Outline

- Biology/epidemiology of Guinea worm disease
- Mathematical model
- Impulsive differential equations
- Thresholds for theoretical control of the disease
- Evaluation of practical control methods
- Implications.

Background

- Guinea worm disease is one of humanity's oldest scourges
- It is mentioned in the bible and afflicted Egyptian mummies
- Europeans first saw the disease on the Guinea coast of West Africa in the 17th century.

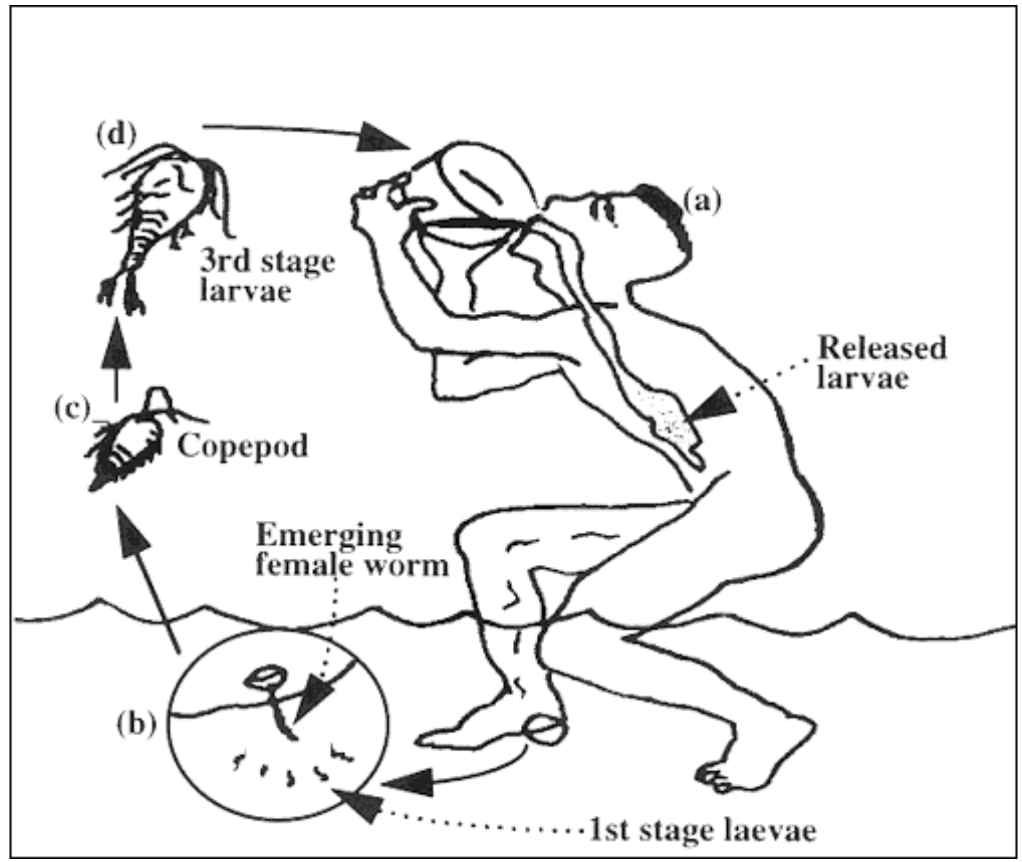
Infection

- It is a parasite that lives in the drinking water
- Carried by water fleas which are ingested by humans
- Stomach acid dissolves the flea, leaving the parasite free to penetrate the body cavity
- The parasite travels to the extremities, usually the foot
- It resides here for about a year.

The Guinea Worm

Transmission

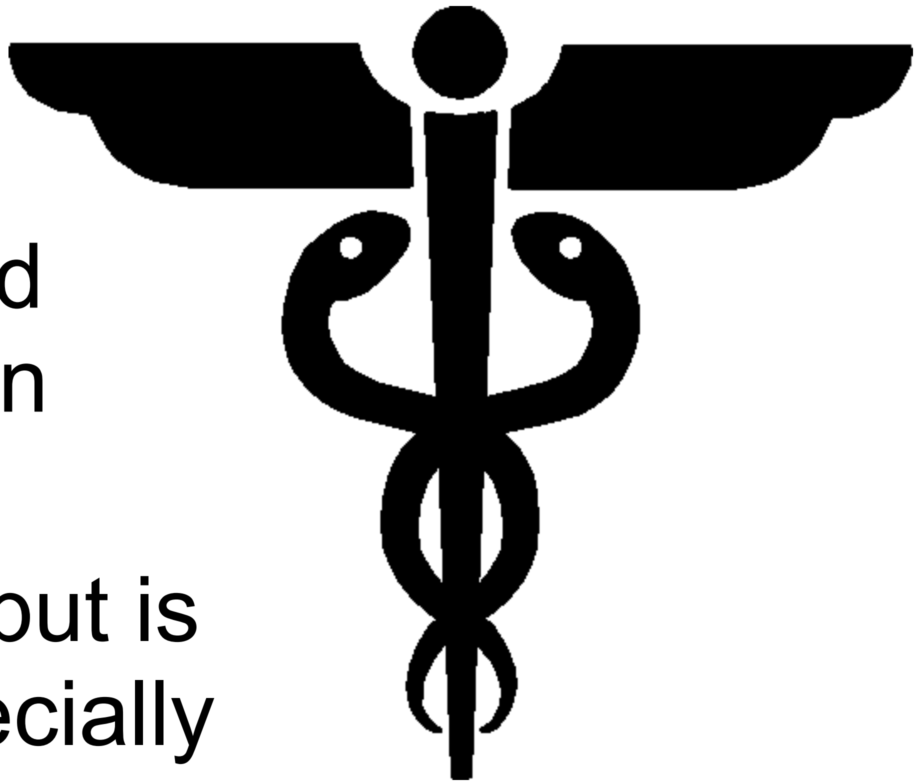
- When ready to burst, the worm causes a burning and itching sensation
- The host places the infected limb in water
- At this point, the worm ejects hundreds of thousands of larvae, restarting the cycle.



The worm

- The worm can grow up to a metre in length
- Can be removed by physically pulling the worm out, wrapped around a stick
- Only 1-2cm can be removed per day
- This takes up to two months.

Burden of infection



- The medical symbol of the Staff of Asclepius is based upon the stick used to extract guinea worms in ancient times
- The disease doesn't kill, but is extremely disabling, especially during the agricultural season
- There is no vaccine or curative drug
- Individuals do not develop immunity.

Geography

- During the 19th and 20th centuries, the disease was found in
  - southern Asia
  - the middle east
  - North, East and West Africa
- In the 1950s, there were an estimated 50 million cases...
- ...however, today it is almost eradicated.

Eradication program

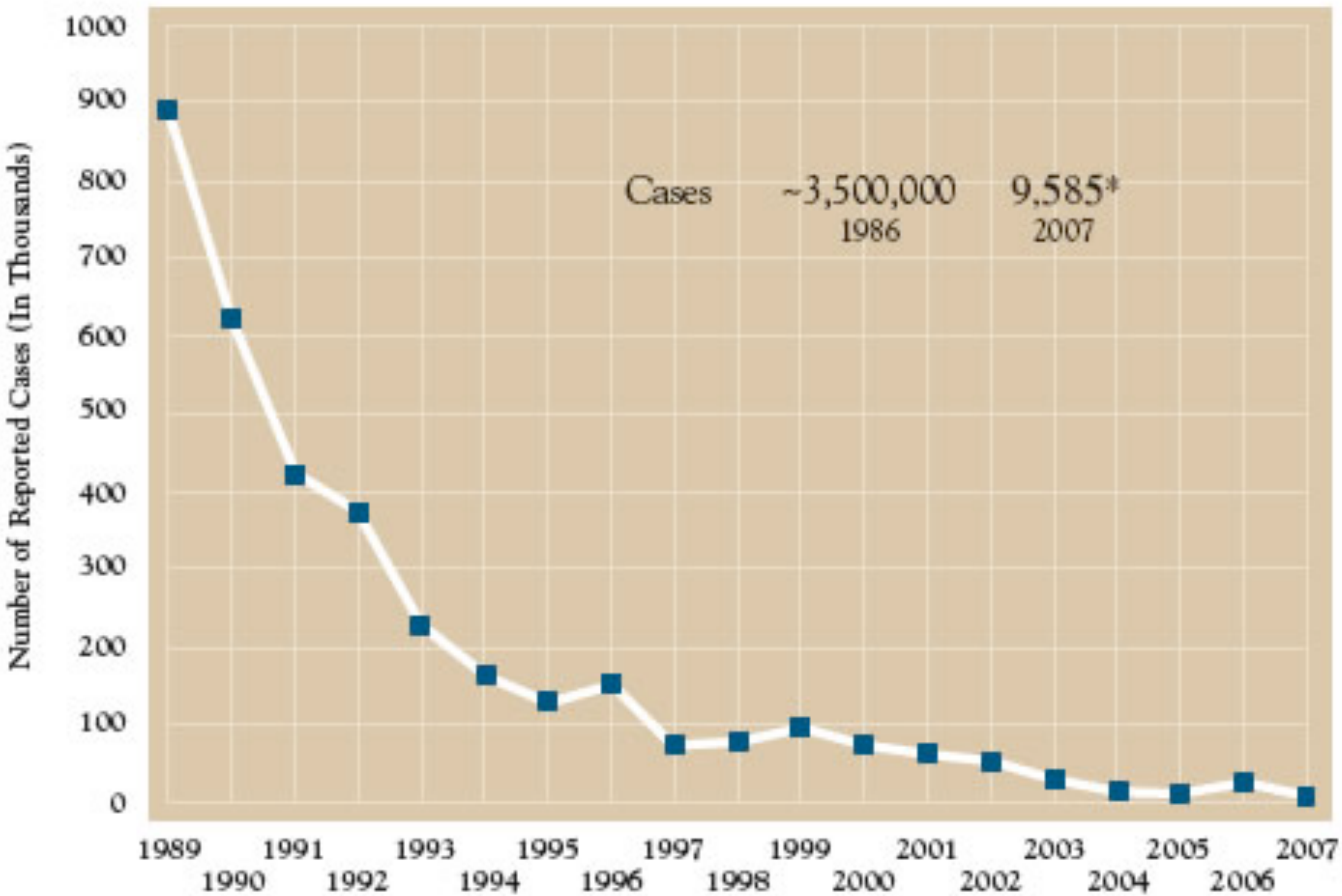
- However, since 1986, concerted eradication programs have been underway
- Largely due to efforts of former president Jimmy Carter
- Organisations:
  - The Carter Center
  - National Guinea worm eradication programs
  - Centers for Disease Control
  - UNICEF
  - World Health Organization.

On the brink of eradication

- 1989: 892,000 cases, widespread countries
- 1996: 96,000 cases, 13 countries (none in Asia)
- 2013: <150 cases, 4 countries
  - South Sudan
  - Ethiopia
  - Mali
  - Chad

- If eradicated, it will be the first parasitic disease and also the first to be eradicated using behaviour changes alone.

Significant decline



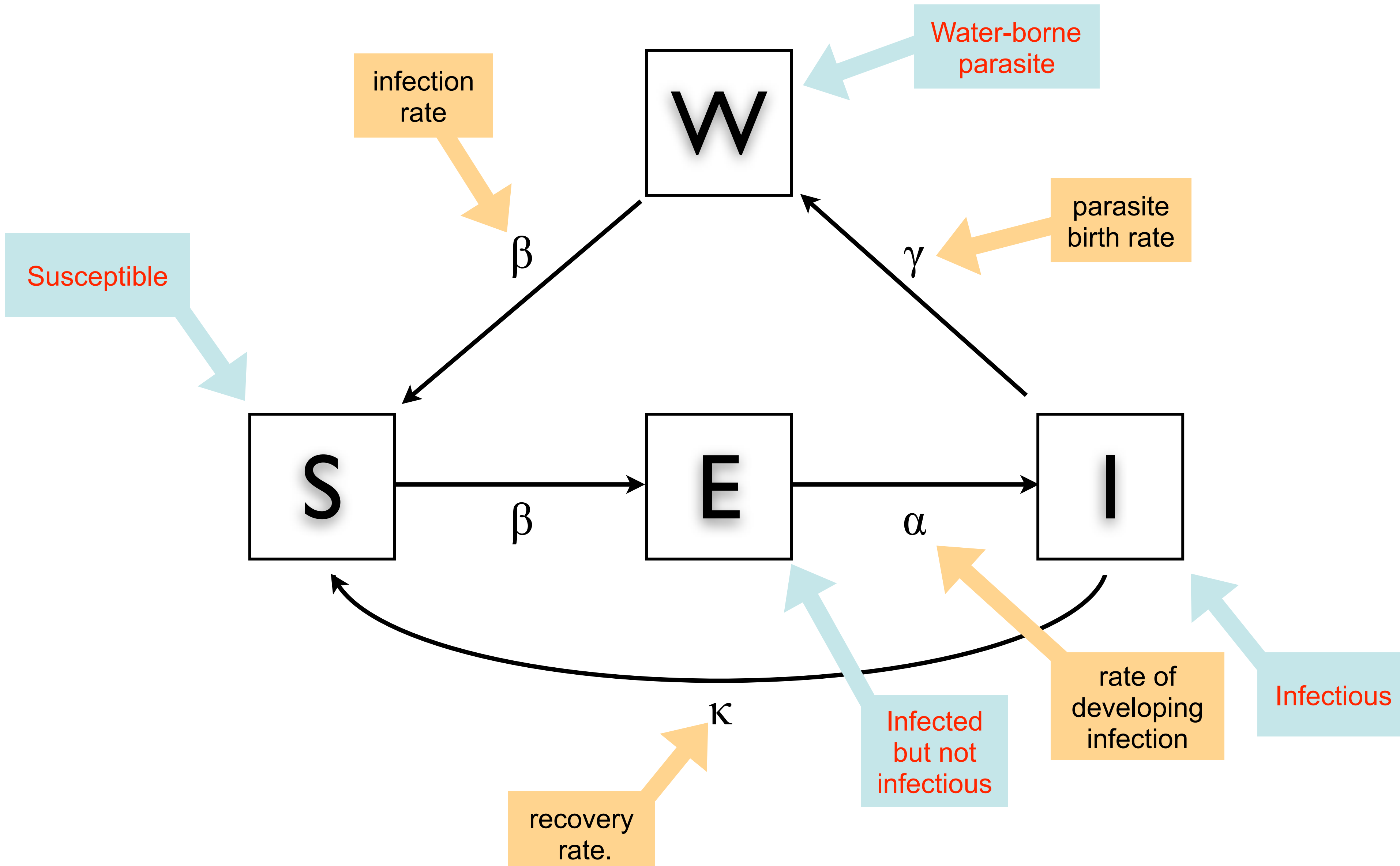
Prevention

- Drinking water from underground sources
- Infected individuals can be educated about not submerging wounds in drinking water
- Cloth filters that fit over pots and pans can be distributed to villages
- Nomadic people have received personal-use cloths fitted over pipes, worn around the neck
- Chemical larvacides can be added to stagnant water supplies.

Continuous treatment

- However, continuous water treatment is neither desirable nor feasible
- There are environmental and toxicity issues
- Also limited supplies of resources
- Thus, we consider chlorination at discrete times.

The model



W
Water-borne parasite
infection rate
β
parasite birth rate
γ
Susceptible
S
β
E
α
I
κ
Infected but not infectious
rate of developing infection
Infectious
recovery rate.

Impulsive Differential Equations

- Assume chlorination is instantaneous
- That is, the time required for the larvicide to be applied and reach its maximum is assumed to be negligible
- Impulsive differential equations are a useful formulation for systems that undergo rapid changes in their state
- The approximation is reasonable when the time between impulses is large compared to the duration of the rapid change.

Putting it together

- The model thus consists of a system of ODEs (humans) together with an ODE and a difference equation (parasite).

Equations

- The mathematical model is

$$
\begin{aligned}
S' &= \Pi - \beta S W - \mu S + \kappa I & t \neq t_k \\
E' &= \beta S W - \alpha E - \mu E & t \neq t_k \\
I' &= \alpha E - \kappa I - \mu I & t \neq t_k \\
W' &= \gamma I - \mu_W W & t \neq t_k \\
\Delta W &= -rW & t = t_k
\end{aligned}
$$

- t_k is the chlorination time
- Chlorination may occur at regular intervals or not.

S=susceptibles Π=birth rate β=transmissability
μ=background death rate E=exposed I=infectious
W=parasite-infested water κ=recovery rate
α=incubation period γ=parasite birth rate
μ_W=parasite death rate r=chlorine effectiveness

The system without impulses

- Two equilibria: disease free and endemic

$$\left(\frac{\Pi}{\mu}, 0, 0, 0\right) \text{ and } (\hat{S}, \hat{E}, \hat{I}, \hat{W})$$

- The former always exists
- The latter only exists for some parameters.

S=susceptibles Π=birth rate
μ=background death rate
E=exposed I=infectious
W=parasite-infested water

The basic reproductive ratio

$$R_0 = \frac{\Pi\alpha\gamma\beta}{\mu(\alpha+\mu)(\kappa+\mu)\mu_W}$$

- We can prove the following:
  - When $R_0<1$, the disease-free equilibrium is the only equilibrium and is stable
  - When $R_0>1$, the disease-free equilibrium is unstable; the endemic equilibrium exists and is stable
- Thus, R_0 is our eradication threshold.

Π=*birth rate* β=*transmissability* μ=*background death rate* κ=*recovery rate* α=*incubation period* γ=*parasite birth rate* μ_W=*parasite death rate*

Effect of interventions

- Education discourages infected individuals from putting infected limbs in the drinking water

$$R_0 = \frac{\Pi\alpha\gamma\beta}{\mu(\alpha+\mu)(\kappa+\mu)\mu_W}$$

- This decreases γ and hence R_0
- Filtration decreases β and hence R_0
- (Continuous) chlorination increases μ_W and hence decreases R_0.

Π=*birth rate* β=*transmissability* μ=*background death rate* κ=*recovery rate* α=*incubation period* γ=*parasite birth rate* μ_W=*parasite death rate* R_0=*basic reproductive ratio*

The system with impulses

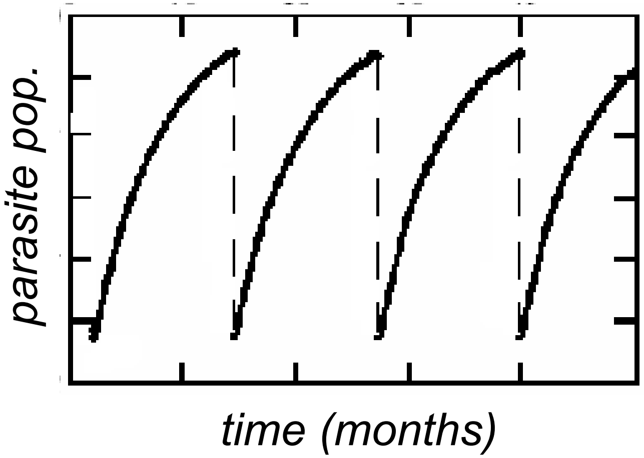
- If we have maximum growth of larvae, then

$$W' = \frac{\alpha \Pi \gamma}{\mu(\kappa + \mu)} - \mu_W W \qquad\qquad t \neq t_k$$

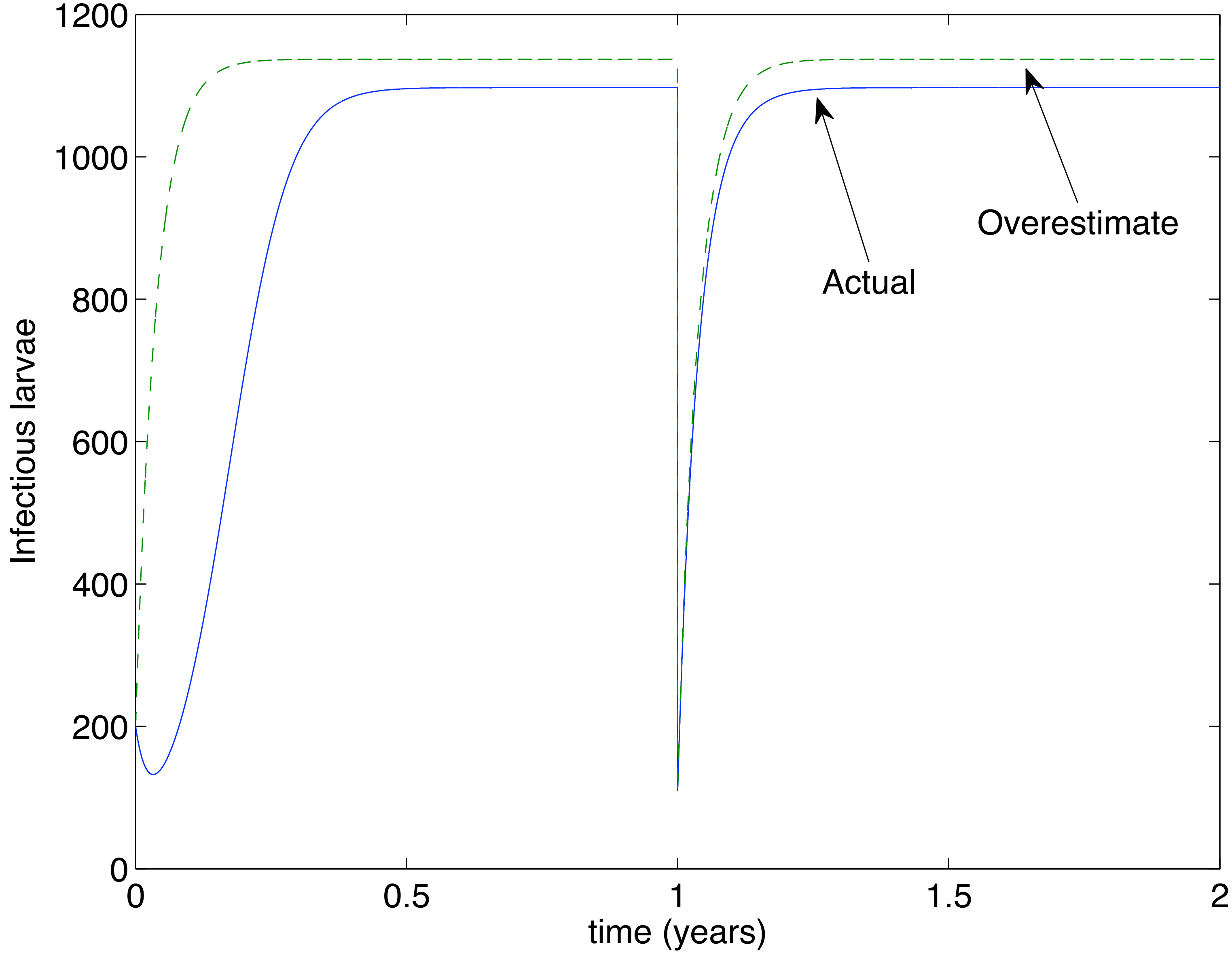
- The endpoints of the impulsive system satisfy the recurrence relation

$$W(t_{k+1}^{-}) = W(t_k^{+})e^{-\mu_W (t_{k+1} - t_k)} + \frac{\alpha \Pi \gamma}{\mu \mu_W (\kappa + \mu)} \left[1 - e^{-\mu_W (t_{k+1} - t_k)}\right].$$

Π=*birth rate* μ=*background death rate*
κ=*recovery rate* α=*incubation period*
γ=*parasite birth rate* μ_W=*parasite death rate* t_k=*chlorination time*
W=parasite-infected water



The degree of overestimation



An explicit solution

- Solving the recurrence relation for the endpoints of the impulsive system yields an explicit solution:

$$W_n^- = \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa+\mu)}\Big[(1-r)^{n-1}e^{-\mu_W(t_n-t_1)} + (1-r)^{n-1}e^{-\mu_W(t_n-t_2)}$$

$$+\cdots+(1-r)e^{-\mu_W(t_n-t_{n-1})}+1$$

$$-(1-r)^{n-2}e^{-\mu_W(t_n-t_1)} - (1-r)^{n-3}e^{-\mu_W(t_n-t_2)}$$

$$-\cdots-e^{-\mu_W(t_n-t_{n-1})}\Big].$$

Π=birth rate μ=background death rate
κ=recovery rate α=incubation period
γ=parasite birth rate μ_W=parasite death rate
W=parasite-infected water t_k=chlorination time r=chlorination effectiveness

Fixed chlorination

- If chlorination occurs at fixed intervals, then $t_n - t_{n-1} = \tau$ is constant
- Thus, the endpoints approach

$$\lim_{n\to\infty} W_n^- = \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa+\mu)}\left[\frac{1-e^{-\mu_W\tau}}{1-(1-r)e^{-\mu_W\tau}}\right]$$

- To keep this below a desired threshold W*, we require

$$\tau < \frac{1}{\mu_W}\ln\left[\frac{\alpha\Pi\gamma-(1-r)W^*\mu\mu_W(\kappa+\mu)}{\alpha\Pi\gamma-W^*\mu\mu_W(\kappa+\mu)}\right].$$

Π=birth rate μ=background death rate κ=recovery rate α=incubation period γ=parasite birth rate μ_W=parasite death rate t_k=chlorination time W=parasite-infected water r=chlorination effectiveness

Non-fixed chlorination

- Regular chlorination may be difficult due to limited resources and infrastructure
- In particular, if chlorination is not fixed, the entire history of chlorination would need to be known
- This is highly unlikely.

Limited knowledge

- Assume that only the two previous chlorination events are known
- Specifically,

$$e^{-\mu_W(t_n - t_k)} \approx 0 \text{ for } k > 2$$

- To keep the parasite below the threshold W*, we thus require

$$t_n < \frac{1}{\mu_W} \ln \left[\frac{2 - r^2}{1 - r(1-r)e^{\mu_W t_{n-2}} - (2-r)e^{\mu_W t_{n-1}} - W^* \mu \mu_W (\kappa + \mu)/(\alpha \Pi \gamma)} \right].$$

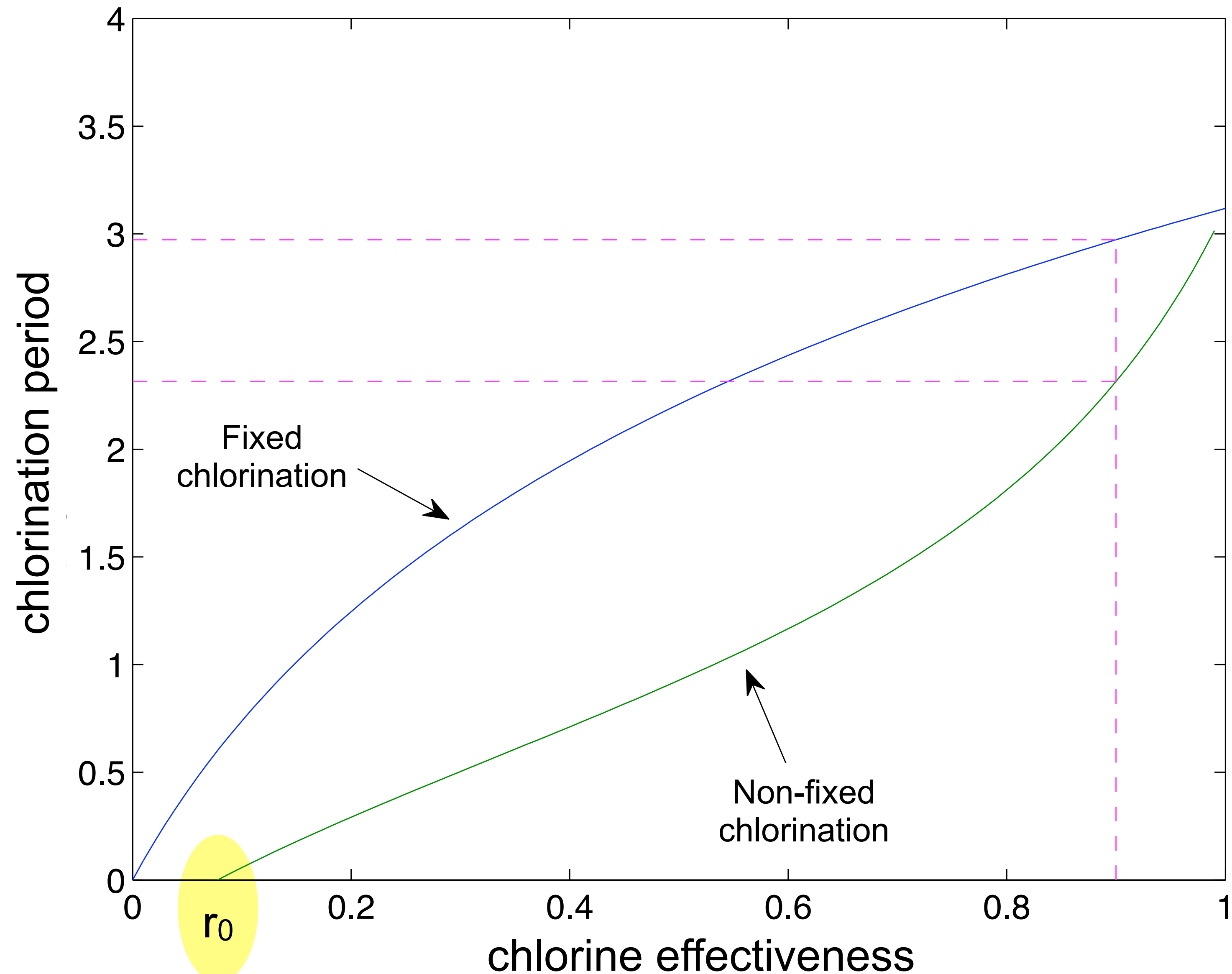
Π=birth rate μ=background death rate κ=recovery rate α=incubation period γ=parasite birth rate μ_W=parasite death rate t_k=chlorination time W=parasite-infected water r=chlorination effectiveness

Comparison

- When r=1, fixed and non-fixed chlorination are equivalent
- There exists r_0 such that non-fixed chlorination will only be successful for $r_0 < r \leq 1$
- Conversely, fixed chlorination is successful for all values of r
- Thus, chlorination, whether fixed or non-fixed, can theoretically control the disease (but not eradicate it).

r=chlorination effectiveness

Fixed chlorination is always better



Latin Hypercube Sampling

- We explored the sensitivity of R_0 to parameter variations using
  - Latin Hypercube Sampling
  - Partial Rank Correlation Coefficients
- Latin Hypercube Sampling
  - samples parameters from a random grid
  - resamples, but not from the same row or column

    (a bit like tic tac toe)
  - runs 1,000 simulations.

Example

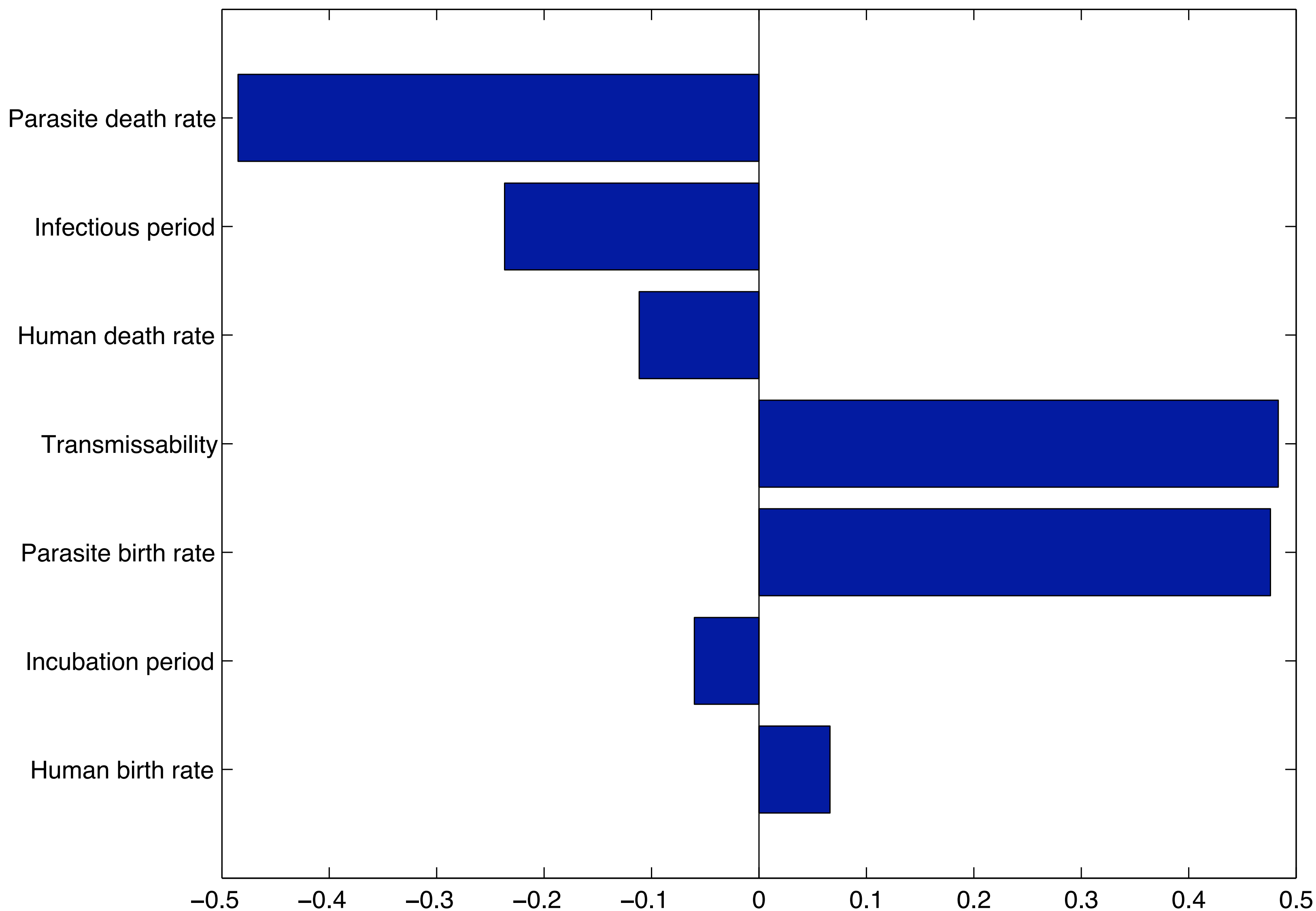
✗	✓	✗
✗	✗	✓
✓	✗	✗

Partial Rank Correlation Coefficients

- Partial Rank Correlation Coefficients (PRCCs)
  - test individual parameters while holding all other parameters at median values
  - rank parameters by the amount of effect on the outcome
- PRCCs > 0 will increase R_0 when they are increased
- PRCCs < 0 will decrease R_0 when they are increased.

R_0=basic reproductive ratio

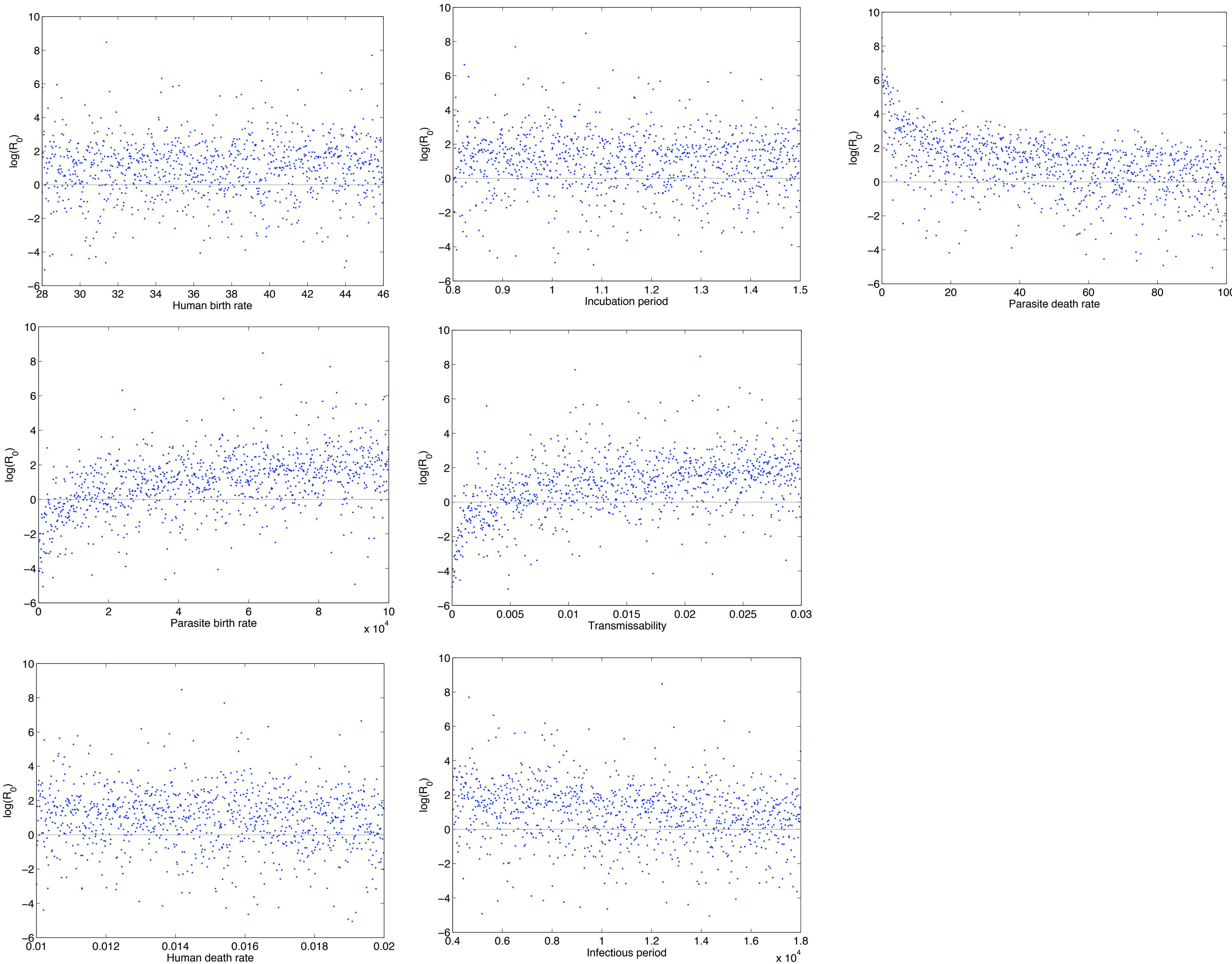
PRCCs


Parasite death rate
Infectious period
Human death rate
Transmissability
Parasite birth rate
Incubation period
Human birth rate
−0.5
−0.4
−0.3
−0.2
−0.1
0
0.1
0.2
0.3
0.4
0.5

Most important parameters

- The three parameters with the most impact on R_0 are
  - the parasite death rate
  - transmissability
  - the parasite birth rate
- These are also the three that we have the most control over, via
  - chlorination
  - filtration
  - education.

R_0=basic reproductive ratio

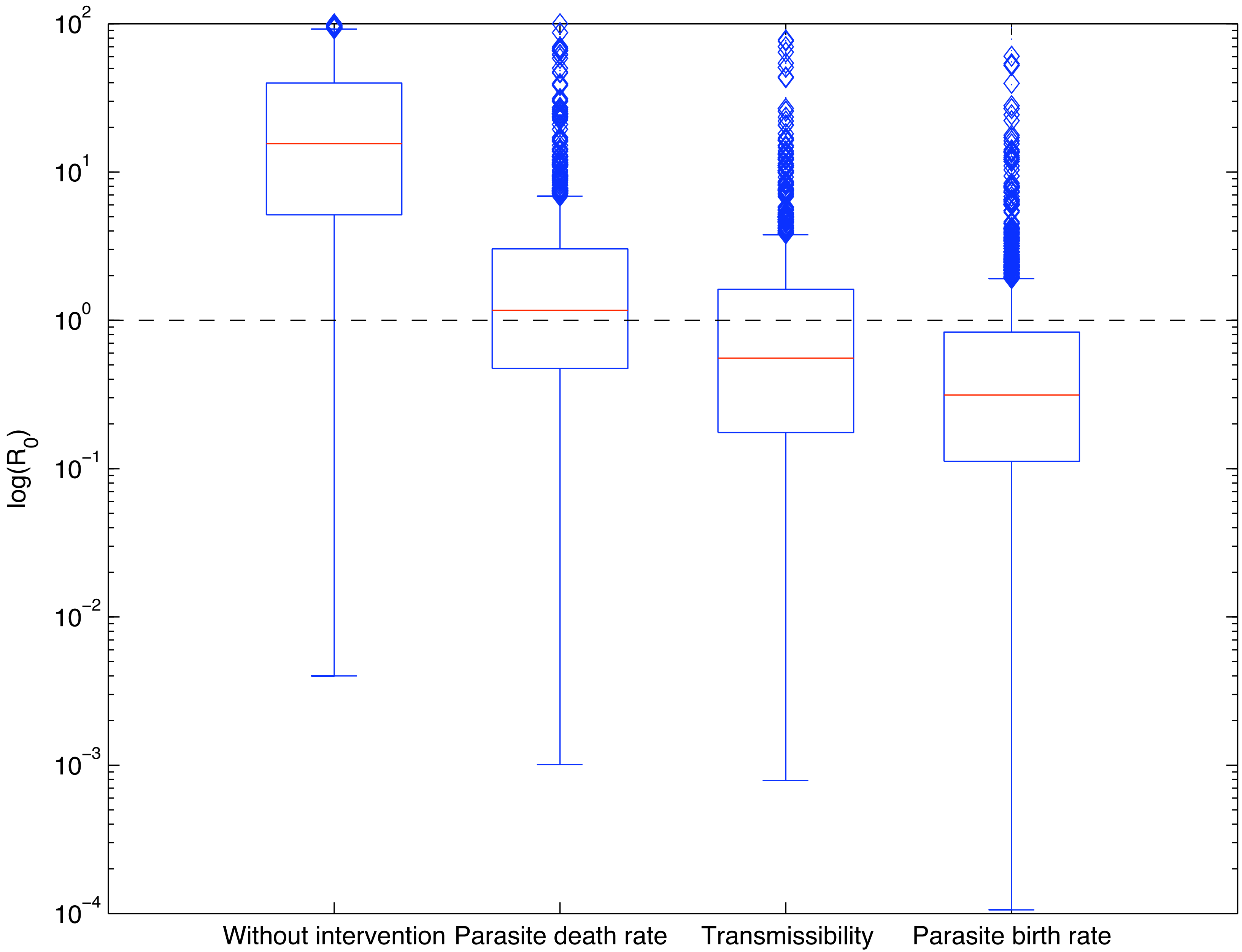

log(R0)
Human birth rate
Incubation period
Parasite death rate
Parasite birth rate
x 10^4
Transmissability
Human death rate
Infectious period
x 10^4

Variation of control parameters

- The same three parameters have the greatest impact
  (as expected)
- However, increasing μ_W (eg via continuous chlorination) is unlikely to lead to eradication
- Conversely, sufficiently decreasing γ (via education) is likely to bring R_0 below 1.

γ=parasite birth rate μ_W=parasite death rate R_0=basic reproductive ratio

Altering parameters by a factor of 100

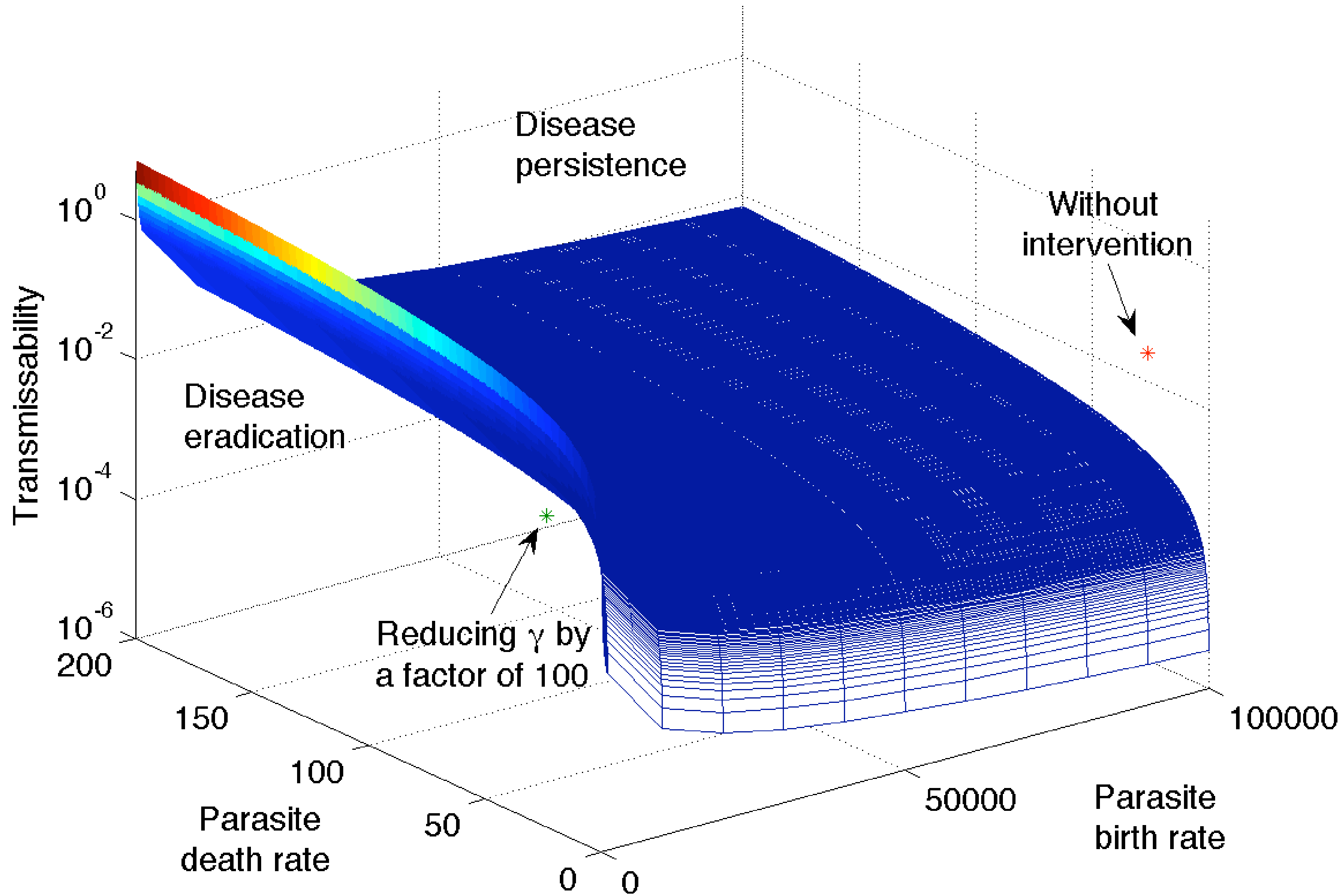


Eradication threshold

- For R_0=1, we can plot the threshold surface for our three control parameters (representing education, filtration and chlorination)
- We fixed all other parameters at median values.

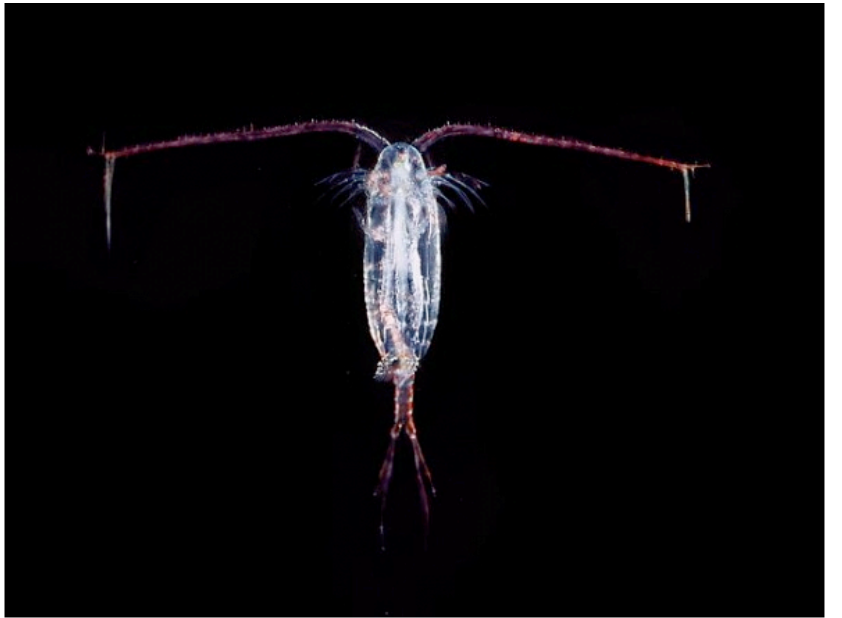
R_0=basic reproductive ratio

Eradication surface



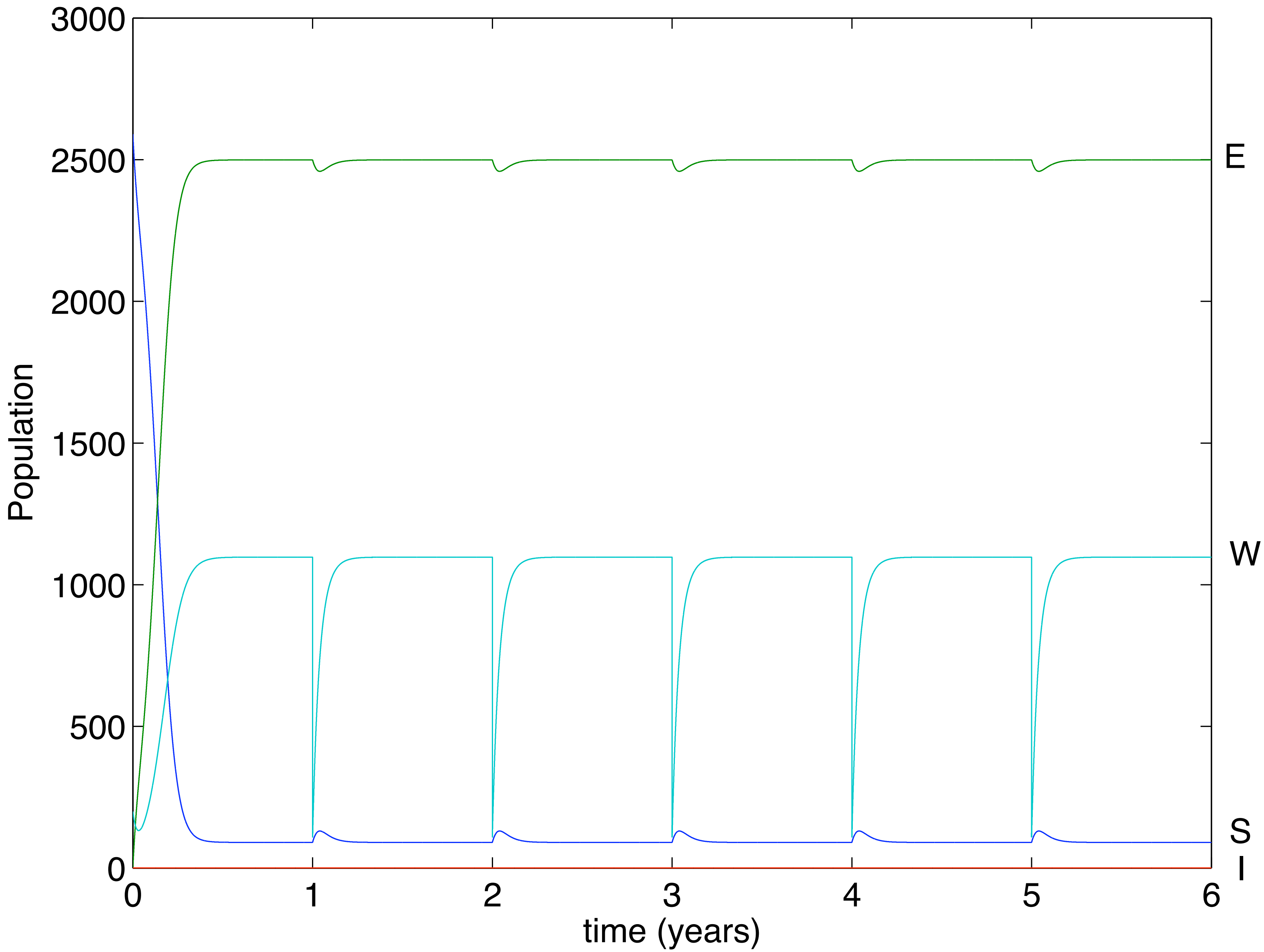
Effect of control parameters

- The outcome is significantly dependent on changes in γ
- Even if μ_W were increased tenfold, it is still unlikely to lead to eradication
- β would have to be reduced to extremely low levels.

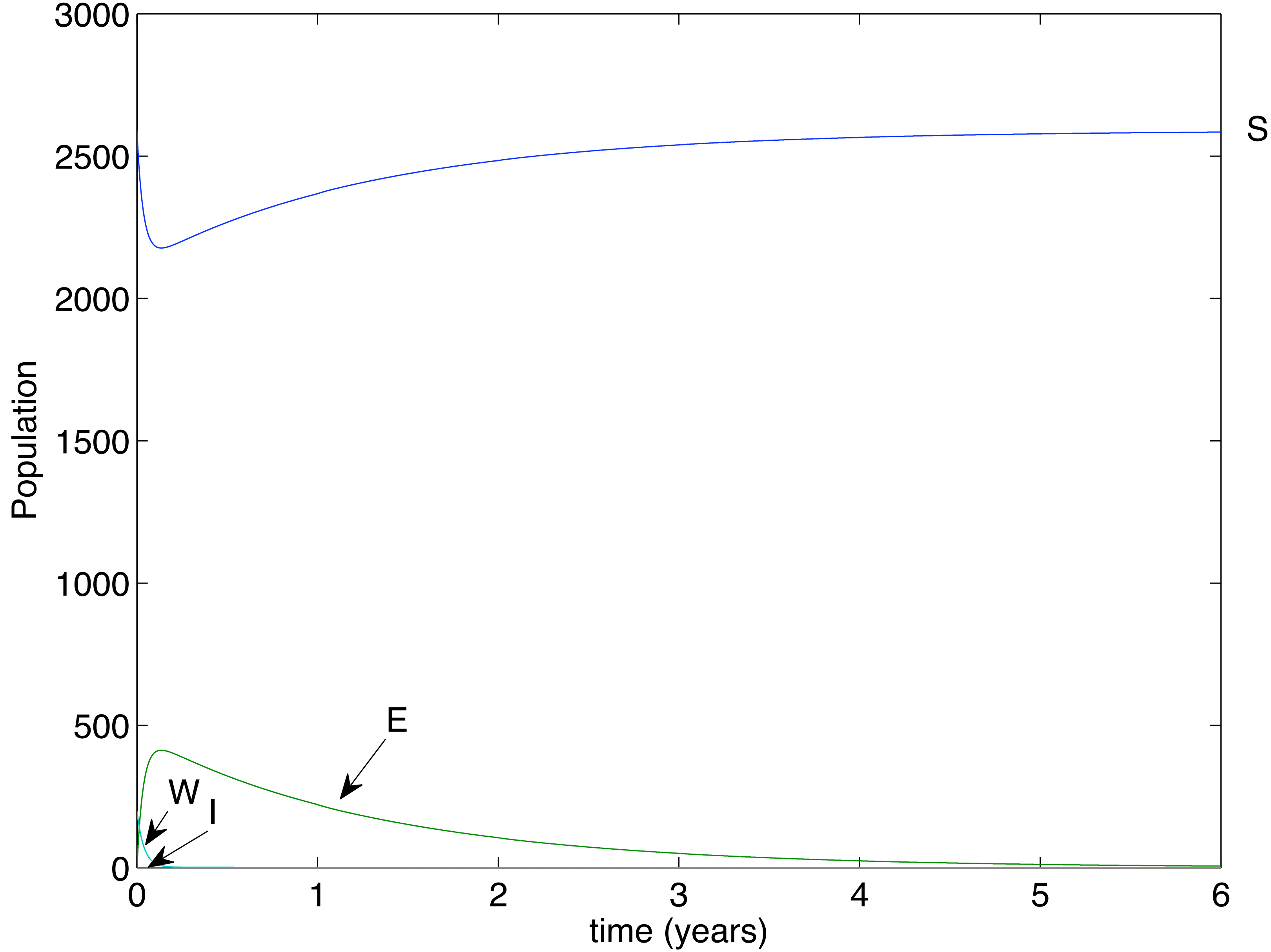


β=transmissability
γ=parasite birth rate
μ_W=parasite death rate

Annual chlorination



Reducing the parasite birthrate by 99%



Long-term dynamics

- Annual chlorination alone has little effect on the disease
- The population quickly returns to high levels following chlorination
- Reducing the parasite birth rate by 99% (eg via education) can lead to eradication
- The entire population becomes uninfected.

Eradication criteria

- There are three criteria for eradication:
  - biological and technical feasibility
  - costs and benefits
  - societal and political considerations
- Guinea worm disease satisfies all three.

Comparison with smallpox

- The only human disease to be eradicated (thanks to a successful vaccine)
- A critical control tool was photographic recognition cards
- Non-biomedical interventions were as important as biomedical ones
- Barriers included
  - cultural traditions
  - religious beliefs
  - lack of societal support.

Other attempts at eradication

- In the 20th century, four diseases were targeted:
  - malaria
  - yellow fever
  - yaws (a tropical infection of the skin, bones and joints)
  - smallpox
- Only one of these was successful
- In 2011, we eradicated rinderpest (a cow disease, from which quarantine was invented)
- This brought our total up to two.

Why they failed

- Malaria failed due to lack of follow-through
  - especially due to "Silent Spring"
- Yellow fever failed when animal reservoirs were discovered
- Yaws was reduced by 95%, but in the 1960s, the campaign shifted from targeted eradication to surveillance and control
- The strategy failed
- However, ongoing efforts mean India was recently declared yaws-free.

Summary

- We can derive optimal times for chlorination, whether fixed or non-fixed, to keep the parasite at low levels...

  ...but chlorination is unlikely to lead to eradication
- Education — persuading people not to put infected limbs in the drinking water — is the best way to eradicate Guinea worm disease
- Of course, a combination of education, chlorination and filtration is most desirable
- Efforts should be focussed on reaching remote communities.

Conclusion

- We stand at the brink of eradicating one of humanity's ancient scourges
- Without a vaccine or drugs, behaviour changes alone will likely lead to eradication of the first parasitic disease
- This may reshape our understanding of what it takes to eradicate a disease
- By mustering both scientific and cultural resources, we can successfully defeat one of the oldest diseases in human history.