of this virulence evolution models.

Model of immune system

• Strength of immune system = lymphocyte density $y$ (not constant)
• Equation:
  - $dy/dt = b + c_1 x_1 + c_2 x_2 - \delta y$
    - $b$: baseline production rate of lymphocyte
    - $c_1, c_2$: increase of lymphocytes production by merozoites and gametocytes, respectively.
    - $\delta$: lymphocyte mortality

Within-host stable state

$$\dot{x}_1(\varphi, m) = \frac{\sigma_2}{\sigma_1} \frac{(1-m) \delta \varphi - b \sigma_1}{c_2 \sigma_1 m - (1-m) c_1 \sigma_2} (1-m)$$
$$\dot{x}_2(\varphi, m) = \frac{(1-m) \delta \varphi - b \sigma_1}{c_2 \sigma_1 m - (1-m) c_1 \sigma_2} m$$
$$\dot{y}(\varphi, m) = \frac{1-m}{\sigma_1} \varphi.$$

• These can be derived from the equations when differentials (increase rates) are zero.