Critical Transitions and Schistosomiasis control

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Critical transitions general theory

Critical transitions thought of in terms of a general process describing a state variable, x:

$$X(t+1) = f(X(t), \theta)Z(t)C(t)$$

where X is the state of the system, $f(X(t), \theta))$ describes the deterministic part of the system, $Z(t)$ describes stoachstic variability in the system, and C(t) describes system controls. Changes in θ can move the system closer to a threshold where a transition is likely to occur. In a disease setting, particularly for parasitic diseases where transmission is a function of infection intensity, $f(X(t), \theta) \approx R_{eff}$, $\theta \approx R_0$, $X(t) \approx W$ (system state = infection intensity), and $Z(t)$ is related to stochastic components and sources of uncertainty in the system including random egg shedding, susceptibility, unkown inputs from external sources, and diagnostic uncertainties.

Relevance and application to NTD control and elimination

Methods for detecting "early warning signals" of critical transitions abound and typically draw from the theory that the rate of return to an equilibirum is decreased as the system approaches a transition (i.e. perturb an unstable system far from the equilibrium and it takes a long time to return). This can be measured e.g. via increased autocorrelation in dense time series.

This also implies that systems that return rapidly to the pre-purturbation equilibrium are very stable and are far from a critical transition. Persistent hotspot phenomena in which community infection intensities return to pre-treatment levels even before the next treatment can be thought of as a highly stable system, far from a critical transition. This is why perturbations to the system (MDA) have little long term impact. Communities with lower bounce back rates are less stable and therefore take longer to return to their endemic (pre-treatment) equilibirum. This implies lower transmission potential, here embodied by R_0.

Rebound can be measured by the bounce back rate, BBR, an empirical estimator of R_{eff}. It is expected to be high in areas with conditions suggestive of a high R_0, indicative of a stable system far from a tipping point. This could be tested in an empirical statistical model with sufficient data pertaining to the determinants of R_0 through time and longitudinal measurement of BBR. For instance, Spear et al [1] express R_0 in terms of invariant biological components of schistosomiasis transmission, P_b, and site-specific parameters related to the behavioral and environmental determinants of transmission, P_s. Parameters included in P_s relate to human water contact, uninfected snail density, contamination behaviors related to sanitation, the amount of snail habitat, the amount of surface water, and seasonally varying factors such as temperature, rainfall, vegetation indices, and seasonal water contact patterns.

General model of helminth parasite transmission

We can connect this to a simplified helminth model similar to those presented previously with two state variables: infection in the environmental reservoir, y, (e.g. snail infection for schistosomiasis) and the mean parasite burden in the definitive human host population, W, assumed to be negative binomially distributed with dispersion parameter, κ:

$$\frac{dW}{dt} = \alpha y - \mu_W W \tag{1}$$

$$\frac{dy}{dt} = \beta 0.5 W \Phi(W, \kappa) \rho(W, \kappa, \gamma) - \mu_y y \tag{2}$$

Where $\Phi(W, \kappa)$ and $\rho(W, \kappa, \gamma)$ represent density dependent mating probability and reductions in fecundity, respectively, and $0.5W$ accounts for the assumed 1:1 sex ratio of male to female worms. We can use equilibrated reservoir infection, $y^* = \frac{\beta W \Phi(W, \kappa) \rho(W, \kappa, \gamma)}{2\mu_y}$ to reduce the worm burden equation to:

$$\frac{dW}{dt} = \frac{\alpha \beta W \Phi(W, \kappa) \rho(W, \kappa, \gamma)}{2\mu_y} - \mu_W W \tag{3}$$

which can be expressed in terms of the basic reproduction number, $R_0 = \frac{\alpha\beta}{2\mu_y\mu_W}$, as:

$$\frac{dW}{dt} = \mu_W W \big(R_0 \Phi(W, \kappa) \rho(W, \kappa, \gamma) - 1 \big) \tag{4}$$

Or in terms of the effective reproduction number, $R_{eff} = R_0 \Phi(W, \kappa) \rho(W, \kappa, \gamma)$, as:

$$\frac{dW}{dt} = \mu_W W \big(R_{eff}(W) - 1 \big) \tag{5}$$

Initial simulations

We can frame this simple model as a discrete process with stochasticity, $Z(t)$, related to measurement error of $W(t)$ since we only observe its proxy, $\mathcal{E}(t)$, and control variable $C(t)$ which simulates MDA interventions

$$W(t+1) = R_{eff}(W(t)) Z(t) C(t) \tag{6}$$

We don't know what the function $R_{eff}(W(t))$ is, though theory tells us that it is unimodal, which produces two stable equilibria ($R_{eff} = 1$), one at endemic equilibrium, W^*, one at elimination and an unstable equilibria referred to as the breakpoint, W_{bp}.
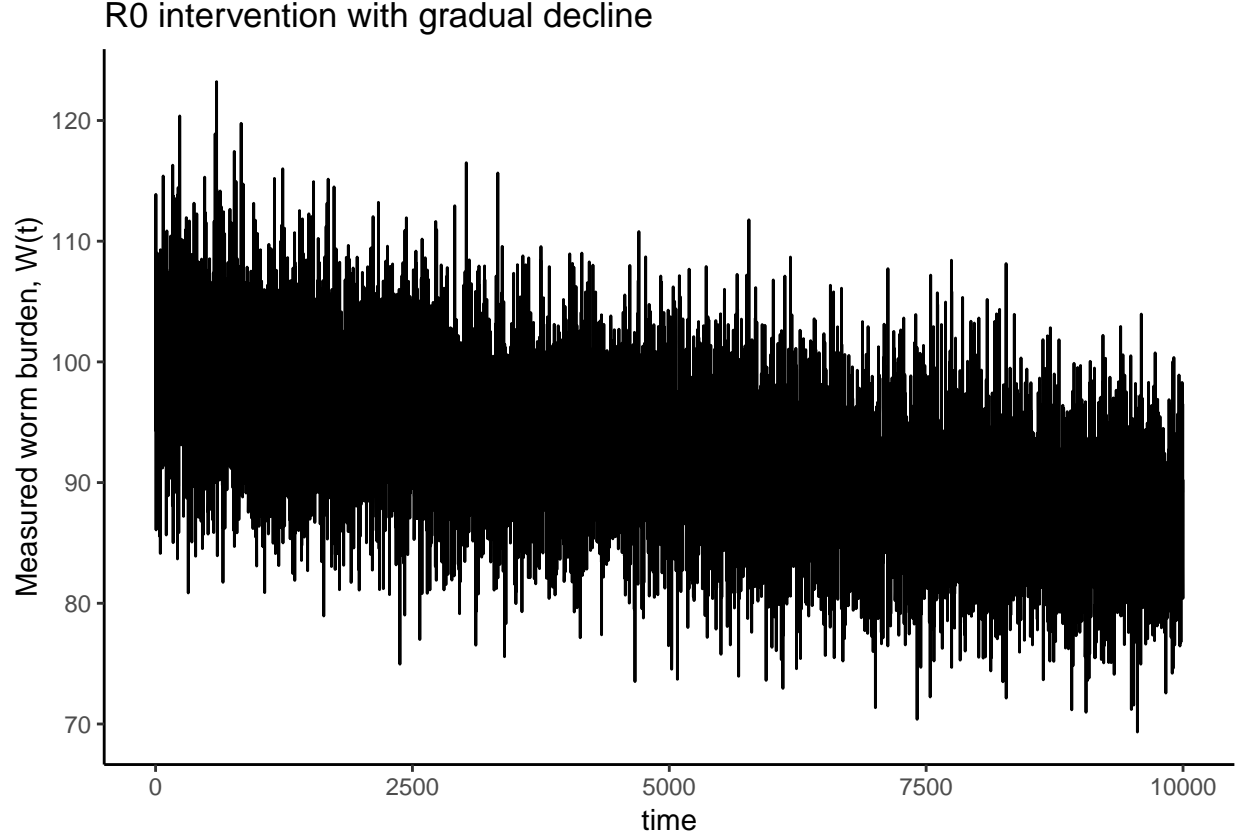
Simulate with no intervention

Base simulation, no intervention
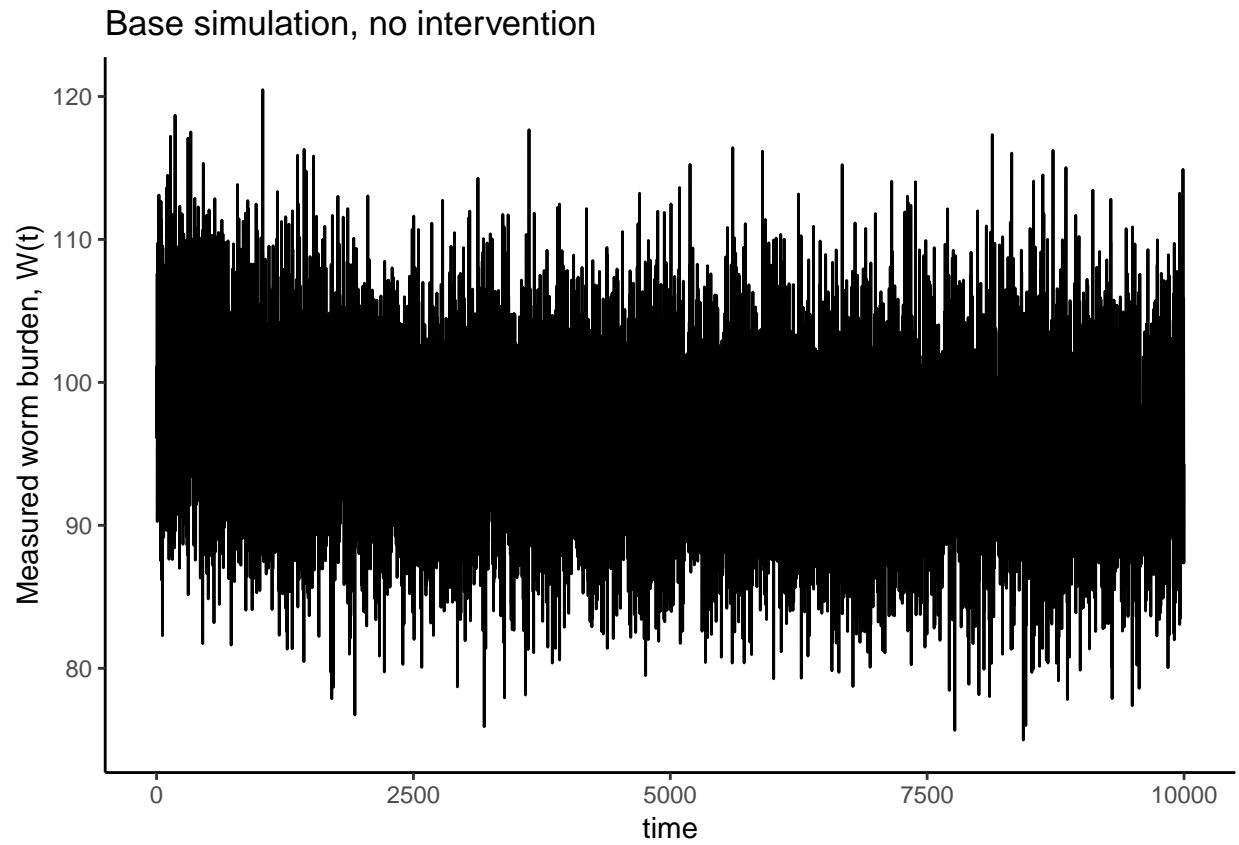
Simulate with control events targeting state variable

State variable intervention with 50% efficacy every 300 days
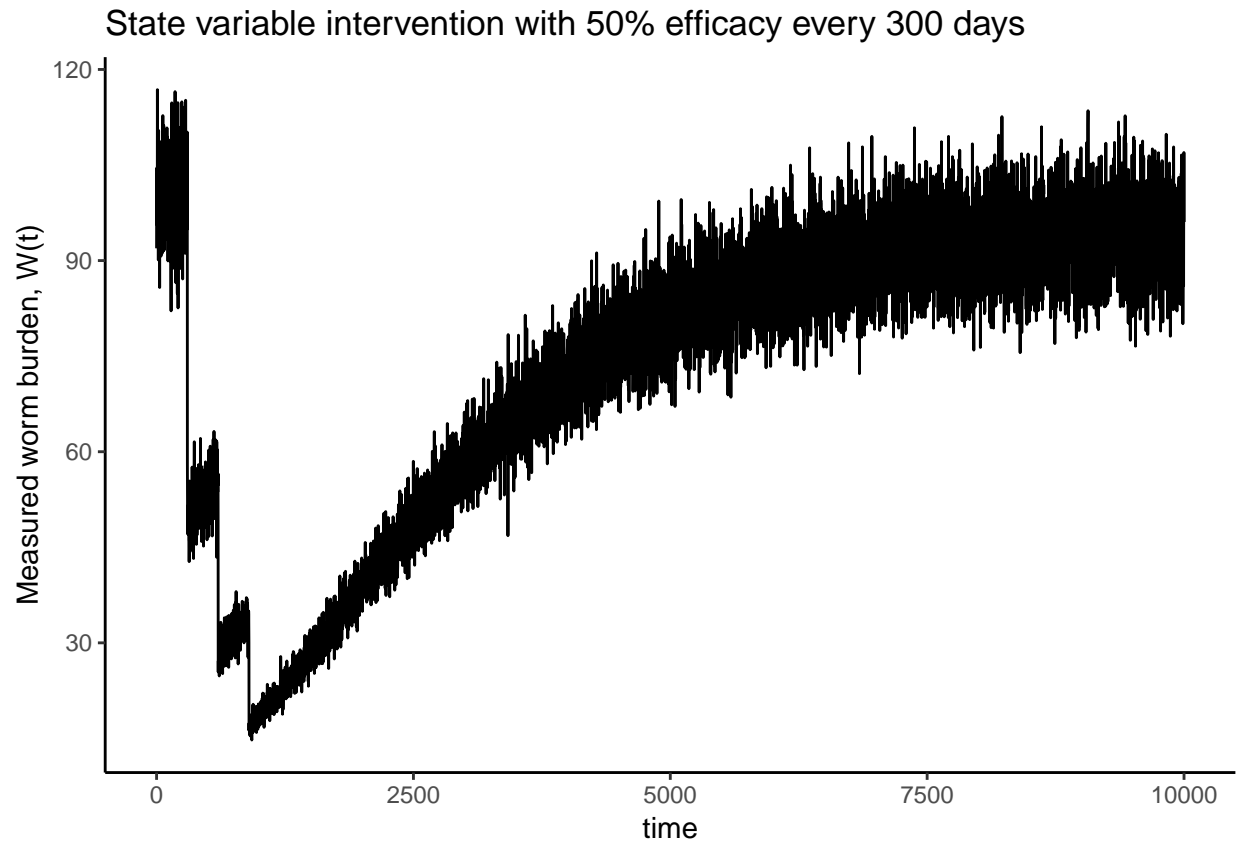
Simulate with control events steadily reducing R0

## R0 intervention with gradual decline

So these results are not showing what we want them to, but they're also not capturing underlying dynamics well, particularly really rapid rebound to pre-infection levels like we see in lots of annual schisto datasets. This just represents a shortcoming of this simplified model where an R_0 high enough to capture rapid reinfection dynamics also implies an unrealistic baseline level of infection. I'm dealing with this via an individual based model that captures individual variability in susceptibility to infection and to exposure. My intuition is that accounting for these heterogeneities will allow for much higher transmission rates, but much lower endemic levels of infection, closer to what we see in the data.
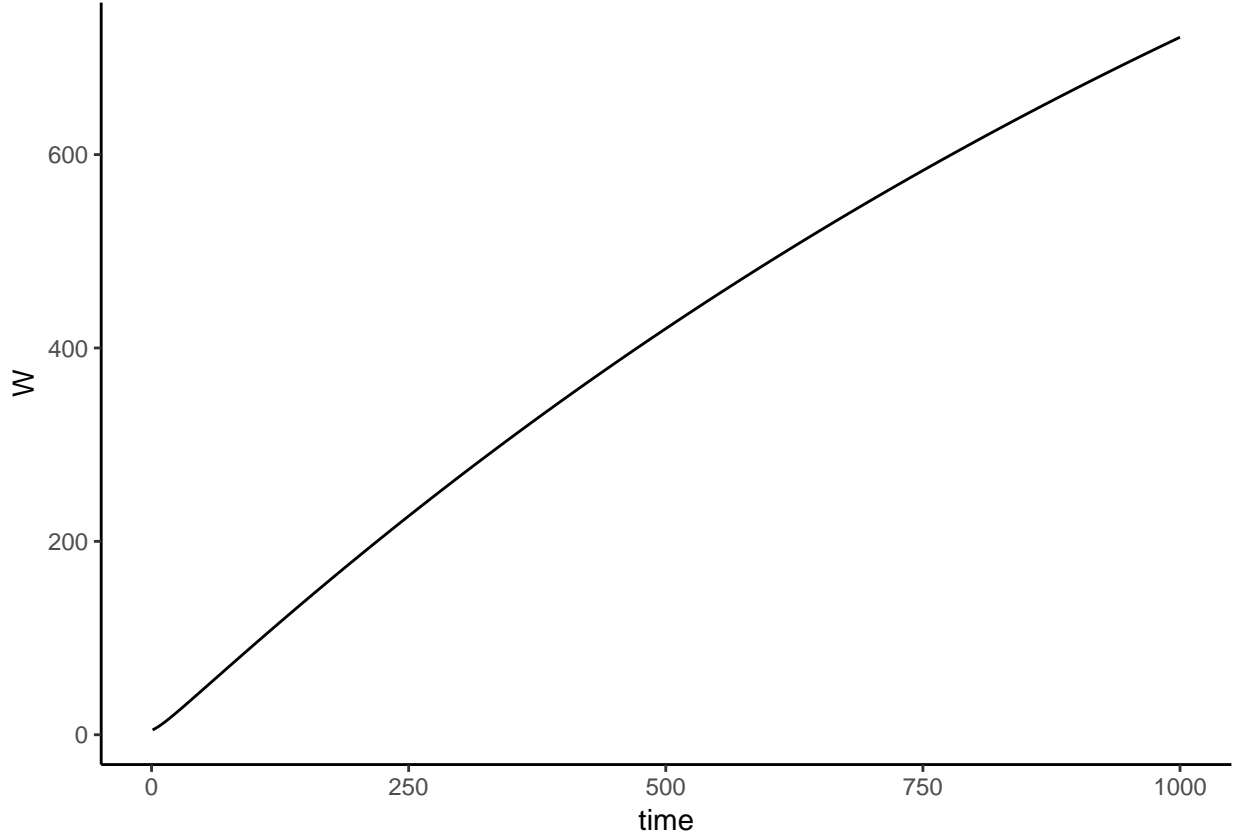
Another option is to turn to simpler generic ecologic models. One suitable model is the Myers model [2], [3] commonly used in fisheries science:

$$dW = \frac{rW^\theta}{1 + W^\theta/K} \tag{7}$$

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Myers model

r = 0.1, K = 10, θ = 1.5 μ = 4 years
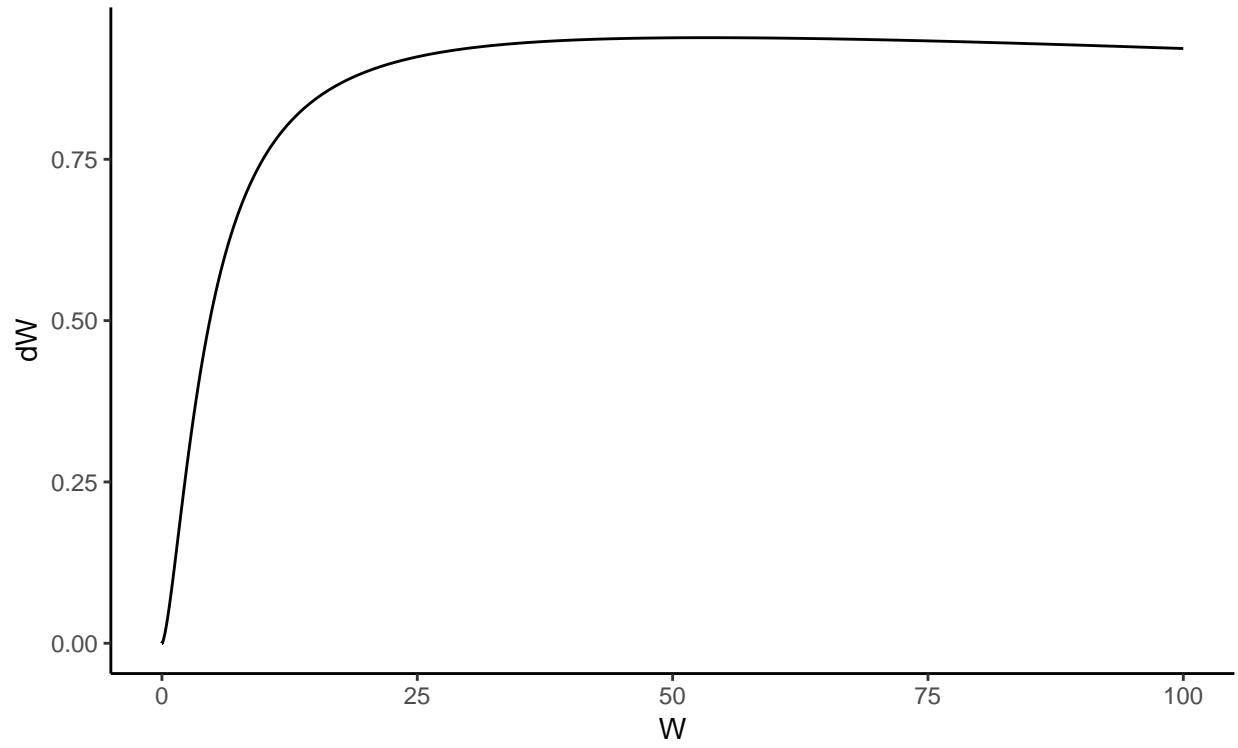
Connection to epidemiological data

Because adult parasites are harbored in human hosts, their direct measurement is not possible. Measurement of infection intensity therefore relies on detecting viable eggs produced by mated adult female worms and shed in the urine or feces of human hosts. We are therefore only able to observe a proxy of the system state, the mean egg intensity, $\mathcal{E}$, estimated from the model as $\mathcal{E} = 0.5 W \Phi(W, \kappa) \rho(W, \kappa, \gamma) m$ and from real world data as the empirical mean of individual egg burdens $\frac{1}{n} \sum_{i=1}^{n} \mathcal{E}_i$. This value is typically assumed to follow a negative binomial distribution with dispersion parameter, $\kappa = \frac{\mathcal{E} + \mathcal{E}^2}{var(\mathcal{E})}$, and observed egg burdens are assumed to be a realization of the data generating process $NB(0.5 W \Phi(W, \kappa) \rho(W, \kappa, \gamma) m, \kappa)$. The figures below shows sampled mean egg burdens from school-aged children in Senegal over the course of an intervention campaign testing the efficacy of two novel intervention strategies: prawn introductions and vegetation removal. All children receieve two doses of Praziquantel 3 weeks apart following parasitological surveys in 2016, 2017 and 2018.
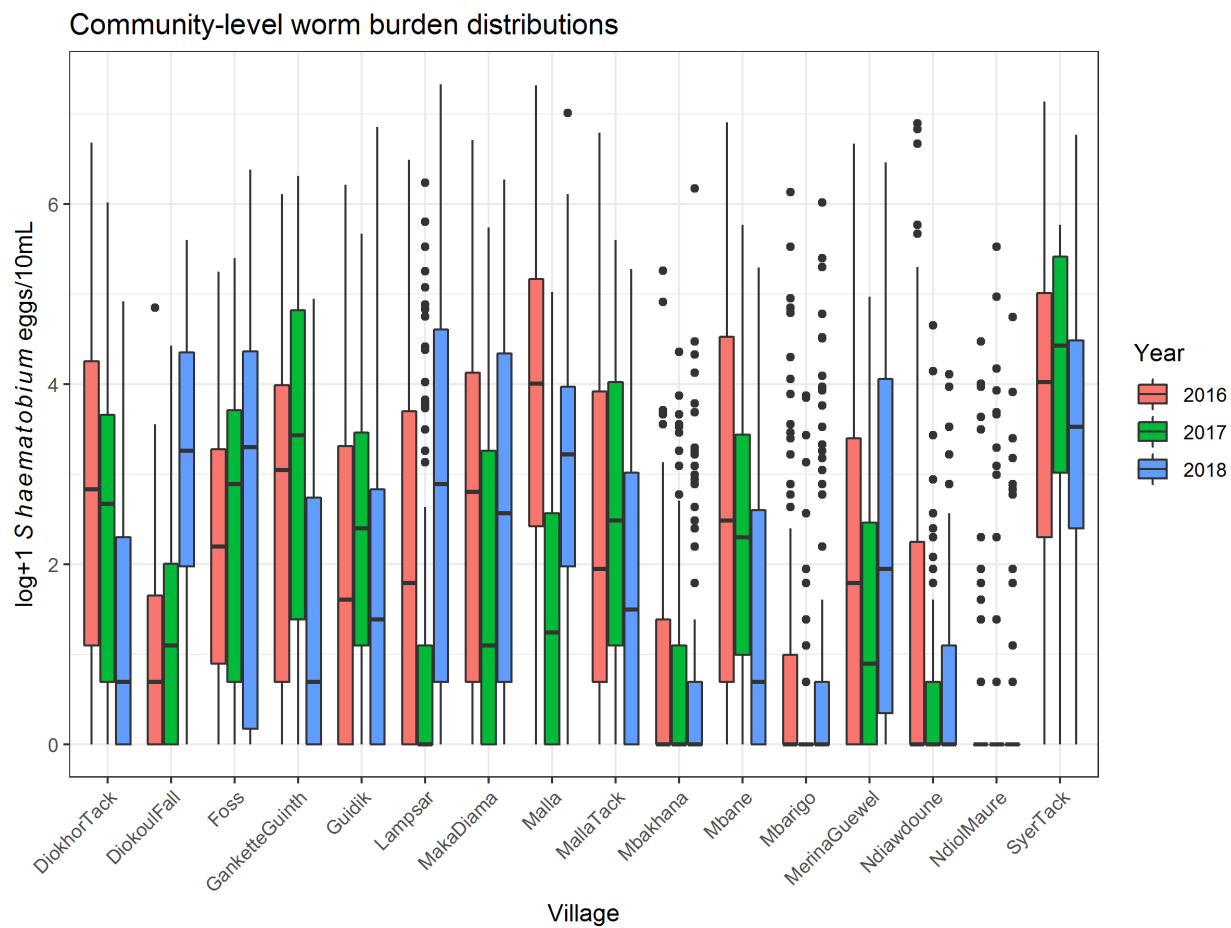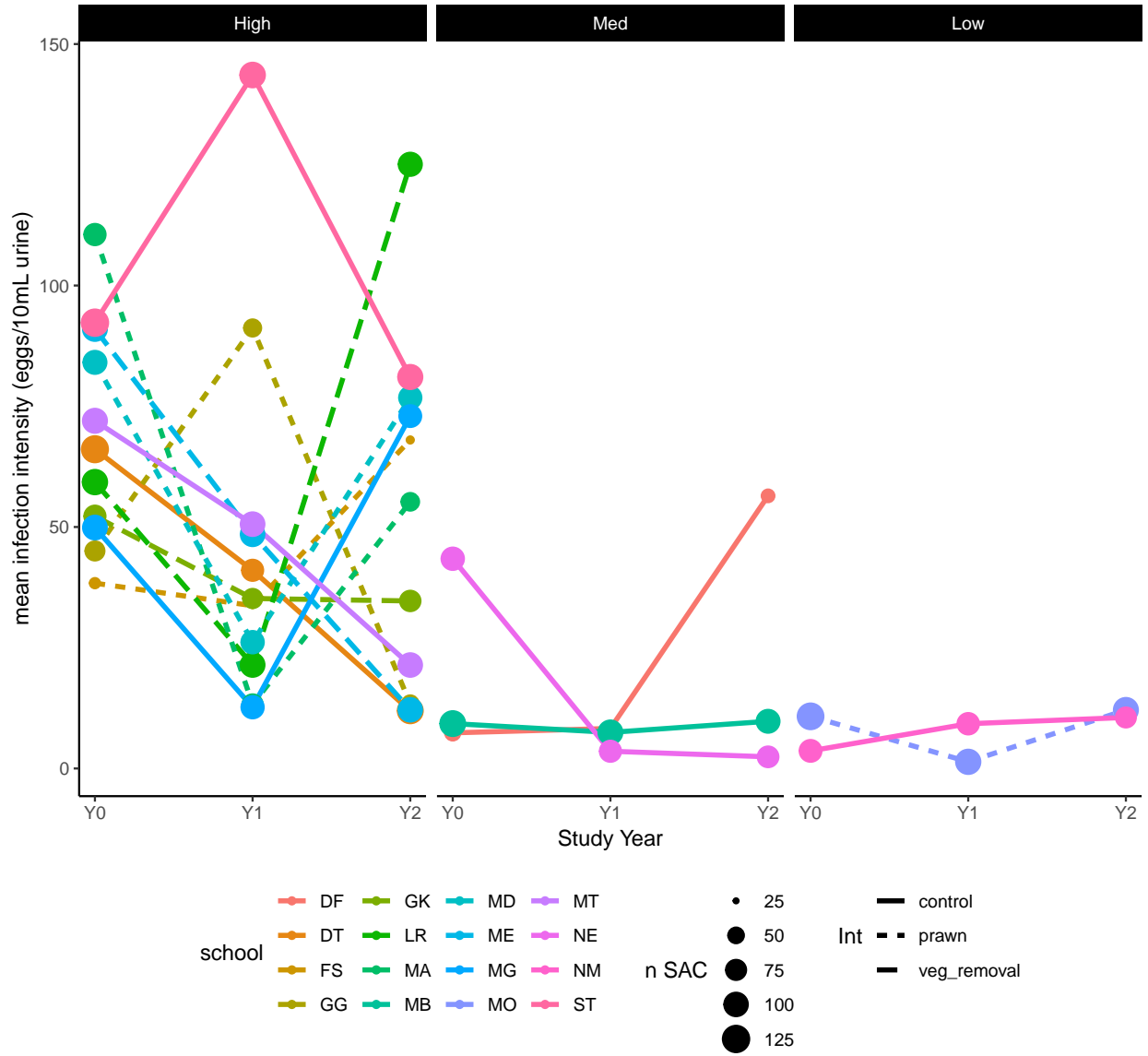
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Figure 1: Individual egg burden distributions by community and year

S. haematobium infection intensity among SAC over time
Stratified by high, medium, and low starting prevalence

Because $\mathcal{E}$ is a proxy for the system state, W, the unmeasured variables γ and m, the dimensionless negative density dependence parameter and the mean number of eggs per female worm per 10mL urine, respectively, are of paramount importance to the estimation of W and therefore R_0. Values of γ used in the past range from 0.005 to 0.08 [4], [5] and values of m range from 3 to 30 [4], [6]. Little observational data on either parameter exists, but autopsy data from Cheever et al [7] suggests the relationsip $\log(1+\mathcal{E}_i) = 0.748+1.467\log(1+W_{f_i})$, shown in the plot below. Though this relationship implies more eggs produced per female worm with increasing worm burdens, evidence of positive density dependence, the relationship implies $m \approx 10$, as indicated by the red dashed line in the plot.

Relationship between adult female worms and egg burden (eggs/10mL uri

From Cheever 1977 autopsy studies of infected individuals
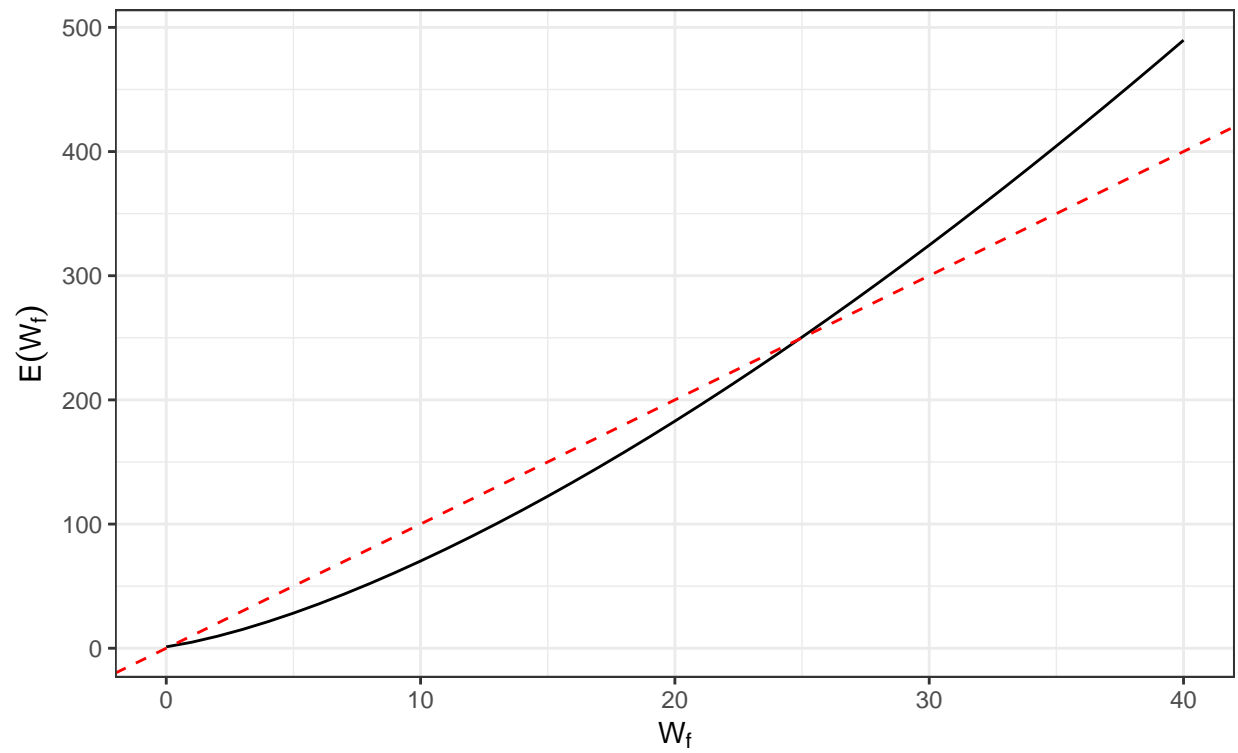
With $m = 10$, we can next observe the relationship between $\mathcal{E}$ and W across values of the dispersion parameter κ and the negative density dependence parameter, γ.

Factors affecting mean egg output given mean worm burden
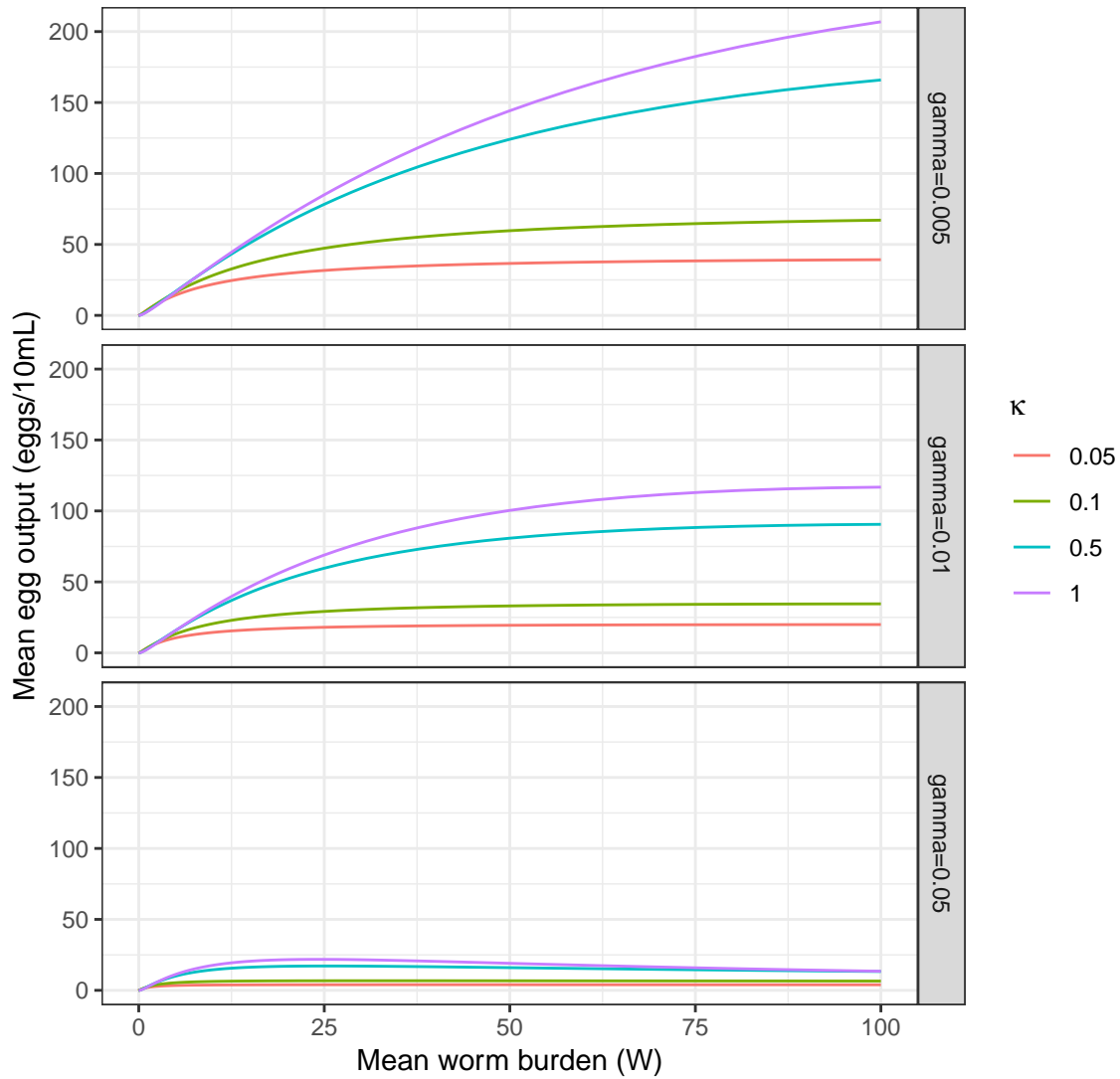
We can also look at the product of the two density dependence functions, a key determinant of R_{eff} across values of κ and W for $\gamma = 0.005$

```r
dd_prod_df <- expand.grid(W = exp_seq(1e-4, 100, 200),
                          kap = seq(0.01, 1, 0.01),
                          gam = 0.005) %>%
  mutate(dd_prod = mapply(function(W, kap, gam){
    phi_Wk(W, kap)*rho_Wk(W, gam, kap)
  }, W, kap, gam))

dd_prod_df %>%
  ggplot(aes(x = W, y = kap, fill = dd_prod, z = dd_prod)) +
    geom_tile() +
    theme_classic() +
    scale_x_continuous(trans = "log",
                       breaks = c(1e-3, 0.01,0.1,1,10,100)) +
    scale_fill_viridis(option = "magma") +
```

```
labs(x = "Mean worm burden (W)",
     y = expression(paste("Dispersion parameter (", kappa, ")")),
     title = "Product of density dependence functions over values of kappa and W")
```

Product of density dependence functions over values of kappa and W
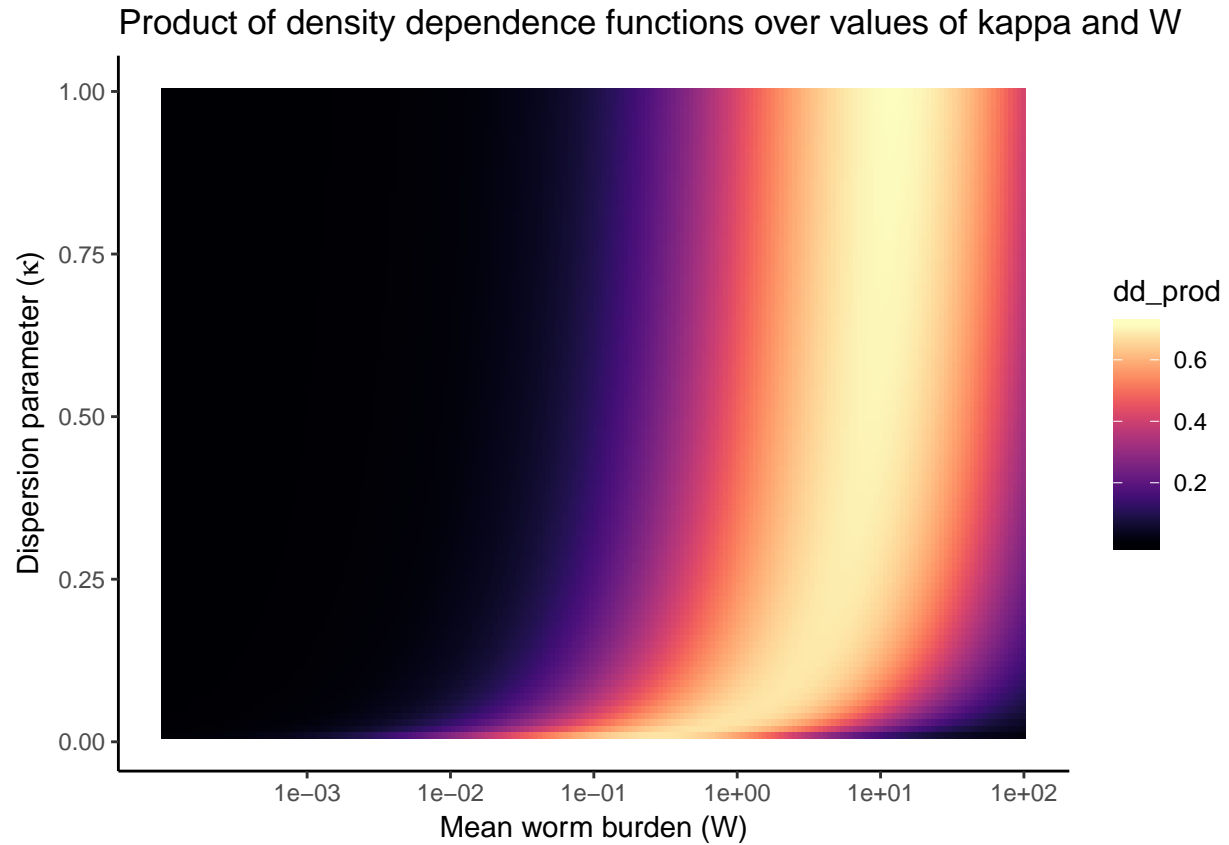
Given the range in egg intensities from Senegal of up to $\mathcal{E} \approx 150$, $\gamma = 0.005$ appears to be the best choice. Now estimate worm burdens from the Senegal egg burdens and then use them to estimate baseline R_0.

S. haematobium R0 estimates across baseline infection intensity
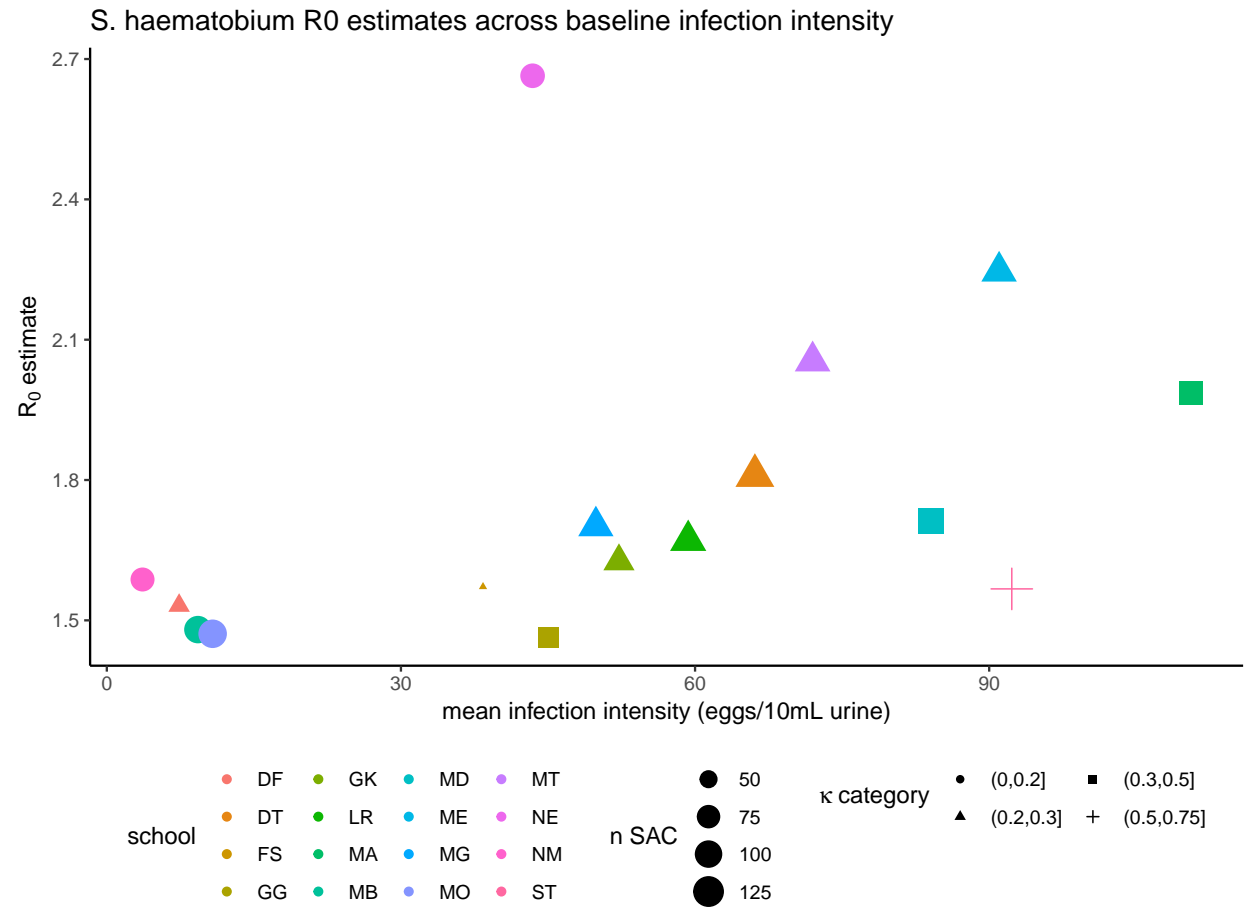
From these equilibria estimates, can now generate phase planes for this system across different values of κ.

Phase planes of W/R0 relationships across values of dispersion parameter
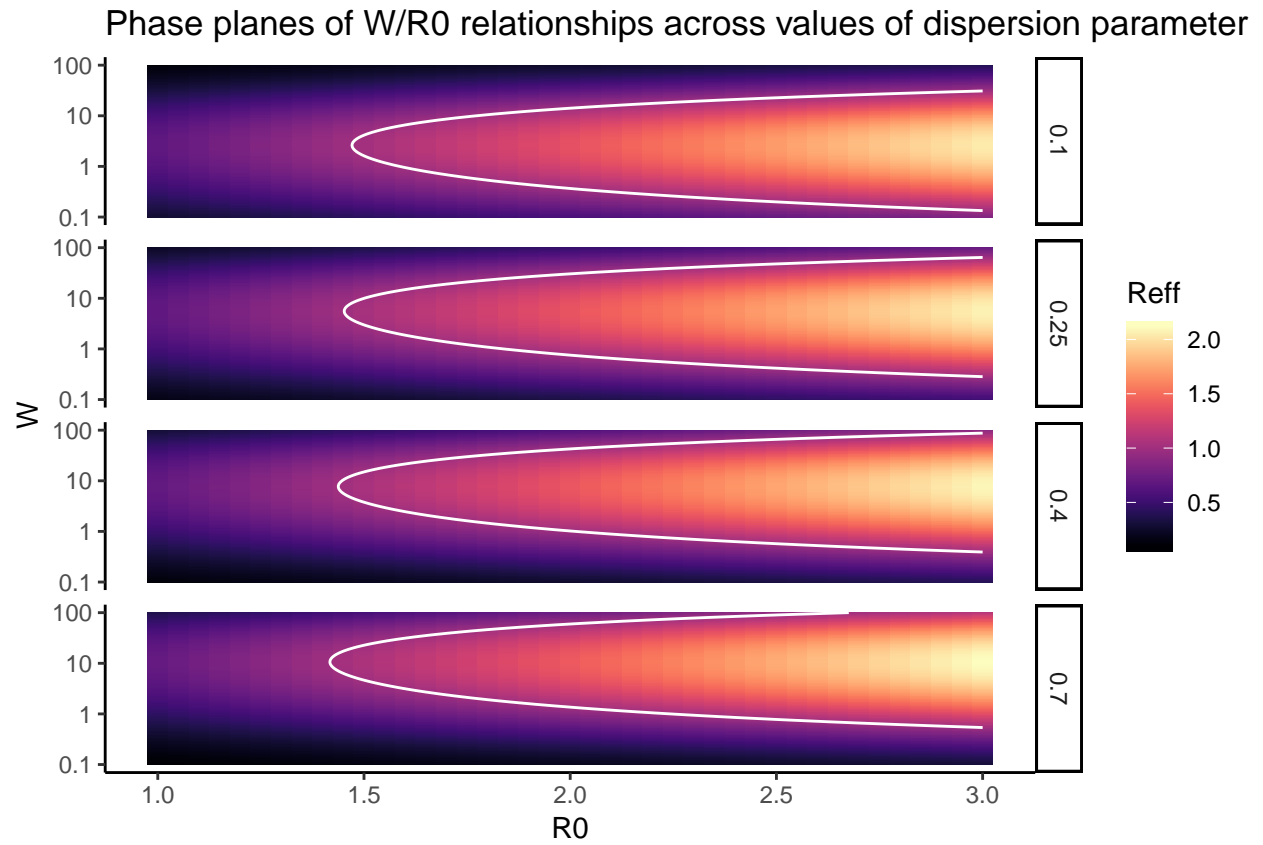
Can also show how equilibrium estimates for communities with $0.2 < \kappa < 0.3$ map onto this phase plane

Phase plane for k~0.25

Points indicate estimated endemic equlibrium values for communities
with observed k between 0.2 and 0.3
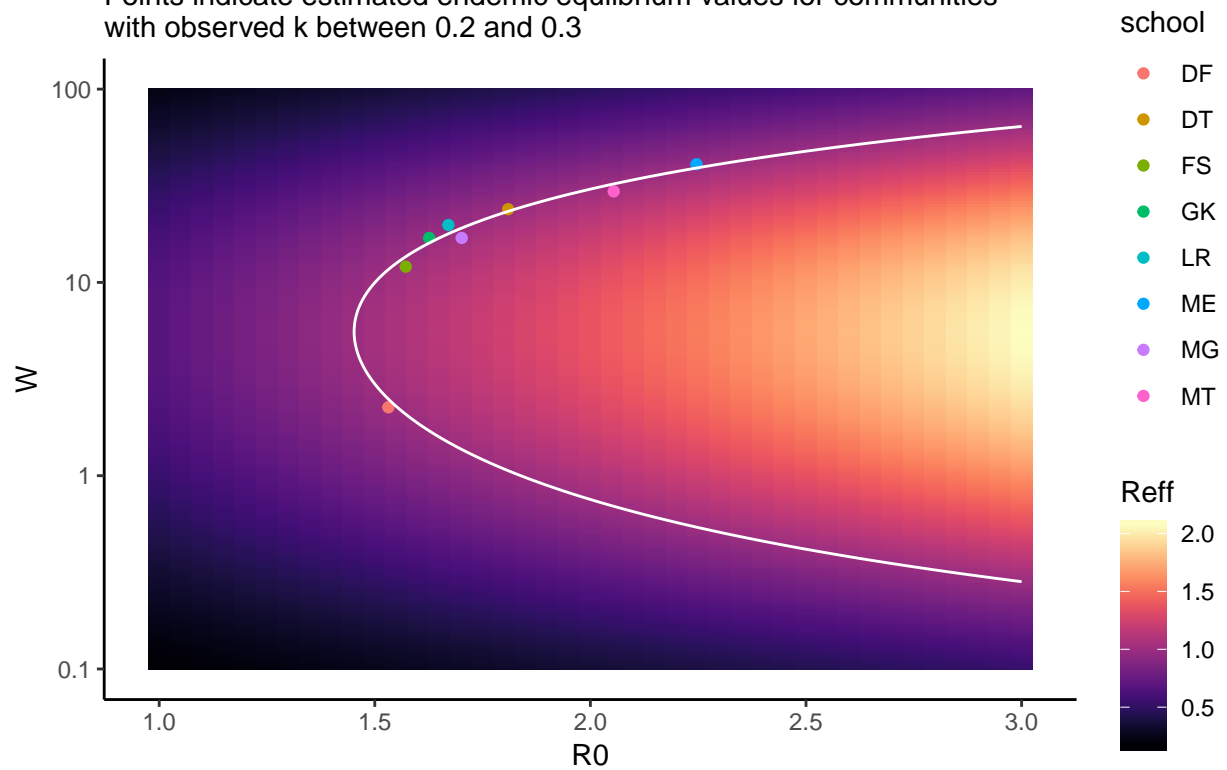
Looks like the root finding estimation for at least one community's endemic equilibrium actually picked up the breakpoint value of W instead, which is problematic... For the sake of progress, going to gloss over this for now

Initial simulation

Simulate egg burden time series for Diokhor Tack (DT), a community with a relatively predictable response to drug treatment (sustained reductions in egg burden following MDA in both 2016 and 2017)

Key infection variables through time
Assuming MDA removes 50% of worm population in treated SAC
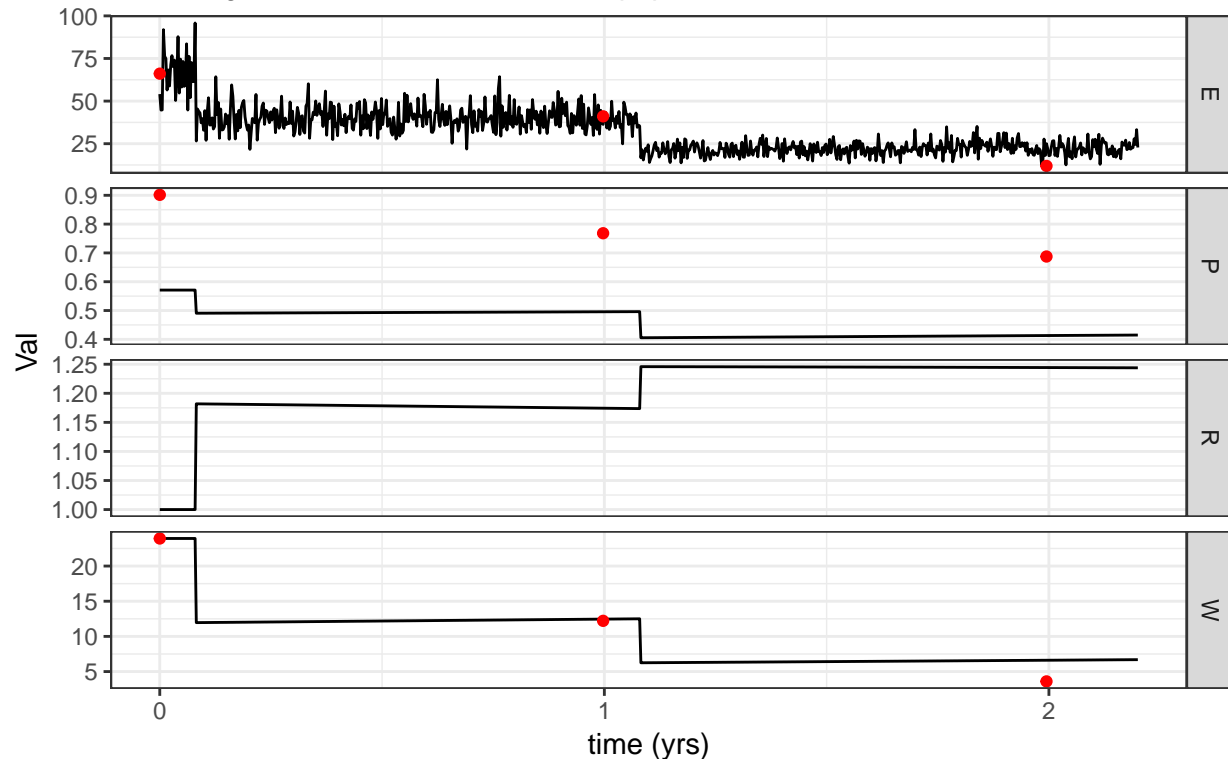
This looks like a pretty good fit, but everyone in this dataset was treated, so an assumption of 50% worm death is probably pretty far off. The prevalence estimates are also way off, with systematic underestimation of prevalence. I don't think this simple model is capable of capturing the transmission dynamics we want

References

1. Spear R, Zhong B, Liang S. Low transmission to elimination: Rural development as a key determinant of the end-game dynamics of schistosoma japonicum in china. Tropical Medicine and Infectious Disease. 2017;2: 35. doi:10.3390/tropicalmed2030035

2. Myers RA, Barrowman NJ, Hutchings JA, Rosenberg AA. Population dynamics of exploited fish stocks at low population levels. Science. 1995;269: 1106–1108. doi:10.1126/science.269.5227.1106

3. Boettiger C, Mangel M, Munch S. Avoiding tipping points in fisheries management through gaussian process dynamic programming. Proceedings of the Royal Society B: Biological Sciences. 2015;282: 20141631. doi:10.1098/rspb.2014.1631

4. Truscott J, Gurarie D, Alsallaq R, Toor J, Yoon N, Farrell S, et al. A comparison of two mathematical models of the impact of mass drug administration on the transmission and control of schistosomiasis. Epidemics. 2017;18: 29–37. doi:10.1016/j.epidem.2017.02.003

5. Hardwick RJ, Vegvari C, Truscott JE, Anderson RM. The "breakpoint" in transmission for soil-transmitted helminths: Dynamical behaviour near the equilibria and the impact of infected human migration. 2019; doi:10.1101/619908

6. Arakala A, Hoover CM, Marshall JM, Sokolow SH, Leo GAD, Rohr JR, et al. Estimating the elimination feasibility in the end game of control efforts for parasites subjected to regular mass drug administration:

Methods and their application to schistosomiasis. Dobson AP, editor. PLOS Neglected Tropical Diseases. 2018;12: e0006794. doi:10.1371/journal.pntd.0006794

7. Cheever AW, Elwi AM, Mosimann JE, Kamel IA, Danner R. Schistosoma mansoni and s. haematobium infections in egypt. The American Journal of Tropical Medicine and Hygiene. 1977;26: 702–716. doi:10.4269/ajtmh.1977.26.702