Infection in heterogeneous population with interventions

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## simulations

# setup
require(dplyr)

## Loading required package: dplyr

##
## Attaching package: 'dplyr'

## The following objects are masked from 'package:stats':
##
## filter, lag

## The following objects are masked from 'package:base':
##
## intersect, setdiff, setequal, union

require(tidyr)

## Loading required package: tidyr

require(ggplot2)

## Loading required package: ggplot2

require(gganimate)

## Loading required package: gganimate

set.seed(123)

theme\_set(theme\_classic())

# size of population
nPop <- 10^5

# end of simulation
tend <- 365

# infective period, assumed to start one day after infection with duration
idur <- 7

# number of repeated simulations
nsim <- 50

# homgenous population
 # rate of new infections per day
 r0a = 0.4
 # between subject variability of r0
 sd0a = 0.0

# heterogenous population
 # rate of new infections per day
 r0b = 0.2
 # between subject variability of r0
 sd0b = 1.0

# simulate spread of infection
mySim <- function(pat1, int1 = NULL, rVac = 0.0) {

 # number of patients that get vaccinated
 nVac <- max(1.0, min(nrow(pat1), rVac\*nrow(pat1)))

 pat1 <-
 pat1 %>%
 mutate(
 is = 0, # day of infection (0 ... not infected)
 ip = 1:n(), # subject identifier
 is = ifelse(ip <= nVac, 99999, is), # vacinated subjects
 is = ifelse(ip %in% ceiling(runif(10,nVac,n())), 1, is), # 10 random subjects get infected
 cru = cumsum(r0) / sum(r0) # to select subjets that get infected with probability proportional to r0
 )

 # simulate day by day
 for(iw in 2:tend) { # iw <- 2

 # intervention
 if(is.null(int1)) {
 if1 <- 1
 } else {
 if1 <- int1 %>% filter(t == iw) %>% select(rf) %>% unlist()
 }

 # select patients that are infective
 pat2 <- pat1 %>% filter(is != 0 & is > iw-idur & is <= iw)

 # rate of transmission
 rt <- sum(pat2$r0) \* if1

 # number of subjects infected
 ni <- rpois(1, rt)

 if(ni > 0) {
 # randomly select the patients who get transmitted
 pt1 <- runif(ni, min = 0.0, max = 1.0)
 ip1 <- findInterval(pt1, pat1$cru) + 1

 # select patients who receive infection
 pat1$sel <- FALSE
 pat1[ip1, "sel"] <- TRUE

 # infect patients who are not immune
 pat1 <-
 pat1 %>%
 mutate(is = ifelse(is == 0 & sel, iw, is))
 }

 }

 return(pat1)
}

# repeated simulations and summarize as median and percentile
mySim2 <- function(r0, sd0, int1 = NULL)
{

 # subjects
 pat1 <- tibble(
 r0l = rnorm(nPop, log(r0), sd0), # log of patient specific rate
 r0 = exp(r0l) / exp(sd0^2/2) # patient specific rate (rescaled to have mean r0)
 )

 sims <- list()
 for(isim in 1:nsim) {

 sim1 <- mySim(pat1, int1)

 pp1 <-
 ggplot(sim1, aes(x=r0, fill=(is!=0))) +
 geom\_density(alpha=0.4, position="stack") +
 scale\_x\_log10()

 s2 <- sim1 %>% group\_by(is) %>% summarise(ni = n())

 ts1 <-
 tibble(t = 1:tend, isim=isim) %>%
 left\_join(s2, by = c("t" = "is")) %>%
 mutate(
 ni = ifelse(is.na(ni), 0, ni),
 nt = cumsum(ni))

 sims[[isim]] <- ts1

 }

 sim2 <-
 bind\_rows(sims) %>%
 group\_by(t) %>%
 summarise(
 ni25 = quantile(ni, probs = 0.25),
 nim = median(ni),
 ni75 = quantile(ni, probs = 0.75),
 nt25 = quantile(nt, probs = 0.25),
 ntm = median(nt),
 nt75 = quantile(nt, probs = 0.75)
 )

}

# Illustrate heterogenous patient population
pat1 <- tibble(
 r0l = rnorm(nPop, log(r0b), sd0b), # log of patient specific rate
 r0 = exp(r0l) / exp(sd0b^2/2) # patient specific rate (rescaled to have mean r0)
)

p0 <-
 ggplot(pat1, aes(x=r0)) +
 geom\_density() +
 scale\_x\_log10() +
 xlab("Infection rate (1/Day)")

print(p0)



# make animated graph of disease progression
mygraph1 <- function(sim1) {
 sim1 <-
 sim1 %>%
 mutate(bin = cut\_interval(log(r0), n = 40)) %>%
 group\_by(bin) %>%
 mutate(
 dbin = median(r0),
 order = as.double(bin)) %>%
 ungroup()

 an1 <-
 sim1 %>%
 expand(ip, iweek) %>%
 rename(lweek = iweek) %>%
 full\_join(sim1, by="ip") %>%
 ungroup()

 an2 <-
 an1 %>%
 group\_by(dbin, bin, order, lweek) %>%
 summarise(
 n = sum(is>0 & iweek<=lweek),
 ntot = n(),
 ninf = sum(is>0),
 reff = mean(r0 \* (is == 0 | iweek>lweek)) \* (idur - 1)) %>%
 ungroup() %>%
 arrange(lweek, dbin)

 mylabs1 <-
 sim1 %>%
 select(order, dbin) %>%
 unique() %>%
 mutate(lab = ifelse((order+2) %% 5 == 0, paste(signif(dbin,2)), ""))

 # Animation
 p <-
 an2 %>%
 ggplot(aes(x = order)) +
 geom\_bar(aes(y=ntot), stat = "identity", fill = "grey20", alpha=0.2) +
 geom\_bar(aes(y=ninf), stat = "identity", fill = "red", alpha=0.2) +
 geom\_bar(aes(y=n), stat = "identity", fill = "#ff9933") +
 labs(title=paste0('Week {closest\_state}\nR(1 year) = ', round(R360, 2)),
 x="Infection rate (1/Day)",
 y="Number of subjects") +
 theme(plot.title = element\_text(hjust = 0.5, size = 18)) +
 scale\_x\_continuous(breaks=mylabs1$order, labels=mylabs1$lab) +
 transition\_states(lweek, transition\_length = 1, state\_length = 5) +
 view\_follow(fixed\_y=TRUE, fixed\_x = TRUE) +
 ease\_aes('cubic-in-out')

 return(p)
}

## No intervention, no Heterogeneity

sim2 <- mySim2(r0a, sd0a)

p1 <-
 ggplot(sim2, aes(x = t, y = ntm / nPop \* 100)) +
 geom\_ribbon(aes(ymin = nt25 / nPop \* 100, ymax = nt75 / nPop \* 100), alpha = 0.3) +
 geom\_line() +
 xlab("Day") +
 ylab("% infected")

print(p1 + coord\_cartesian(ylim = c(0, 100)))



print(p1 + scale\_y\_log10() + coord\_cartesian(ylim = c(1, 100)))



print(p1 + scale\_y\_log10() + coord\_cartesian(xlim = c(10,30)))



p2 <-
 ggplot(sim2, aes(x = t, y = nim / nPop \* 100)) +
 geom\_ribbon(aes(ymin = ni25 / nPop \* 100, ymax = ni75 / nPop \* 100), alpha = 0.3) +
 geom\_line() +
 xlab("Day") +
 ylab("% infectious")

print(p2)



ts2 <- sim2 %>% mutate(Scenario = "Base")

## No intervention, with Heterogeneity

sim2 <- mySim2(r0b, sd0b)

p1 <-
 ggplot(sim2, aes(x = t, y = ntm / nPop \* 100)) +
 geom\_ribbon(aes(ymin = nt25 / nPop \* 100, ymax = nt75 / nPop \* 100), alpha = 0.3) +
 geom\_line() +
 xlab("Day") +
 ylab("% infected")

print(p1 + coord\_cartesian(ylim = c(0, 100)))



p2 <-
 ggplot(sim2, aes(x = t, y = nim / nPop \* 100)) +
 geom\_ribbon(aes(ymin = ni25 / nPop \* 100, ymax = ni75 / nPop \* 100), alpha = 0.3) +
 geom\_line() +
 xlab("Day") +
 ylab("% infectious")

print(p2)



ts2 <- bind\_rows(
 ts2,
 sim2 %>% mutate(Scenario = "Heterogeneity")
)

p1 <-
 ggplot(ts2 %>% filter(Scenario %in% c("Base", "Heterogeneity")), aes(x = t, y = ntm / nPop \* 100)) +
 geom\_line(aes(linetype = Scenario)) +
 geom\_ribbon(data = ts2 %>% filter(Scenario == "Base"),
 aes(ymin = nt25 / nPop \* 100, ymax = nt75 / nPop \* 100), alpha = 0.3) +
 xlab("Day") +
 ylab("% infected")

print(p1 + coord\_cartesian(ylim = c(0, 100)))



print(p1 + coord\_cartesian(xlim = c(4, 30)) + scale\_y\_log10())



## Intervention from day 20 to 50, no Heterogeneity

# intervention
int1 <-
 tibble(t = 1:tend) %>%
 mutate(rf = ifelse(t>20 & t<50, 0.3, 1.0)) # period of social distancing

sim2 <- mySim2(r0a, sd0a, int1)

p1 <-
 ggplot(sim2, aes(x = t, y = ntm / nPop \* 100)) +
 geom\_ribbon(aes(ymin = nt25 / nPop \* 100, ymax = nt75 / nPop \* 100), alpha = 0.3) +
 geom\_line() +
 xlab("Day") +
 ylab("% infected")

print(p1 + coord\_cartesian(ylim = c(0, 100)))



p2 <-
 ggplot(sim2, aes(x = t, y = nim / nPop \* 100)) +
 geom\_ribbon(aes(ymin = ni25 / nPop \* 100, ymax = ni75 / nPop \* 100), alpha = 0.3) +
 geom\_line() +
 xlab("Day") +
 ylab("% infectious")

print(p2)



ts2 <- bind\_rows(
 ts2,
 sim2 %>% mutate(Scenario = "Intervention")
)

p1 <-
 ggplot(ts2 %>% filter(Scenario %in% c("Base", "Intervention")), aes(x = t, y = ntm / nPop \* 100)) +
 geom\_line(aes(linetype = Scenario)) +
 geom\_ribbon(data = ts2 %>% filter(Scenario == "Base"),
 aes(ymin = nt25 / nPop \* 100, ymax = nt75 / nPop \* 100), alpha = 0.3) +
 xlab("Day") +
 ylab("% infected")

print(p1 + coord\_cartesian(ylim = c(0, 100)))



## Intervention from day 20 to 50, with Heterogeneity

sim2 <- mySim2(r0b, sd0b, int1)

p1 <-
 ggplot(sim2, aes(x = t, y = ntm / nPop \* 100)) +
 geom\_ribbon(aes(ymin = nt25 / nPop \* 100, ymax = nt75 / nPop \* 100), alpha = 0.3) +
 geom\_line() +
 xlab("Day") +
 ylab("% infected")

print(p1 + coord\_cartesian(ylim = c(0, 100)))



p2 <-
 ggplot(sim2, aes(x = t, y = nim / nPop \* 100)) +
 geom\_ribbon(aes(ymin = ni25 / nPop \* 100, ymax = ni75 / nPop \* 100), alpha = 0.3) +
 geom\_line() +
 xlab("Day") +
 ylab("% infectious")

print(p2)



ts2 <- bind\_rows(
 ts2,
 sim2 %>% mutate(Scenario = "Both")
)

p1 <-
 ggplot(ts2 %>% filter(Scenario %in% c("Heterogeneity", "Both")), aes(x = t, y = ntm / nPop \* 100)) +
 geom\_line(aes(linetype = Scenario)) +
 geom\_ribbon(data = ts2 %>% filter(Scenario == "Both"),
 aes(ymin = nt25 / nPop \* 100, ymax = nt75 / nPop \* 100), alpha = 0.3) +
 xlab("Day") +
 ylab("% infected")

print(p1 + coord\_cartesian(ylim = c(0, 100)))



## Intervention from day 20 to 50 with follow up to day 80, with Heterogeneity

# intervention
int2 <-
 tibble(t = 1:tend) %>%
 mutate(rf = case\_when(
 t <= 20 ~ 1,
 t < 50 ~ 0.3,
 t < 80 ~ 0.6,
 TRUE ~ 1
 )) # period of social distancing

sim2 <- mySim2(r0b, sd0b, int2)

p1 <-
 ggplot(sim2, aes(x = t, y = ntm / nPop \* 100)) +
 geom\_ribbon(aes(ymin = nt25 / nPop \* 100, ymax = nt75 / nPop \* 100), alpha = 0.3) +
 geom\_line() +
 xlab("Day") +
 ylab("% infected")

print(p1 + coord\_cartesian(ylim = c(0, 100)))



p2 <-
 ggplot(sim2, aes(x = t, y = nim / nPop \* 100)) +
 geom\_ribbon(aes(ymin = ni25 / nPop \* 100, ymax = ni75 / nPop \* 100), alpha = 0.3) +
 geom\_line() +
 xlab("Day") +
 ylab("% infectious")

print(p2)



ts2 <- bind\_rows(
 ts2,
 sim2 %>% mutate(Scenario = "Follow up to day 80")
)

p1 <-
 ggplot(ts2 %>% filter(Scenario %in% c("Follow up to day 80", "Both")), aes(x = t, y = ntm / nPop \* 100)) +
 geom\_line(aes(linetype = Scenario)) +
 geom\_ribbon(data = ts2 %>% filter(Scenario == "Both"),
 aes(ymin = nt25 / nPop \* 100, ymax = nt75 / nPop \* 100), alpha = 0.3) +
 xlab("Day") +
 ylab("% infected")

print(p1 + coord\_cartesian(ylim = c(0, 100)))



## Intervention from day 20 to 50 with follow up to day 180, with Heterogeneity

# intervention
int3 <-
 tibble(t = 1:tend) %>%
 mutate(rf = case\_when(
 t <= 20 ~ 1,
 t < 50 ~ 0.3,
 t < 180 ~ 0.6,
 TRUE ~ 1
 )) # period of social distancing

sim2 <- mySim2(r0b, sd0b, int3)

p1 <-
 ggplot(sim2, aes(x = t, y = ntm / nPop \* 100)) +
 geom\_ribbon(aes(ymin = nt25 / nPop \* 100, ymax = nt75 / nPop \* 100), alpha = 0.3) +
 geom\_line() +
 xlab("Day") +
 ylab("% infected")

print(p1 + coord\_cartesian(ylim = c(0, 100)))



p2 <-
 ggplot(sim2, aes(x = t, y = nim / nPop \* 100)) +
 geom\_ribbon(aes(ymin = ni25 / nPop \* 100, ymax = ni75 / nPop \* 100), alpha = 0.3) +
 geom\_line() +
 xlab("Day") +
 ylab("% infectious")

print(p2)



ts2 <- bind\_rows(
 ts2,
 sim2 %>% mutate(Scenario = "Follow up to day 180")
)

p1 <-
 ggplot(ts2 %>% filter(Scenario %in% c("Follow up to day 180", "Both")), aes(x = t, y = ntm / nPop \* 100)) +
 geom\_line(aes(linetype = Scenario)) +
 geom\_ribbon(data = ts2 %>% filter(Scenario == "Follow up to day 180"),
 aes(ymin = nt25 / nPop \* 100, ymax = nt75 / nPop \* 100), alpha = 0.3) +
 xlab("Day") +
 ylab("% infected")

print(p1 + coord\_cartesian(ylim = c(0, 100)))



## Intervention from day 20 to 50 with pronounced follow up to day 180, with Heterogeneity

# intervention
int4 <-
 tibble(t = 1:tend) %>%
 mutate(rf = case\_when(
 t <= 20 ~ 1,
 t < 50 ~ 0.3,
 t < 180 ~ 0.5,
 TRUE ~ 1
 )) # period of social distancing

sim2 <- mySim2(r0b, sd0b, int4)

p1 <-
 ggplot(sim2, aes(x = t, y = ntm / nPop \* 100)) +
 geom\_ribbon(aes(ymin = nt25 / nPop \* 100, ymax = nt75 / nPop \* 100), alpha = 0.3) +
 geom\_line() +
 xlab("Day") +
 ylab("% infected")

print(p1 + coord\_cartesian(ylim = c(0, 100)))



p2 <-
 ggplot(sim2, aes(x = t, y = nim / nPop \* 100)) +
 geom\_ribbon(aes(ymin = ni25 / nPop \* 100, ymax = ni75 / nPop \* 100), alpha = 0.3) +
 geom\_line() +
 xlab("Day") +
 ylab("% infectious")

print(p2)



ts2 <- bind\_rows(
 ts2,
 sim2 %>% mutate(Scenario = "Pronounced follow up to day 180")
)

## Intervention from day 20 to day 180, with Heterogeneity

# intervention
int5 <-
 tibble(t = 1:tend) %>%
 mutate(rf = case\_when(
 t <= 20 ~ 1,
 t < 50 ~ 0.3,
 t < 180 ~ 0.3,
 TRUE ~ 1
 )) # period of social distancing

sim2 <- mySim2(r0b, sd0b, int5)

p1 <-
 ggplot(sim2, aes(x = t, y = ntm / nPop \* 100)) +
 geom\_ribbon(aes(ymin = nt25 / nPop \* 100, ymax = nt75 / nPop \* 100), alpha = 0.3) +
 geom\_line() +
 xlab("Day") +
 ylab("% infected")

print(p1 + coord\_cartesian(ylim = c(0, 100)))



p2 <-
 ggplot(sim2, aes(x = t, y = nim / nPop \* 100)) +
 geom\_ribbon(aes(ymin = ni25 / nPop \* 100, ymax = ni75 / nPop \* 100), alpha = 0.3) +
 geom\_line() +
 xlab("Day") +
 ylab("% infectious")

print(p2)



ts2 <- bind\_rows(
 ts2,
 sim2 %>% mutate(Scenario = "Intervention to day 180")
)

p1 <-
 ggplot(ts2, aes(x = t, y = ntm / nPop \* 100)) +
 geom\_line(aes(colour = Scenario)) +
 geom\_ribbon(data = ts2 %>% filter(Scenario == "Follow up to day 180"),
 aes(ymin = nt25 / nPop \* 100, ymax = nt75 / nPop \* 100), alpha = 0.3) +
 xlab("Day") +
 ylab("% infected")

print(p1 + coord\_cartesian(ylim = c(0, 100)))



print(p1 + scale\_y\_log10() + coord\_cartesian(ylim = c(1, 100)))



print(p1 + scale\_y\_log10() + coord\_cartesian(xlim = c(4,30)))



p1 <-
 ggplot(ts2, aes(x = t, y = nim / nPop \* 100, colour = Scenario)) +
 geom\_line(aes(colour = Scenario)) +
 geom\_ribbon(data = ts2 %>% filter(Scenario == "Follow up to day 180"),
 aes(ymin = ni25 / nPop \* 100, ymax = ni75 / nPop \* 100), alpha = 0.3) +
 xlab("Day") +
 ylab("% infectious")

print(p1 )



# plots of density

# subjects
set.seed(123)
pat0 <- tibble(
 r0l = rnorm(nPop, log(r0a), 0.001), # log of patient specific rate
 r0 = exp(r0l) / exp(0.001^2/2) # patient specific rate (rescaled to have mean r0)
)

set.seed(123)
sim1 <- mySim(pat0)

R360 = sim1 %>% summarise(mr = mean(r0 \* (is == 0)) \* (idur - 1)) %>% unlist()

sim1 <-
 sim1 %>%
 mutate(
 iweek = pmin((is + 6) %/% 7, 52))

pp1 <-
 ggplot(sim1, aes(x=r0)) +
 # geom\_freqpoly(fill = NA, size=2) +
 geom\_histogram(aes(fill = (is>0)), bins=40, alpha=0.2) +
 geom\_freqpoly(aes(colour=factor(iweek)), position="stack", bins=40) +
 scale\_x\_log10() +
 xlab("Infection rate (1/Day)") +
 scale\_fill\_discrete(labels = c("No", "Yes")) +
 guides(colour = "none", fill = guide\_legend("Infected")) +
 ggtitle(paste0("Homogeneous\nR(1 year) = ", round(R360, 2)))

print(pp1)



p <- mygraph1(sim1)
animate(p, nframes=50, fps=4)



anim\_save("animHom.gif", p)

# including vaccination
set.seed(123)
sim1 <- mySim(pat0, rVac = 1-1/r0a/(idur - 1))

R360 = sim1 %>% summarise(mr = mean(r0 \* (is == 0)) \* (idur - 1)) %>% unlist()

sim1 <-
 sim1 %>%
 mutate(
 iweek = pmin((is + 6) %/% 7, 52))

pp1 <-
 ggplot(sim1, aes(x=r0)) +
 # geom\_freqpoly(fill = NA, size=2) +
 geom\_histogram(aes(fill = (is>0)), bins=40, alpha=0.2) +
 geom\_freqpoly(aes(colour=factor(iweek)), position="stack", bins=40) +
 scale\_x\_log10() +
 xlab("Infection rate (1/Day)") +
 scale\_fill\_discrete(labels = c("No", "Yes")) +
 guides(colour = "none", fill = guide\_legend("Infected")) +
 ggtitle(paste0("Vaccination\nR(1 year) = ", round(R360, 2)))

print(pp1)



p <- mygraph1(sim1)
animate(p, nframes=50, fps=4)



anim\_save("animHomVac.gif", p)

# intervention
set.seed(123)
sim1 <- mySim(pat0, int4)

R360 = sim1 %>% summarise(mr = mean(r0 \* (is == 0)) \* (idur - 1)) %>% unlist()

sim1 <-
 sim1 %>%
 mutate(
 iweek = pmin((is + 6) %/% 7, 52))

pp1 <-
 ggplot(sim1, aes(x=r0)) +
 # geom\_freqpoly(fill = NA, size=2) +
 geom\_histogram(aes(fill = (is>0)), bins=40, alpha=0.2) +
 geom\_freqpoly(aes(colour=factor(iweek)), position="stack", bins=40) +
 scale\_x\_log10() +
 xlab("Infection rate (1/Day)") +
 scale\_fill\_discrete(labels = c("No", "Yes")) +
 guides(colour = "none", fill = guide\_legend("Infected")) +
 ggtitle(paste0("Homogeneous with follow up to day 180\nR(1 year) = ", round(R360, 2)))

print(pp1)



p <- mygraph1(sim1)
animate(p, nframes=50, fps=4)



anim\_save("animHomI4.gif", p)

# subjects
set.seed(123)
pat1 <- tibble(
 r0l = rnorm(nPop, log(r0b), sd0b), # log of patient specific rate
 r0 = exp(r0l) / exp(sd0b^2/2) # patient specific rate (rescaled to have mean r0)
)

set.seed(123)
sim1 <- mySim(pat1)

R360 = sim1 %>% summarise(mr = mean(r0 \* (is == 0)) \* (idur - 1)) %>% unlist()

sim1 <-
 sim1 %>%
 mutate(
 iweek = pmin((is + 6) %/% 7, 52))

pp1 <-
 ggplot(sim1, aes(x=r0)) +
 # geom\_freqpoly(fill = NA, size=2) +
 geom\_histogram(aes(fill = (is>0)), bins=40, alpha=0.2) +
 geom\_freqpoly(aes(colour=factor(iweek)), position="stack", bins=40) +
 scale\_x\_log10() +
 xlab("Infection rate (1/Day)") +
 scale\_fill\_discrete(labels = c("No", "Yes")) +
 guides(colour = "none", fill = guide\_legend("Infected")) +
 ggtitle(paste0("Heterogeneous\nR(1 year) = ", round(R360, 2)))

print(pp1)



p <- mygraph1(sim1)
animate(p, nframes=50, fps=4)



anim\_save("animHetBase.gif", p)

set.seed(123)
sim1 <- mySim(pat1, int4)

R360 = sim1 %>% summarise(mr = mean(r0 \* (is == 0)) \* (idur - 1)) %>% unlist()

sim1 <-
 sim1 %>%
 mutate(
 iweek = pmin((is + 6) %/% 7, 52))

pp1 <-
 ggplot(sim1, aes(x=r0)) +
 # geom\_freqpoly(fill = NA, size=2) +
 geom\_histogram(aes(fill = (is>0)), bins=40, alpha=0.2) +
 geom\_freqpoly(aes(colour=factor(iweek)), position="stack", bins=40) +
 scale\_x\_log10() +
 xlab("Infection rate (1/Day)") +
 scale\_fill\_discrete(labels = c("No", "Yes")) +
 guides(colour = "none", fill = guide\_legend("Infected")) +
 ggtitle(paste0("Heterogeneous with follow up to day 180\nR(1 year) = ", round(R360, 2)))

print(pp1)



p <- mygraph1(sim1)
animate(p, nframes=50, fps=4)



anim\_save("animHetI4.gif", p)