Competition and Evolutionary Models

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May 26, 2020

Announcements

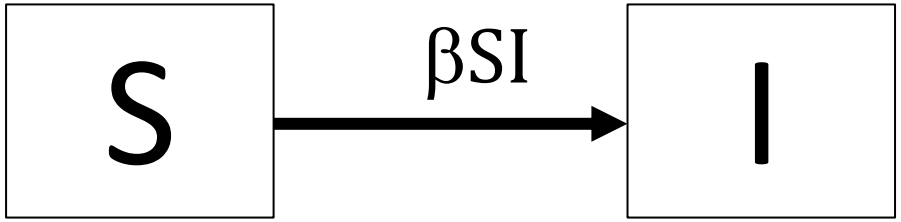
Midterm Review

Question 1c:
What is the equilibrium incidence (expressed in cases per 100,000 person-years)?

(Have reproductive number, life expectancy, and β at this point)

Force of Infection, Incidence, Prevalence

- Force of infection = $\beta I(t)$
- Incidence = $\beta S(t)I(t)$
- Prevalence = $I(t)$



SIR model with demography:
Endemic Equilibrium

(S^*, I^*, R^*), such that:

$$\frac{dS}{dt} = 0, \frac{dI}{dt} = 0, \text{ and } \frac{dR}{dt} = 0 \text{ AND } I^* > 0$$

$$\frac{dS}{dt} = \mu - \beta IS - \mu S = 0$$

$$\mu - \beta I^* \frac{1}{R_0} - \mu \frac{1}{R_0} = 0$$

$$\boldsymbol{I^* = \frac{\mu}{\beta}(R_0 - 1)}$$

$R_0 > 1$ for endemic equilibrium because Infection must sustain itself

Midterm Review

Question 1c:
What is the equilibrium incidence (expressed in cases per 100,000 person-years)?

Equilibrium incidence = βS*I*
R_0=5
β= 0.18
μ = 1/80
S* = 1/R0 = 0.2

$$I^* = \frac{\mu}{\beta}(R_0 - 1)$$

Equilibrium incidence = β*0.2* $\frac{\mu}{\beta}(R_0 - 1)$ = 0.2* μ * $(R_0 - 1)$ = 0.2*(1/80)*(5-1) = 0.01

Equilibrium incidence per 100,000 = 100,000*0.01 = 1,000

Midterm Review

Question 1d: What proportion of the population would have been infected by age 40?

Force of Infection

- The **force of infection** (λ) is the rate at which susceptible individuals are infected.
- It is a function of the proportion (or number) of infected individuals and the rate at which they infect others
- We call this the **effective contact rate** (β)

$$\lambda(t) = \beta I(t)$$

Rates versus Probabilities

$$S(t) = S(0) \times (1 - p)^t$$

p = probability event occurs during a time interval

$$S(t) = S(0) \times e^{-\lambda t}$$

λ = rate = events / time

$$p = 1 - e^{-\lambda t}$$

$$\lambda = -\frac{1}{t}\ln(1 - p)$$

Rates versus Probabilities

Suppose on average, individuals have 2 upper respiratory infections per year. What is the probability that an individual will have at least 1 respiratory infection in a given year?

$$p = 1 - e^{-\lambda t}$$

$$\lambda = 2,\ t=1$$

$$p = 0.86$$

Question 1d: What proportion of the population would have been infected by age 40?

β= 0.18 per day = 365*0.18 per year = 65.7 per year

λ = force of infection = βI^*= 65.7*0.000761 = 0.05 per year

P(t) = 1 - $e^{-rt} = 1 - e^{-0.05*40} = 0.865$ = 86.5%

Question 2. With SARS-CoV-2, it is believed that individuals often become infectious before becoming symptomatic. Assume that the latent period is 3 days, the incubation period is 5 days, and the infectious period is 5 days. Assume that the basic reproductive number is 3, and infectiousness does not affect symptoms.

Question 2. With SARS-CoV-2, it is believed that individuals often become infectious before becoming symptomatic. Assume that the latent period is 3 days, the incubation period is 5 days, and the infectious period is 5 days. Assume that the basic reproductive number is 3, and infectiousness does not affect symptoms.

Ignoring demography (births/deaths), if a program were instituted that identified all cases and individually quarantined them from the moment they became symptomatic, would this be sufficient to prevent outbreaks of SARS-CoV-2?

While this is a SEIR model, without demography the reproductive number reduces to:

$$R_0 = \frac{\beta}{\lambda}$$

$3 = \frac{\beta}{1/5}$

$$\beta = 0.6$$

Reducing the infectious period from 5 to 2 days would result in:

$R_0 = \frac{0.6}{1/2} = 1.2$

This would be insufficient, by itself, to control SARS-CoV-2.

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Los Angeles Times

Scientists say a now-dominant strain of the coronavirus could be more contagious than original

Scientists say COVID-19 mutation more contagious than original strain is increasing at 'alarming rate'

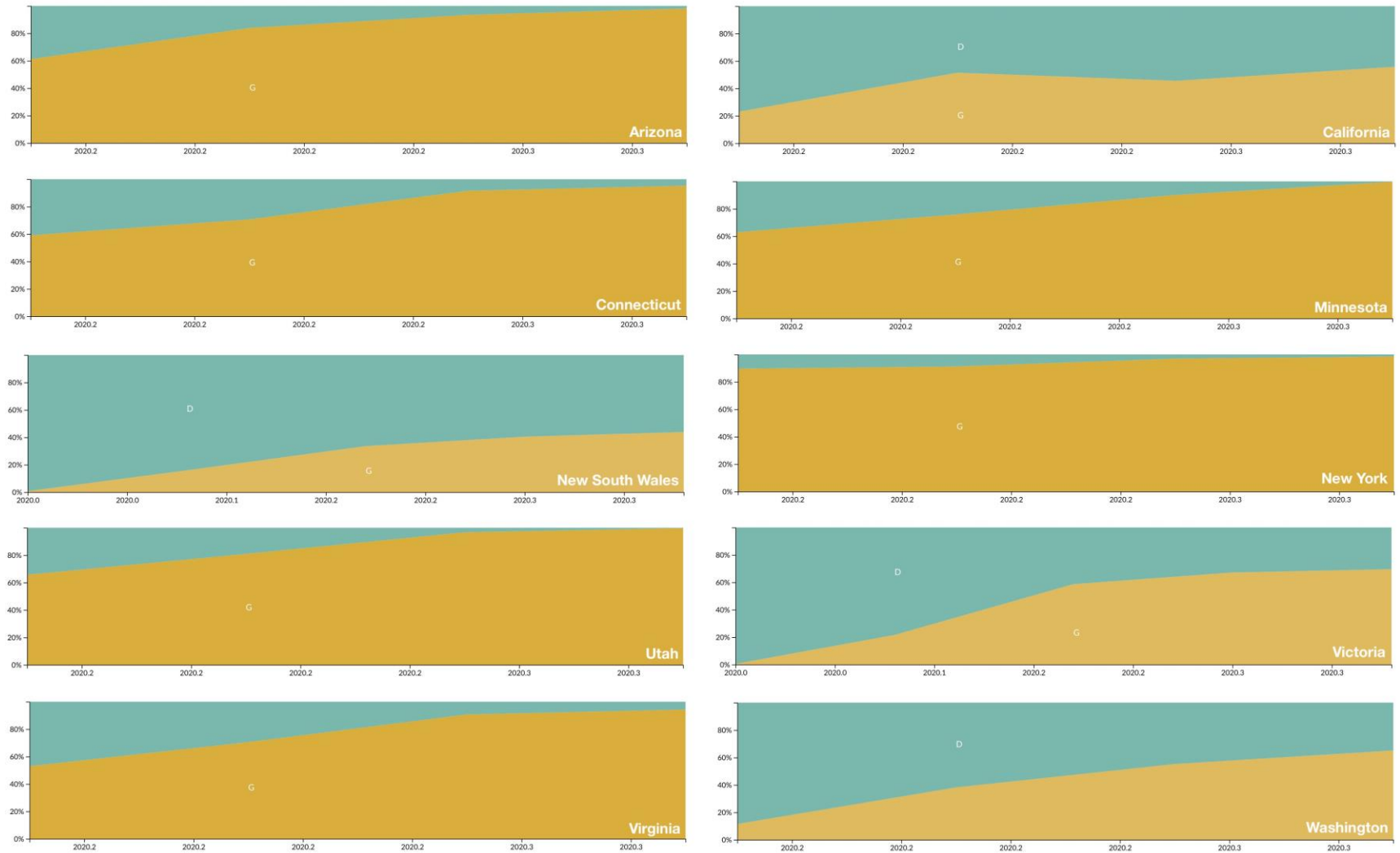
By Austin Williams | **Published** May 5 | Coronavirus | FOX TV Digital Team

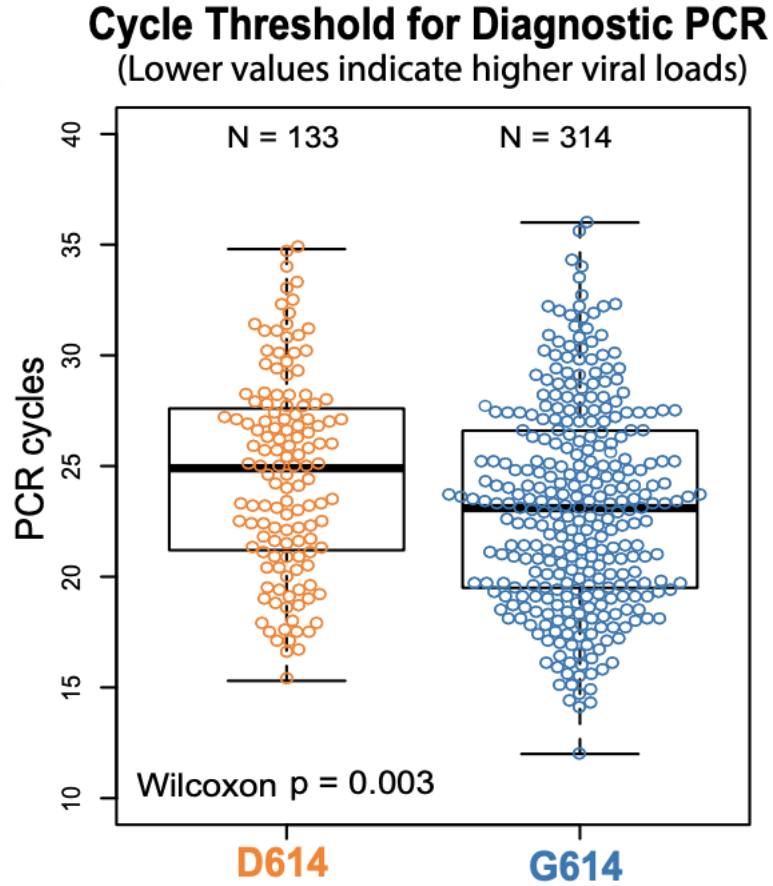
COVID-19 mutations helping virus spread in humans: UK scientists

A police officer wears a thermal headgear to monitor the temperature of commuters in New Delhi. (Reuters)

Spike mutation pipeline reveals the emergence of a more transmissible form of SARS-CoV-2

Korber B[1], Fischer WM[1], Gnanakaran S[1], Yoon H[1], Theiler J[1], Abfalterer W[1], Foley B[1], Giorgi EE[1], Bhattacharya T[1], Parker MD[3], Partridge DG[4], Evans CM[4], Freeman TM[3], de Silva TI[4,5], on behalf of the Sheffield COVID-19 Genomics Group[#], LaBranche CC[2], and Montefiori DC[2]





S 614 Mutation Global Distribution

https://nextstrain.org/ncov/global/2020-05-18

https://nextstrain.org/ncov/global/2020-05-18?c=gt-S_614&p=full

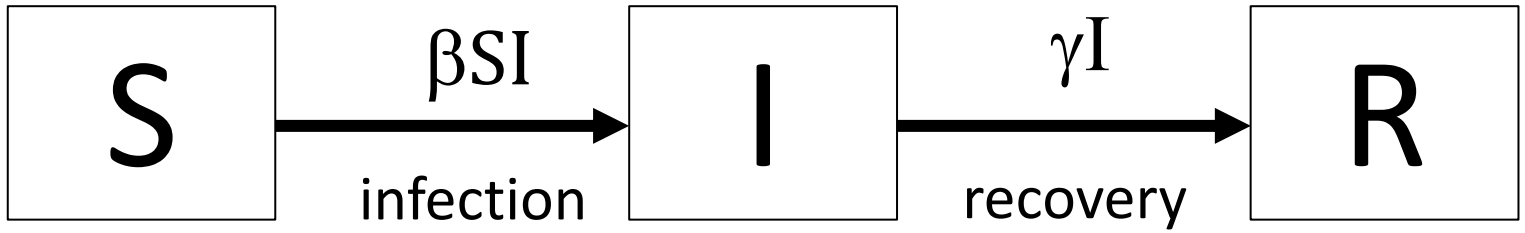
Questions regarding SARS-CoV-2 evolution

- Will it become more fit?
- Will it become more virulent?
- Will it evade natural or vaccine induced immune responses?
- Will it become resistant to Remdesivir?

Learning Objectives

- Become familiar with mathematical underpinnings of the concepts of strain fitness, mutations, and adaption
- Learn about how mutations enable evolution to guide adaption across fitness landscapes, and what constrains this
- Understand how evolution can alter virulence of organisms and what may constrain this

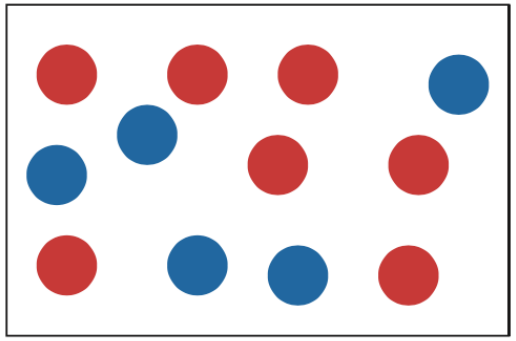
Reading for today was Chapter 2 in Nowak
Will cover parts of chapter 3 and 11 (not required readings)



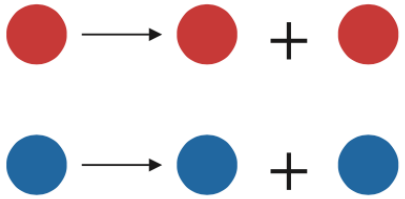
Until now, we've talked about I as a single type of unchanging organism.

What happens when there is >1 type of organism and they compete?

A population of reproducing individuals:

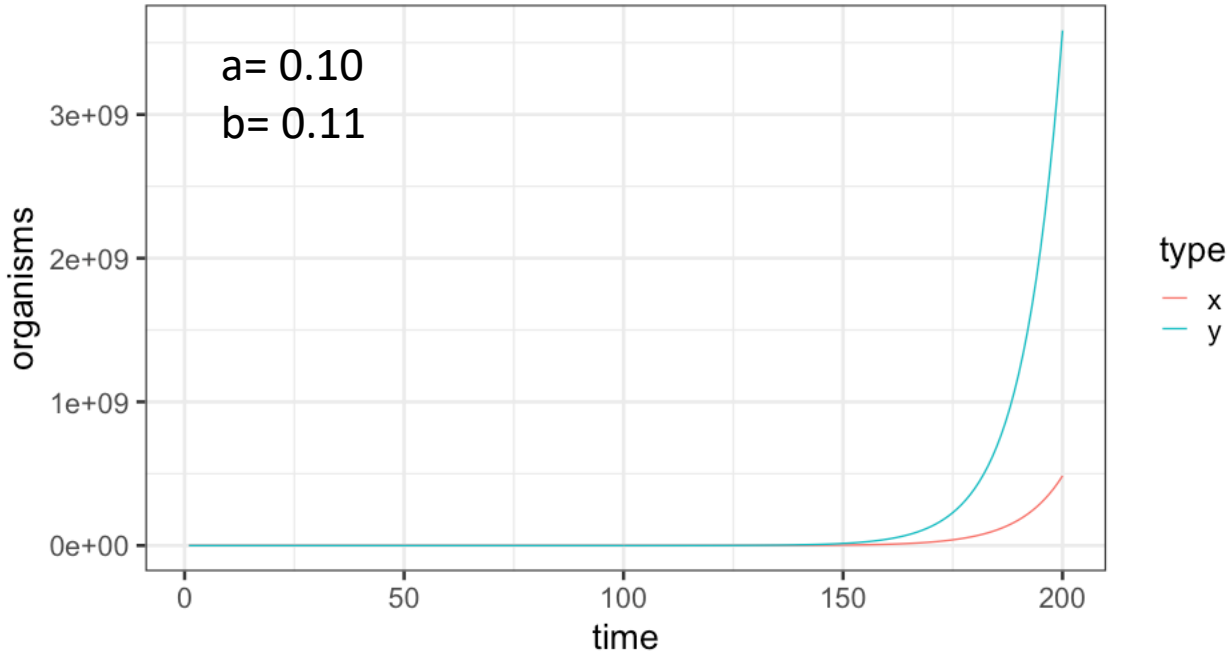


Reproduction:



$$\frac{dx}{dt} = \dot{x} = ax$$

$$\frac{dy}{dt} = \dot{y} = bx$$



$$p(t) = \frac{x_0 e^{at}}{y_0 e^{bt}} = \frac{x_0}{y_0} e^{(a-b)t} = p_0 e^{(a-b)t}$$

$$x(t) = x_0 e^{at}$$
$$y(t) = y_0 e^{bt}$$

$$p(t) = \frac{x(t)}{y(t)}$$

$$if\ a > b, \quad p(\infty) = \infty$$
$$if\ a < b, \quad p(\infty) = 0$$
$$if\ a = b, \quad p(\infty) = p_0$$

Nowak, *Evolutionary Dynamics*

Expressing with frequencies

$$x + y = 1$$

$$\dot{x} = x(a - \phi)$$

$$\dot{y} = y(b - \phi)$$

$$0 = x(a - \phi) + y(b - \phi)$$

$$0 = xa - \phi x + yb - y\phi$$

$$\phi(x + y) = xa + yb$$

$$\phi = xa + yb = average\ fitness$$

Equilibria

$$\dot{x} = x(a - \phi)$$

$$\dot{y} = y(b - \phi)$$

$$\phi = xa + yb$$

$\dot{x} = 0\ when$:

$x = 0\ and\ y = 1$
$or\ x = 1\ and\ y = 0$
$or\ a = b$

$$\dot{x} = xa - \phi x = xa - x(xa + yb)$$

$$= x(a - xa - yb)$$

$$= x(a - xa - (1 - x)b) = x(a - xa - b + bx) =$$

$$= x(1 - x)(a - b)$$

"Survival of the fitter"

$$\dot{x} = x(1 - x)(a - b)$$

Survival of the fittest

$$\dot{x_1} = x_1(f_1 - \phi)$$
$$\dot{x_2} = x_2(f_2 - \phi)$$
$$\vdots$$
$$\dot{x_i} = x_i(f_i - \phi)$$

$$\phi = \sum_{i=1}^{n} x_i f_i = average\ fitness$$

Mutations

$$\dot{x} = x(a - \phi)$$

$$\dot{y} = y(b - \phi)$$

Now, assume equal fitness (a=b) and let:

u1: mutation rate from x to y

u2: mutation rate from y to x

$$\dot{x} = x(1 - u_1) + yu_2 - \phi x$$

$$\dot{y} = y(1 - u_2) + xu_1 - \phi y$$

$$x + y = 1, a = b = 1, \phi = 1$$

$$\dot{x} = x(1 - u_1) + (1 - x)u_2 - x$$

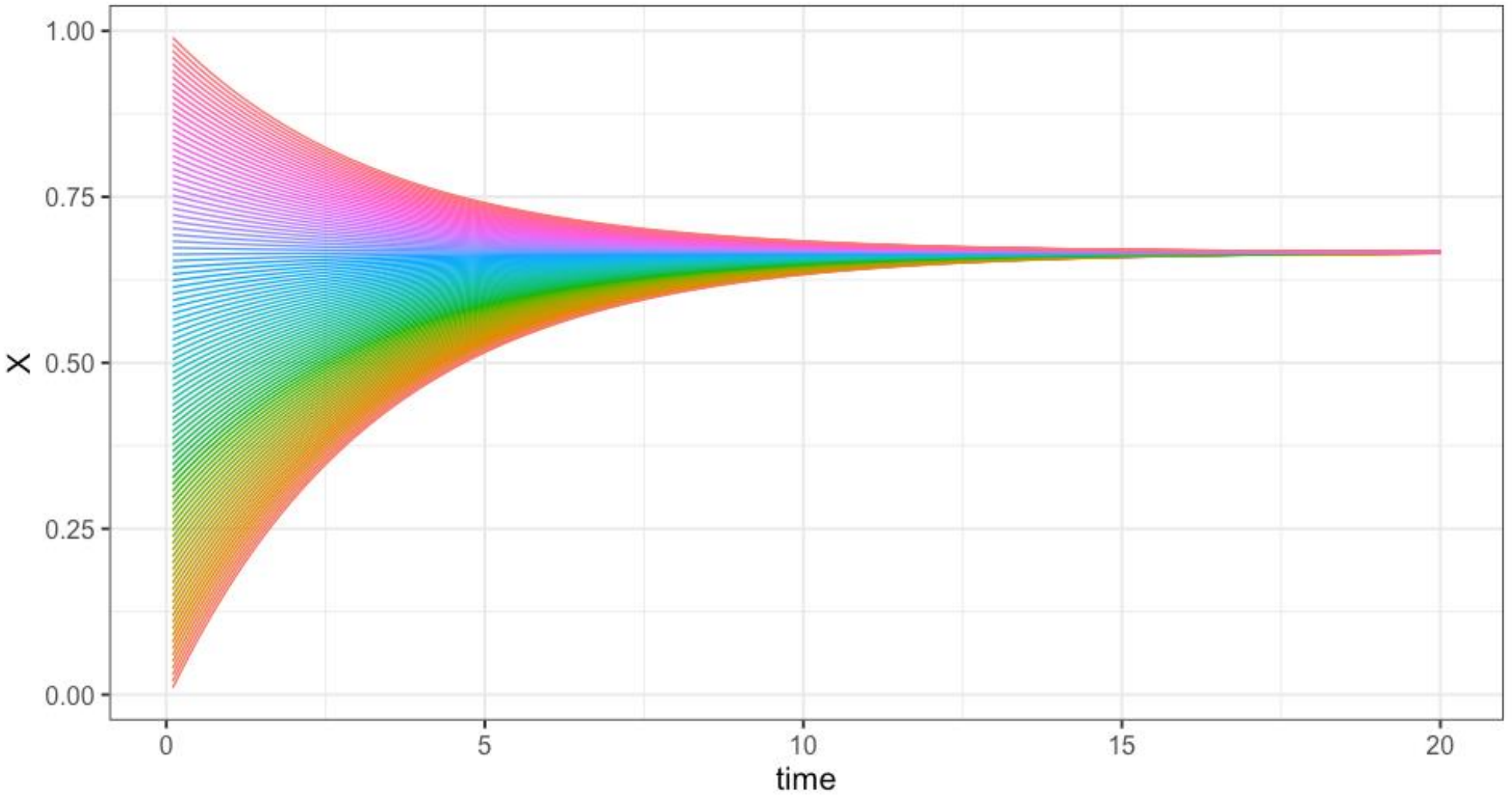
$$\dot{x} = u_2 - x(u_1 + u_2)$$

$$At\ equilibrium, \dot{x} = 0, so:$$

$$x^* = \frac{u_2}{u_1 + u_2}$$

Mutations in a neutral model

$u_2 = 0.2$, $u_1 = 0.1$, $x^* = 2/3$



Fitness and Evolution

Basic Primer on Genomics and Evolution

DNA: ACTG

RNA: ACUG

ACATGCTACAGGCTACCGATCAATG

ACATGCTACAGGCTACAGATCAATG

Single Nucleotide Polymorphism (SNP)

- Substitutions can be neutral or can change protein functions, sometimes changing the organism's fitness
- Substitution (mutation) rate differs between organisms
- Faster for RNA than DNA

Sequence Space

100

101

110

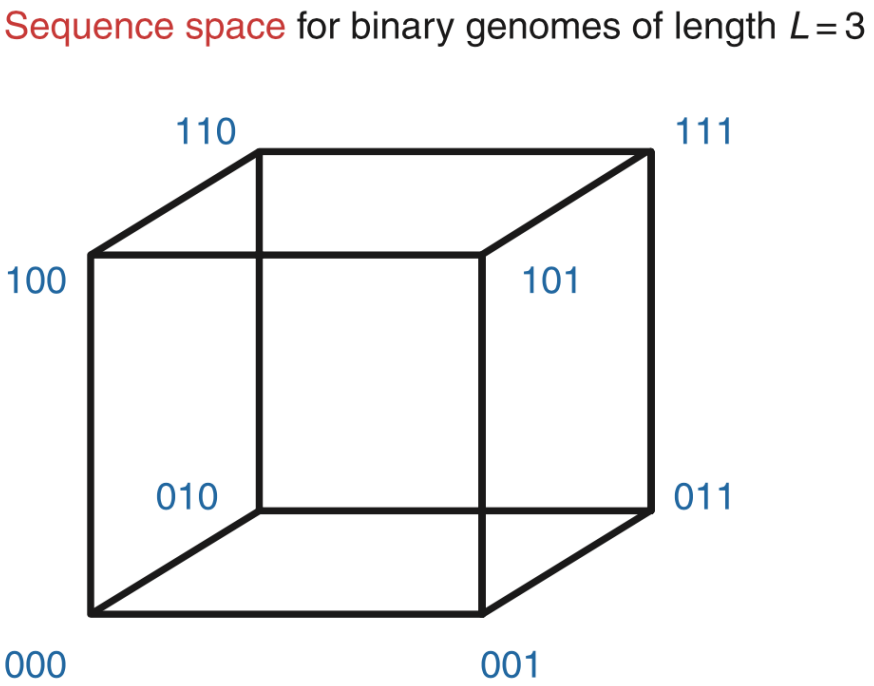
L= length of genome

Possible sequences = 2^L

Viral genomes: ~20,000 base pairs

Bacterial genomes: ~$5x10^6$ base pairs

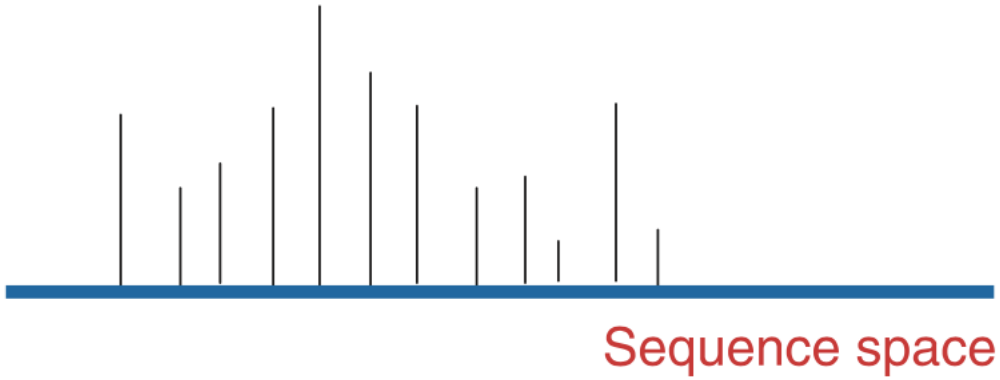
Evolution navigates this massive space



Nowak, *Evolutionary Dynamics*

Fitness landscapes

Fitness landscape = each sequence has a reproduction rate (= fitness)



Do species find the maximum?
Does the entire population within the species sit at the maximum?

Quasispecies

"Population of self-replicating organisms with similar genomic sequences generated by mutation-selection processes"

$x_0 = 0000$

$x_1 = 0001$

$x_2 = 0010$

$x_{15} = 1111$

$$Q = \begin{bmatrix} q_{11} & \cdots & q_{1n} \\ \vdots & \ddots & \vdots \\ q_{n1} & \cdots & q_{nn} \end{bmatrix}$$

$$q_{ij} = probability\ of\ mutation\ from\ i\ to\ j$$

Quasispecies equation

Selection without mutations

$$\dot{x}_i = x_i(f_i - \phi)$$

$$\phi = \sum_{i=1}^{n} x_i f_i = average\ fitness$$

Selection without mutations (Quasispecies model)

$$\dot{x}_i = \sum_{j=1}^{n} x_j f_j q_{ji} - \phi x_i$$

$$q_{ij} = probability\ of\ mutation\ from\ i\ to\ j$$

- If Q is identity matrix (no mutations), reduces to left side
- Admits a unique, globally stable equilibrium
- Equilibrium has lower average fitness than in absence of mutations

Solving for equilibrium in quasispecies equation

$$\dot{x_i} = \sum_{j=1}^{n} x_j f_j q_{ji} - \phi x_i$$

$$W = \vec{f} Q$$

$$\dot{\vec{x}} = \vec{x} W - \phi \vec{x}$$

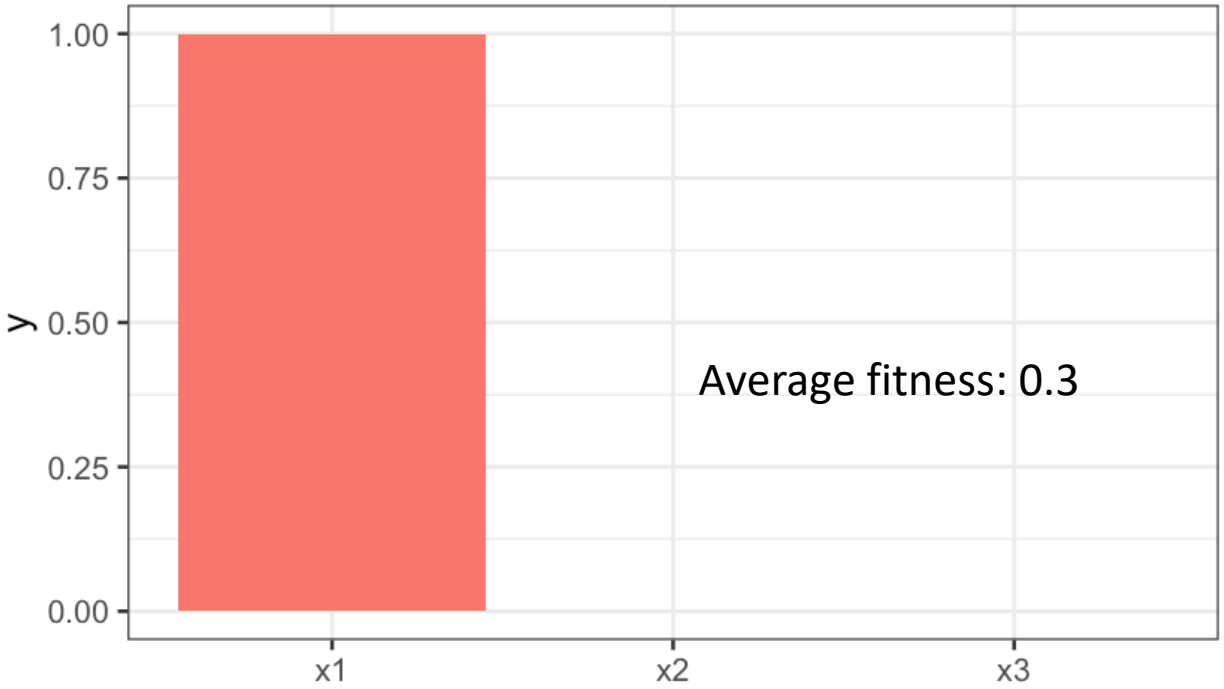
$$\vec{x} W = \phi \vec{x}$$

Equilibrium fitness = largest eigenvalue
Equilibrium prevalence = left eigenvector

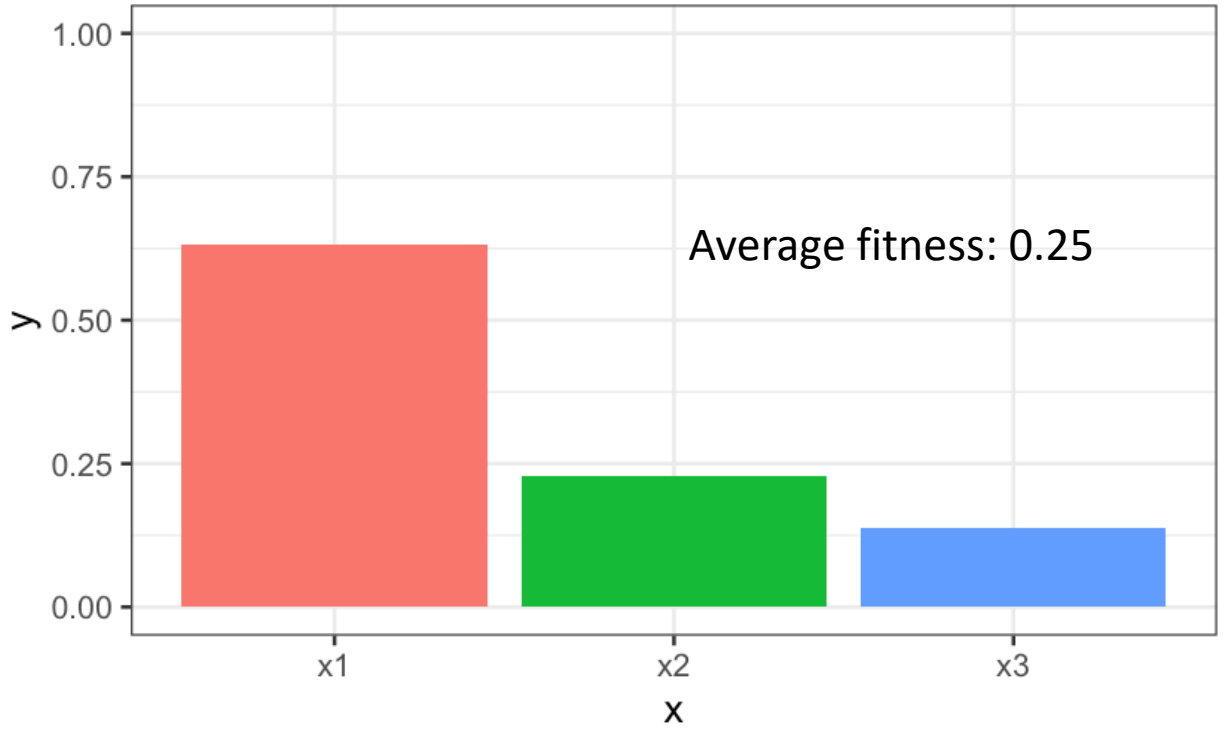
Quasispecies examples

Fitness = $\vec{f}$ = (0.3, 0.2, 0.1)

$$\begin{matrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{matrix}$$



$$\begin{matrix} 0.8 & 0.1 & 0.1 \\ 0.1 & 0.8 & 0.1 \\ 0.1 & 0.1 & 0.8 \end{matrix}$$



If mutations lead to a lower equilibrium fitness, why have mutations?

Do faster mutation rates navigate better to fitness maxima?

Mutations across the genome

x(t=0)= 1011

x(t=1)= 1011

u = probability of mutation in each position

L = length of genome

q= probability of making exact copy with no mutants = $(1-u)^L$

x_0 = master sequence, with $f_0>1$

x_1 = all other mutants, with f = 1

$x_0 + x_1 = 1$

$$\dot{x}_0 = x_0(f_0 q - \phi)$$
$$\dot{x}_1 = x_0 f_0 (1-q) + x_1 - \phi x_1$$

Constraints on mutation rates

$$\dot{x}_0 = x_0(f_0 q - \phi)$$
$$\dot{x}_1 = x_0 f_0 (1-q) + x_1 - \phi x_1$$

$$\phi = f_0 x_0 + x_1$$

Rewrite as:

$$\dot{x_0} = x_0(f_0 q - 1 - x_0(f_0 - 1))$$

At equilibrium:

$$\dot{x_0} = 0$$

$$x_0^* = \frac{f_0 q - 1}{f_0 - 1}$$

$$for\ x_0^*\ to\ be > 0:$$
$$f_0 q > 1$$

$$f_0 q > 1$$

$$q = (1-u)^L$$

$$f_0 (1-u)^L > 1$$

$$\log(f_0 (1-u)^L) > 0$$

$$\log(f_0) + L\log(1-u) > 0$$

$$L\log(1-u) > -\log(f_0)$$

for small u, $\log(1-u) \approx -u$

$\log(f_0) \approx 1$

So:

$$u < \frac{1}{L}$$

Mutation rates and adaptation

$$u < \frac{1}{L}$$

$$uL < 1$$

Mutations per genome < 1 in order to adapt

Table 3.1 Genome length (in bases), mutation rate per base, and mutation rate per genome for organisms ranging from DNA viruses to humans

Organism	Genome length in bases	Mutation rate per base	Mutation rate per genome
RNA viruses			
Lytic viruses			
Qβ	4.2×10^3	1.5×10^{-3}	6.5
Polio	7.4×10^3	1.1×10^{-4}	0.84
VSV	1.1×10^4	3.2×10^{-4}	3.5
Flu A	1.4×10^4	7.3×10^{-6}	0.99
Retroviruses			
SNV	7.8×10^3	2.0×10^{-5}	0.16
MuLV	8.3×10^3	3.5×10^{-6}	0.029
RSV	9.3×10^3	4.6×10^{-5}	0.43
Bacteriophages			
M13	6.4×10^3	7.2×10^{-7}	0.0046
λ	4.9×10^4	7.7×10^{-8}	0.0038
T2 and T4	1.7×10^5	2.4×10^{-8}	0.0040
E. coli	4.6×10^6	5.4×10^{-10}	0.0025
Yeast *(S. cerevisiae)*	1.2×10^7	2.2×10^{-10}	0.0027
Drosophila	1.7×10^8	3.4×10^{-10}	0.058
Mouse	2.7×10^9	1.8×10^{-10}	0.49
Human *(H. sapiens)*	3.5×10^9	5.0×10^{-11}	0.16

Sources: Drake (1991, 1993) and Drake et al. (1998).

Note: Most organisms have a mutation rate per genome which is less than one, as predicted by the error threshold theory. Why Qβ and VSV have such a high mutation rate is at present unexplained.

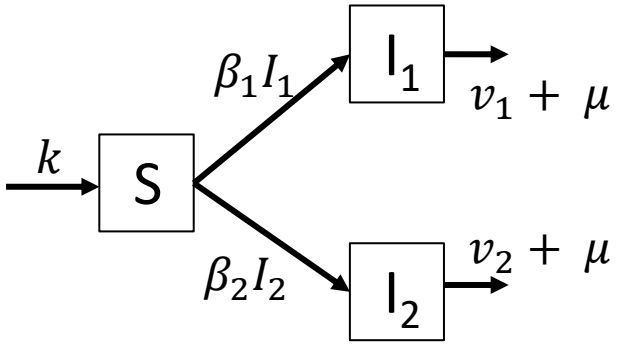
Nowak, *Evolutionary Dynamics*

Summary of fitness and adaptation

- Selection occurs when organisms have different rates of reproduction
- When growth is exponential, selection leads to survival of the fittest
- Mutations enable co-existence of strains with different fitness
- Quasispecies are populations of genetically related organisms, formed by mutation and selection
- There is typically one stable equilibrium of quasispecies, it is often not the fittest but rather a distribution around the fittest
- Adaptation cannot occur if mutation rates are too high

Evolution of virulence

Selection when competing for hosts



$$\dot{S} = k - S(\beta_1 I_1 + \beta_2 I_2) - \mu S$$

$$\dot{I}_1 = I_1(\beta_1 S - v_1 - \mu)$$

$$\dot{I}_2 = I_2(\beta_1 S - v_2 - \mu)$$

$$k = birth\ rate$$

$$v = virulence = excess\ mortality\ associated\ with\ infection$$

$$R0_1 = \frac{\beta_1}{\mu + v_1}\frac{k}{\mu}$$

$$R0_2 = \frac{\beta_2}{\mu + v_2}\frac{k}{\mu}$$

Question: Assuming $R0_1 > 1$ and $R_{02} > 1$, can there be an endemic equilibrium for I_1 and I_2?

$$\dot{I}_1 = 0, I_1 > 0$$

$$\dot{I}_1 = I_1(\beta_1 S - v_1 - \mu) = 0$$

$$S = \frac{v_1 + \mu}{\beta_1} = \frac{1}{R0_1}$$

$$S = \frac{v_2 + \mu}{\beta_2} = \frac{1}{R0_2}$$

$$S = \frac{1}{R0_1} = \frac{1}{R0_2}$$

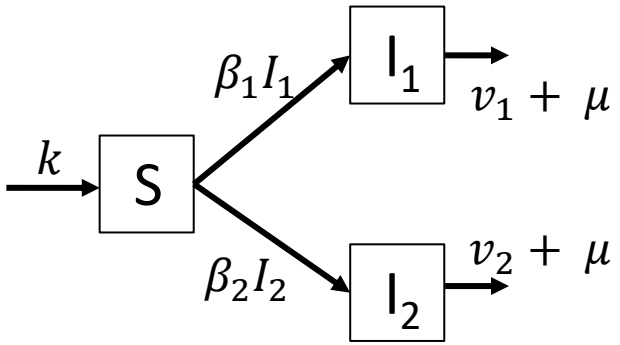
$$R0_1 = R0_2$$

The only way to have coexistence of two species in full competition for hosts is for equal R_0.

Evolution maximizes R_0

$$R_0 = \frac{\beta}{\mu + v}\frac{k}{\mu}$$

Is virulence helpful or harmful to the organism here?
If no constraints, evolution will increase transmission (β) and decrease virulence (v)



What if infectivity is proportionate to virulence?

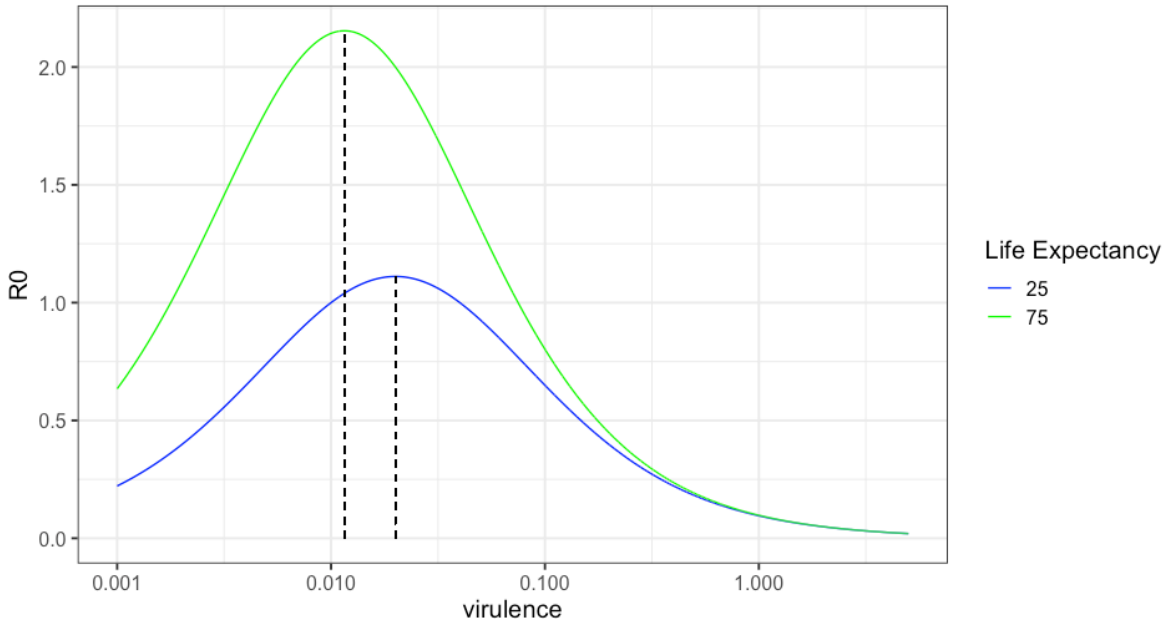
$$\beta = av$$

$$R_0 = \frac{av}{\mu + v}\frac{k}{\mu} = \frac{ak}{\mu}\left(\frac{v}{v + \mu}\right)$$

What if infectivity is a saturating function of virulence?

$$\beta = a\,\frac{v}{c + v}, \qquad as\ v \to \infty, \beta \to a$$

$$R_0 = \left(a\,\frac{v}{c + v}\right)\left(\frac{k}{\mu}\right)\left(\frac{1}{u + v}\right)$$



$$\frac{dR_0(v)}{dt} = 0\ to\ find\ maximum. Maximum\ at\ v = \sqrt{cu}$$

Virulence Summary

- When there is competition for hosts, evolution generally maximizes R_0
- If virulence and infectivity scale linearly, organisms would increase virulence to their maximum
- Usually there are constraints in relationship between virulence and infectivity, such that organisms will evolve towards intermediate virulence to maximize R_0

Superinfection

- When a new strain is able to infect a host who is already infected
- Leads to:
  - Higher virulence than optimal for maximizing R0
  - Co-existence of strains with range of virulence
  - Fewer infected hosts than without superinfection

Further Reading

Nowak, *Evolutionary Dynamics,* Chapter 11

Otto and Day, *A Biologists Guide to Mathematical Modeling in Ecology and Evolution,* Chapter 12