Bridging the gap between theory and data: the Red Queen hypothesis for sex

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Abstract

1 Introduction

The evolution of sexual reproduction poses a continuing question (Otto, 2009). Despite being the dominant mode of reproduction (Vrijenhoek, 1998), sexual reproduction entails numerous costs (Lehtonen et al., 2012). The most commonly mentioned is the cost of producing males (Smith, 1978). As males cannot produce offspring, sexual lineages are expected to be outgrown by their asexual counterpart that can grow as twice as fast (assuming that the sexual population produces 50% male and 50% female). This infamous *two-fold cost of sex* (Smith, 1978) relies on the assumption that everything else is equal. Then, what else is not equal and drives the sex to persist?

One explanation for the persistence of sexual reproduction is the Red Queen Hypothesis (Bell, 1982). The Red Queen Hypothesis for sex suggests that sexually reproducing hosts overcome the cost of sex under strong parasite selection by producing genetically diverse offspring that are resistant to infection (Haldane, 1949; Jaenike, 1978; Hamilton, 1980).

Much of the theoretical literature has focused on determining qualitative conditions under which parasite selection can maintain sexual reproduction in the host population. Here, we describe a few important qualitative requirements in order for parasites to promote sexual reproduction within host population. First, hosts and parasites must coevolve [CITE]. Host-parasite coevolution creates time-lagged selective advantage for rare host genotypes, creating oscillation in genotypic frequencies and allowing for sexual reproduction to persist in the host population (Clarke, 1976; Hamilton, 1980). Second, parasites must be highly virulent to maintain sexual reproduction (May and Anderson, 1983). Although sexual and asexual hosts can coexist at intermediate virulence (Howard et al., 1994), sexual reproduction will not provide enough advantage to overcome cost of sex against avirulent parasites [CITE?]. Finally, sexual hosts must be genetically more diverse than asexual hosts as high clonal diversity may mask the advantage of sexual reproduction (Lively, 2010c; Ashby and King, 2015).

[**BMB:** *More on qualitative requirement*] [**SWP:** *How is this? I might need more citations...*]

Some theoretical studies have departed from the classical population genetics framework to study effects of ecological and epidemiological structures on the Red Queen dynamics. Number of studies showed that incorporating ecological and epidemiological details can assist in supporting sexual reproduction in the host population (Galvani et al., 2001, 2003; Lively, 2009, 2010b). In contrary to these findings, MacPherson and Otto (2017) showed that Red Queen dynamics (i.e., cycles in allele frequencies) fail to persist when explicit epidemiological structure is taken into account with coevolutionary dynamics.

On the other hand, empirical studies have mostly focused on confirming predictions that stem from the Red Queen Hypothesis. Typical among them are local adaptation, time-lagged selection, and association between parasite prevalence and host reproductive mode (see Tobler and Schlupp (2008) and Vergara et al. (2014b) for reviews). A key example is the snail population in New Zealand that serve as an intermediate hosts for trematodes [CITE]. Through several decades of work, Lively *et al.* demonstrated that the population satisfies necessary conditions for the host-parasite coevolutionary dynamics and provide support for the hypothesis (e.g., Lively (1987, 1989); Dybdahl and Lively (1995, 1998); Jokela et al. (2009); Vergara et al. (2014b); Gibson et al. (2016)). While many studies provide only indirect evidence for the hypothesis, recent studies show that more direct evidence can be achieved using experimental systems (Auld et al., 2016; Slowinski et al., 2016).

Even though the Red Queen Hypothesis has gained some support both theoretically and empirically, there still remains a gap between theory and data. Many theoretical models rely on simplifying assumptions that are not applicable to natural populations and make indirect connections to empirical studies. For example, none of the Red Queen models reviewed by Ashby and King (2015) use statistical tools to relate model to data. It is unclear how well these models represent the observed prevalence of sexual reproduction.

However, simple models can still be used to make qualitatively useful predictions about the nature. Lively (1992) postulated that infection prevalence should be positively correlated with frequency of sexual hosts and later formalized the idea using a mathematical model (Lively, 2001). The prediction has since been confirmed by a number of empirical studies, most of which are based on the snail-trematode system (Lively and Jokela, 2002; Kumpulainen et al., 2004; Vergara et al., 2013; McKone et al., 2016; Gibson et al., 2016). Surprisingly, such correlation was not observed in a different snail-trematode system (Dagan et al., 2013a).

Here, we try to bridge the gap between theory and data further and make quantitative inference about the nature. We extend the model used by Lively (2010b) to account for demographic stochasticity and simple population structure. Then, we fit the model to observational data from three studies (Dagan et al., 2013a; McKone et al., 2016; Vergara et al., 2014b) using Approximate Bayesian Computation (ABC) to estimate biologically relevant parameters. We assess model fits and discuss discrepancies between a theoretical model and the

observed data. Using biologically realistic parameters, we test for power (probability of observing a significant effect) to detect a positive correlation bdetween frequency of sexual reproduction and prevalence of infection Lively (2001). By performing power analysis, we discuss underlying factors that drive the correlation and provide practical guidance for studying the Red Queen Hypothesis. [**BMB:** *More on power analysis*] [**SWP:** *Edited.*]

2 Methods

2.1 Data

We consider observational data from two snail-trematode populations in New Zealand (Vergara et al., 2014b; McKone et al., 2016) and a similar snail-trematode population in Israel (Dagan et al., 2013a). The snail-trematode system has been extensively studied under the context of the Red Queen Hypothesis so we expect a simple Red Queen model to fit reasonably well. Israel population is of particular interest as the expected correlation was not observed [CITE]. Data collected by Dagan et al. (2013a) and Vergara et al. (2014b) were obtained from their Dryad repositories (Dagan et al., 2013b; Vergara et al., 2014a) and data collected by McKone et al. (2016) was extracted from their figure.

2.2 Model

[**SWP:** *TODO: read Lively 2018*] We model obligately sexual hosts competing with obligately asexual hosts in a meta-population by extending the model introduced by Lively (2010b). The model is a discrete time susceptible-infected (SI) model with natural mortality and virulence (defined as reduction in offspring production among infected hosts). It is a suitable canditate model for this study as it captures essential structures that are present in basic epidemiological and population genetics models and is sufficiently general to be applied to broad range of natural systems.

For simplicity, We do not consider mechanistic details of the snail-trematode system such as life history of trematodes (Vergara et al., 2014b). We incorporate metapopulation structure and allow for mixing between populations. Each population can be equivalently considered as a sampling site in the observed populations. A similar metapopulation model was developed by Lively (2017) and was used to study local adaptaion of parasites.

All hosts are assumed to be diploids with two biallelic loci, and parasites are assumed to be haploids. Let $S_{ij}^k(t)$ and $A_{ij}^k(t)$ be the number of sexual and asexual hosts with genotype ij from population k at generation t. For simplicity, we drop the superscript representing population and write $S_{ij}(t)$ and $A_{ij}(t)$; every population is governed by the same set of equations unless noted otherwise (e.g., when we account for interaction between populations). Following Lively (2010b), the expected amount of genotypic contribution (before recombination

or outcrossing) by sexual hosts is given by

$$S'_{ij} = c_b(1-s)\left(W_U S_{ij,U}(t) + W_I S_{ij,I}(t)\right), \tag{1}$$

where s is the proportion of males produced by sexual hosts, and $S_{ij,U}$ and $S_{ij,I}$ are the number of uninfected and infected sexual hosts in a population. W_U and W_I represent their corresponding fitnesses where virulence is defined as $V = 1 - W_I/W_U$. We allow for cost of sex to vary by multiplying a scale parameter, c_b, to the growth term, where $2/c_b$ corresponds to a two fold cost of sex (Ashby and King, 2015). Recombination and outcrossing are modeled after incorporating genotypic contributions from other populations.

We define

$$W_U = \frac{b_U}{1 + a_U N(t)}, W_I = \frac{b_I}{1 + a_I N(t)}$$

where b_U and b_I are number of offspring produced by uninfected and infected hosts, respectively, and a_U and a_I determine their corresponding density dependent effects (Lively, 2010b; Smith and Slatkin, 1973). For simplicity, we assume that $a_U = a_I$ so that virulence can be defined strictly in terms of decrease in offspring production and is density independent: $V = 1 - b_I/b_U$. [**BMB:** *more specific*] [**SWP:** *Lively doesn't say much beyond this... I think it's OK?*]

Asexual hosts are assumed to be strictly clonal. Then, the expected amount of genotypic contribution by asexual hosts is given by

$$A'_{ij} = W_U A_{ij,U}(t) + W_I A_{ij,I}(t), \tag{2}$$

where $A_{ij,U}$ and $A_{ij,I}$ are the number of uninfected and infected asexual hosts in a population.

We assume that proportion ϵ_{mix} of a population mix with other populations. Then, the expected number of offspring in the next generation (accounting for contributions from all populations) is given by

$$\begin{aligned} \mathrm{E}\left(S^k_{ij}(t+1)\right) &= f_{\text{sex}}\left((1-\epsilon_{\text{mix}})\left(S^k_{ij}\right)' + \frac{\epsilon_{\text{mix}}}{n_{\text{pop}}-1}\sum_{h\neq k}\left(S^h_{ij}\right)'\right), \\ \mathrm{E}\left(A^k_{ij}(t+1)\right) &= (1-\epsilon_{\text{mix}})\left(A^k_{ij}\right)' + \frac{\epsilon_{\text{mix}}}{n_{\text{pop}}-1}\sum_{h\neq k}\left(A^h_{ij}\right)', \end{aligned} \tag{3}$$

where $f_{\text{sex}}(x)$ is the function that models sexual reproduction, including recombination probability r_{host} and outcrossing, and n_{pop} is the number of populations modeled. Then, the total number of sexual and asexual hosts in the next generation given by Poisson random variables with mean specified previously. We also allow for stochastic migration to avoid fixation:

$$\begin{aligned} S^k_{ij}(t+1) &\sim \text{Poisson}\left(\lambda = \mathrm{E}\left(S^k_{ij}(t+1)\right)\right) + \text{Bernoulli}\left(p = p_{ij,\text{sex}}\right), \\ A^k_{ij}(t+1) &\sim \text{Poisson}\left(\lambda = \mathrm{E}\left(A^k_{ij}(t+1)\right)\right) + \text{Bernoulli}\left(p = p_{ij,\text{asex}}\right), \end{aligned} \tag{4}$$

where $p_{ij,\text{sex}}$ and $p_{ij,\text{asex}}$ are the probabilities of a sexual and an asexual host with genotype ij entering a popualation.

[BMB: *No epistasis?*] [SWP: *Is this clearer?*] Infection is modeled using the matching alleles model (Otto and Michalakis, 1998). We assume that snails are equally susceptible to parasites that match either haplotype. However, parasites must carry same alleles in both loci in order to match a host haplotype. The total number of infected hosts that carry parasite with genotype i at generation t is given by:

$$I_i(t) = \sum_p 2^{\delta_{ij}} \left(S_{ij,i,I}(t) + A_{ij,i,I}(t) \right), \tag{5}$$

where a δ_{ij} is Kronecker delta. δ_{ij} equals 1 when $i = j$ and 0 otherwise. $S_{ij,i,I}(t)$ and $A_{ij,i,I}(t)$ represent the expected numbers of sexual and asexual hosts that have genotype ij and are infected with genotype i parasite. Following Ashby and King (2015), we assume that mutation can occur in one locus with probability r_{parasite}. Mutation is modeled using a deterministic process, as we introduce stochasticity during the actual infection process. We also allow for stochastic external migration of an infected host carrying parasite i with probability $p_{i,\text{parasite}}$ to avoid fixation.

The total expected number of infectious contacts made by infected hosts within a population is given by $\lambda_i^k = \beta^k I_i'^k(t)$, where β^k is the transmission rate of each population, and $I_i'(t)$ is the number of infected hosts accounting for mutation and migration. Since we allow for mixing between populations, infected hosts can make contact with susceptible hosts in other populations. [SWP: *TODO: explain mixing*] Then, the total amounf of infectious contacts, coming from hosts that carry genotype i parasite, that is received by susceptible hosts in population k is given by

$$\lambda_{i,\text{total}}^k = (1 - \epsilon_{\text{mix}})\lambda_i^k + \frac{\epsilon_{\text{mix}}}{n_{\text{pop}} - 1} \sum_{l \neq k} \lambda_i^l \tag{6}$$

Then, the force of infection that a susceptible host with genotype ij experiences in generation $t + 1$ is given by

$$\text{FOI}_{ij}^k = \frac{\lambda_{i,\text{total}}^k + \lambda_{j,\text{total}}^k}{2N^k(t+1)}, \tag{7}$$

where $N^k(t+1) = \sum_{i,j} S_{ij}^k(t+1) + A_{ij}^k(t+1)$ is the total number of hosts in generation $t + 1$. The probability that a susceptible host with genotype ij in population k becomes infected in the next generation is given by

$$P_{ij}^k(t+1) = 1 - \exp\left(\text{FOI}_{ij}^k\right). \tag{8}$$

Finally, number of infected hosts in the next generation is determined by a binomial process:

$$\begin{aligned} S_{ij,I}^k(t+1) &\sim \text{Binom}(S_{ij}^k(t+1), P_{ij}^k(t+1)), \\ A_{ij,I}^k(t+1) &\sim \text{Binom}(A_{ij}^k(t+1), P_{ij}^k(t+1)). \end{aligned} \tag{9}$$

The expected number of infected hosts that have genotype ij and are infected by parasites with genotype i in the next generation is given by a ratio of λ:

$$\begin{aligned} S^k_{ij,i,I}(t+1) &= \frac{\lambda^k_{i,\text{total}}}{\lambda^k_{i,\text{total}} + \lambda^k_{j,\text{total}}} S^k_{ij,I}(t+1) \\ A^k_{ij,i,I}(t+1) &= \frac{\lambda^k_{i,\text{total}}}{\lambda^k_{i,\text{total}} + \lambda^k_{j,\text{total}}} A^k_{ij,I}(t+1) \end{aligned} \tag{10}$$

2.3 Simulation design and parameterization

Many Red Queen models have focused on competition between a single asexual genotype and multiple sexual genotypes or have assumed equal genetic diversity between asexual and sexual hosts (see (Ashby and King, 2015) for a review of previous Red Queen models) but neither of these assumptions are realistic. Instead, Ashby and King (2015) adopted a more realistic approach by allowing for stochastic migration of an asexual genotype to a population. Here, we combine these methods. We allow for stochastic external migration of asexual hosts with different genotypes into the system but fix the number of asexual genotypes (denoted by G_{asex}) that can be present in the system. The number of sexual genotypes (G_{sex}) that can be present in the population remains equal to the size of the genotypic space (= 10 for diploid hosts with two biallelic loci).

[**BMB:** *Explain?*] [**SWP:** *Is this clearer?*] In the beginning of the simulation, asexual genotypes that can be introduced to the population are uniformly chosen from the entire genotypic space such that the number of asexual genotypes is equal to G_{asex}. By limiting the number of asexual genotypes that can be present in the system, we account for intrinsic difference in sexual and asexual genotypic diversity. We estimate G_{asex} to test whether greater asexual genetic diversity can be supported than a typically assumed one-to-many ratio [CITE].

To account for differing number of sexual and asexual genotypes, we let

$$\begin{aligned} p_{ij,\text{sex}} &= 1 - (1 - p_{\text{host}})^{1/G_{\text{sex}}}, \\ p_{ij,\text{asex}} &= \begin{cases} 1 - (1 - p_{\text{host}})^{1/G_{\text{asex}}} & \text{if } ij \in \{\text{asexual genotypes}\} \\ 0 & \text{otherwise} \end{cases}, \end{aligned} \tag{11}$$

where p_{host} is the probability that at least one sexual and asexual host enters the population in a generation. We scale the probability of infected host carrying parsite genotype i in a similar way for interpretability:

$$p_{i,\text{parasite}} = 1 - (1 - p_{\text{infected}})^{1/4}, \tag{12}$$

where p_{infected} is the probability that at least one infected host enters the population in a generation.

Each simulation consists of 40 populations. Every population is initiallized with 2000 sexual hosts, of which 80 are infected. They are assumed to be in Hardy-Weinberg equilibrium with ratio between alleles being exactly half.

Transmission rate, β^k, is randomly drawn for each population from a gamma distribution with mean β_{mean} and coefficient of variation β_{CV}. Simulation runs for 500 generations without introduction of asexuals. At generation 501, 10 asexual hosts of a single genotype are introduced to each population (note that asexual genotype introduced can vary across population) and simulation runs for 600 generations while allowing for stochastic migration of asexuals.

2.4 Approximate Bayesian Computation

[**BMB:** *More on probe matching; Kendall et al.?*] [**SWP:** *Not clear what you're looking for...*]

We use Approximate Bayesian Computation (ABC) to fit the model (Toni et al., 2009). ABC relies on comparing summary statistics of observed data and those of simulated data and is particularly useful when the exact likelihood function is not available. We consider mean proportion of infected and sexually reproducing snails in the system and variation in these proportions – measured by coefficient of variation (CV) – across space (population) and time as our focal summary statistics. These summary statistics are calculated for both observed and simulated data and are used in ABC. As Dagan et al. (2013a) and McKone et al. (2016) only reported proportion of males, proportion of sexual hosts are assumed to be twice proportion of males.

CV across space is calculated by first calculating mean proportions by averaging across time (generation) for each site (population) and then taking the the CV of these mean proportions. CV across time (generation) is calculated by first averaging proportions across space (population) at each generation and then taking the CV. For purely spatial data (Dagan et al. (2013a) and McKone et al. (2016)), CV across space is calculated without averaging across time. Sampling error is not taken into account when summary statistics are calculated from simulated populations.

We use weakly informative priors for all parameters that we estimate except c_b, a scale parameter for the cost of sex (see Table 1 for prior distributions used and parameters assumed). The prior distribution for the scale parameter is chosen so that 95% quantile of cost of sex ($2/c_b$) is approximately equal to the 95% confidence interval reported by Gibson et al. (2017). All other parameters are assumed to be fixed for simplicity.

We start by performing basic ABC. For each random parameter sample drawn from the prior distribution, the model is simulated and a sample of simulated populations is drawn from the simulated system such that the number of sampled population is equal to the number of sites collected in a study. Then, summary statistics are calculated based on the last 100 generations out of 1100 generations and the parameter is accepted if the distance between simulated and observed data is less than a tolerance value. Distance is measured by the sum of absolute differences in summary statistics between simulated and observed data. This process is repeated until 100 parameter sets are accepted.

After the first run ($t = 1$), equal weights ($w_{i,1} = 1/100$) are assigned to each accepted parameter set $\boldsymbol{\theta}_{i,1}$, where $1 \leq i \leq 100$. For any run $t > 1$, a weighted

Notation	Description	Prior distribution/parameter values	Source
β_{mean}	Mean transmission rate	Gamma($k = 2, \theta = 10$)	Assumption
β_{CV}	CV transmission rate	Gamma($k = 2, \theta = 0.5$)	Assumption
V	Virulence	Beta($\alpha = 6, \beta = 2$)	Assumption
ϵ_{mix}	Mixing proportion	Beta($\alpha = 1, \beta = 9$)	Assumption
$G_{\text{asex}} - 1$	Number of asexual genotypes - 1	BetaBinomial($N = 9, p = 3/9, \theta = 5$)	Assumption
c_b	Cost of sex scale	LogNormal($\mu = -0.07, \sigma = 0.09$)	Gibson et al. (2017)
s	Proportion of male offsprings produced	0.5	Assumption
b_U	Number of offsprings produced by an uninfected host	20	Lively (2010b)
b_I	Number of offsprings produced by an infected host	$(1 - V)b_U$	Lively (2010b)
a_U	Density dependent effect coefficient of uninfected hosts	0.001	Lively (2010b)
a_U	Density dependent effect coefficient of infected hosts	0.001	Lively (2010b)
r_{host}	Host recombination probability	0.2	Lively (2010b)
r_{parasite}	Parasite mutation probability	0.05	Assumption
p_{host}	Probability that at least one sexual and asexual host enters the population	0.1	Assumption
p_{infected}	Probability that at least one infected host enters the population	0.02	Assumption

Table 1: **Parameter descriptions and values**. Parameters with prior distributions are estimated via Approximate Bayesian Computation (ABC). k and θ in Gamma distribution represent shape and scale parameters where mean and squared CV are given by $k\theta$ and $1/k$, respectively. α and β in Beta distribution represent shape parameters where mean and squared CV are given by $\alpha/(\alpha + \beta)$ and $\beta/(\alpha^2 + \alpha\beta + \alpha)$. N, p and θ in Beta binomial distributions represent number of trials, probability of success, and overdispersion parameters (Morris et al., 1983). We define prior on $G_{\text{asex}} - 1$ instead to always maintain at least one asexual genotype in the system. μ and σ in log-normal distribution represent mean and standard deviation on a log scale. All other parameters are fixed throughout simulations.

random sample ($\boldsymbol{\theta}^*$) is drawn from the accepted parameters of the previous run $(t-1)$ with weights $w_{i,t-1}$ and a parameter sample ($\boldsymbol{\theta}_{i,t}$) is proposed from a multivariate normal distribution with a mean $\boldsymbol{\theta}^*$ and a variance covariance matrix that is equal to $\sigma^2_{t-1} = 2\text{Var}(\boldsymbol{\theta}_{1:N,t-1})$, where $\text{Var}(\boldsymbol{\theta}_{1:N,t-1})$ is the weighted variance covariance matrix of the accepted parameters from the previous run. N is the total number of accepted parameters from the previous run.

G_{asex} is rounded to the nearest integer and the model is simulated. If a proposed parameter is accepted, the following weight is assigned:

$$w_{i,t} = \frac{\pi(\boldsymbol{\theta}_{i,t})}{\sum_{i=1}^{100} w_{j,t-1} q(\boldsymbol{\theta}_{j,t-1}|\boldsymbol{\theta}_{i,t}, \sigma^2_{t-1})}$$

where $\pi(\cdot)$ is a prior density and $q(\cdot|\boldsymbol{\theta}_{i,t}, \sigma^2_{t-1})$ is a multivariate normal density with mean $\boldsymbol{\theta}_{i,t}$ and variance covariance matrix σ^2_{t-1}. For each run, 100 parameters are accepted and weights are normalized at the end to sum to 1. This method, known as the Population Monte Carlo approach (Turner and Van Zandt, 2012), allows for sampling more efficiently while ensuring that final result still satisfies criteria to be a correct (approximate) Bayesian posterior. All statistical results reported are weighted by parameter weights of the final run.

For each observed datum, we perform 4 runs with decreasing tolerance every run. For spatial data (Dagan et al., 2013a; McKone et al., 2016), four summary statistics are compared: mean proportion of infected and sexually reproducing snails and CV in these proportions across populations. Tolerance values of 1.6, 0.8, 0.6 and 0.4 are used for each run. For spatiotemporal data (Vergara et al., 2014b), six summary statistics are compared: mean proportion of infected and sexually reproducing snails, CV in these proportions across populations and CV in these proportions across generations. Larger tolerance values (2.4, 1.2, 0.9 and 0.6) are used for each run to account for higher number of summary statistics being compared. Tolerance value of the final run is chosen so that a parameter set will be accepted if its each simulated summary statistic deviates from the corresponding observed summary statistic by 0.1 units on average. First three tolerance values are chosen in a decreasing order to reach the final step quicker. [**BMB:** *Intuition for biological meaning of distances?*] [**SWP:** *I don't think there is one*] [**BMB:** *What are the summary stats?*] [**SWP:** *They're explained in the beginning of the section*]

2.5 Power analysis

Using estimated parameters for each data, we calculate the power to detect a correlation between infection prevalence and frequency of sexual hosts. For each parameter sample from the final run of the ABC, 10 simulations are ran. For each simulation, we take the final two generations – assuming that a year contains two snail generations [CITE] – from the simulation and choose n populations at random from 40 simulated populations. For each selected population, hosts are divided into four categories based on their infection status

(infected/uninfected) and reproductive mode (asexual/sexual), and mean proportion of hosts in each category is calculated by averaging over two generations. Independent multinomial samples of size m are drawn from each selected population based on the proportions in each four categories. Correlation between proportion of infected hosts and proportion of sexual hosts is tested using the Spearman's rank correlation at 5% significance level.

3 Results

Fig. 1 compares observed summary statistics with fitted and predicted summary statistics. Fitted summary statistics are those that are accepted via ABC and can be interpreted as underlying summary statistics of the study sites estimated by the model. [**SWP:** *Is this interpretation OK?*] Predicted summary statistics are obtained by simulating from estimated parameters and represent what could have been the underlying summary statistics if other sites were chosen from the system. As we account for uncertainty in unobserved sites by simulating a greater number of populations, there is large variation in predicted summary statistics.

We find that our simple meta-population Red Queen model can capture observed variation in infection prevalence and frequency of sexual hosts reasonably well; both temporal and spatial variation (measured by CV across mean proportions) are well-matched by the model. However, as model fitting is performed by minimizing the sum of absoute distance between observed and simulated summary statistics, our method does not gurantee all summary statistics to be equally well fitted. The model tends of overestimate mean proportion of infected hosts. Dagan et al. (2013a), McKone et al. (2016) and Vergara et al. (2014b) reported mean infection prevalence of 17.5%, 5.1% and 44% in their study sites, respectively. The *estimated* mean (95% quantile) infection prevalence is 24.0% (17.4% - 28.6%), 31.3% (23.3% - 40.4%) and 54.2% (36.0% - 73.0%), respectively. The model also underestimates mean frequency of sexual hosts for Dagan et al. (2013a) and Vergara et al. (2014b) study sites. Observed mean frequency of sexual hosts is 4.5% and 70.4%, respectively, whereas corresponding estimated mean (95% quantile) are 2.6% (0.7% - 4.8%) and 59.6% (44.1% - 67.9%). [**SWP:** *44.1% is actually 2.82% quantile rather than 2.5%. Should I write a sentence about it? It feels just a little gratuitous, although I think it is better to be clear and honest.*]

To further diagnose the fit, we compare the predicted relationships between mean infection prevalence and mean frequency of sexual hosts in each population (averaged over last 100 generations) with the observed data (Fig. 2). Note that Fig. 2 appears to be more variable than Fig. 1 as it plots density of all simulated populations and hence accounts for uncertainty in unsampled populations. Despite being able to reproduce the summary statistics reported by Dagan et al. (2013a) well, our model is unable to capture the qualitative trend between proportion of sexual hosts and proportion of infected hosts (Fig. 2; Dagan et al. (2013a)). Both simulated data and observed data mostly con-

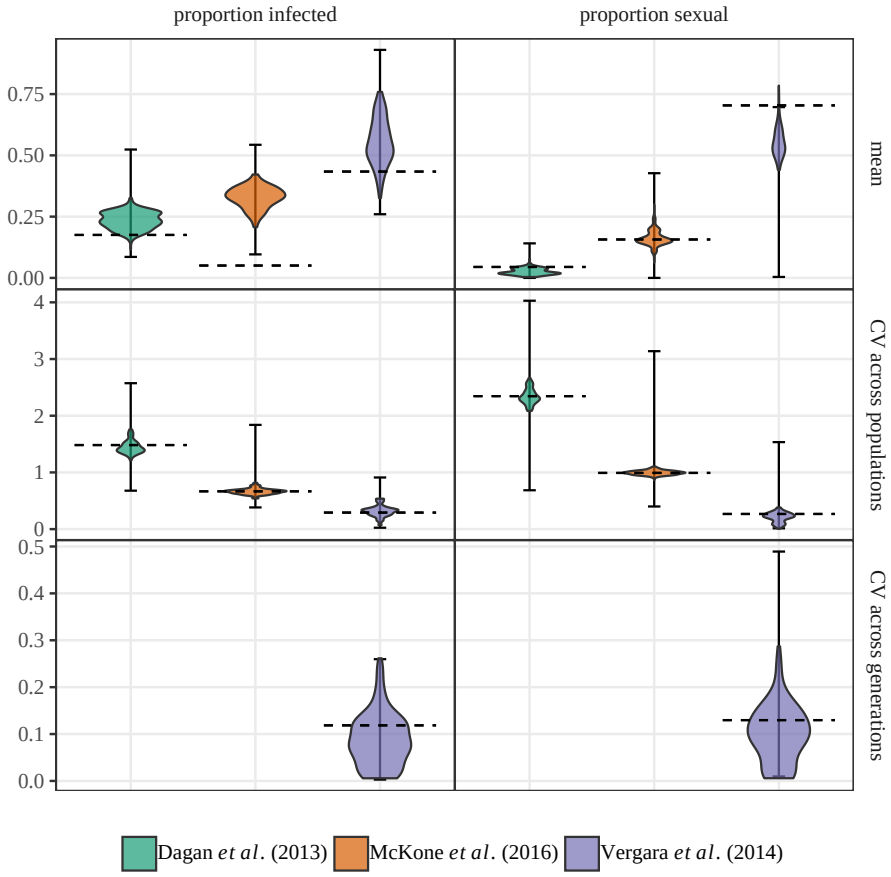

Figure 1: **Summary statistics of the observed data vs. distribution of summary statistics of the simulated data from the posterior samples.** Dotted horizontal line represents observed summary statistics. Violin plots show weighted distribution of fitted summary statistics (i.e., summary statistics that were accepted during Approximate Bayesian Computation). Error bars show 95% weighted quantiles of predicted summary statistics. For each posterior sample, 10 simulations are run and each simulated system is sampled at random 100 times so that each sample consists of equal number of populations as number of sites in fitted data. Then, summary statistics are calculated for each sample and are weighted by their corresponding weights.

sist of asexual populations but our model predicts sexual reproduction to be maintained when infection prevalence is high ($> 40\%$). On the other hand, Dagan et al. (2013a) data suggests that sexual reproduction is only maintained when infection prevalence is low ($< 20\%$). Similarly, overestimation of infec-

tion prevalence is strongly pronounced in our prediction of system studied by McKone et al. (2016).

While there are a few data points that appear to be outliers compared to our predictions for Vergara et al. (2014b), it is important to note that Fig. 2 does not capture temporal variation as we average over 100 generations to obtain the "mean" relationship. The observed data are more likely to be samples across a few generations and the cyclic nature of the Red Queen dynamics is likely to have created more variation in the data. On the other hand, Vergara et al. (2014b) reported greater than 90% sexual snails throughout 5 years in one of their study sites but it seems unusually high based on our model prediction.

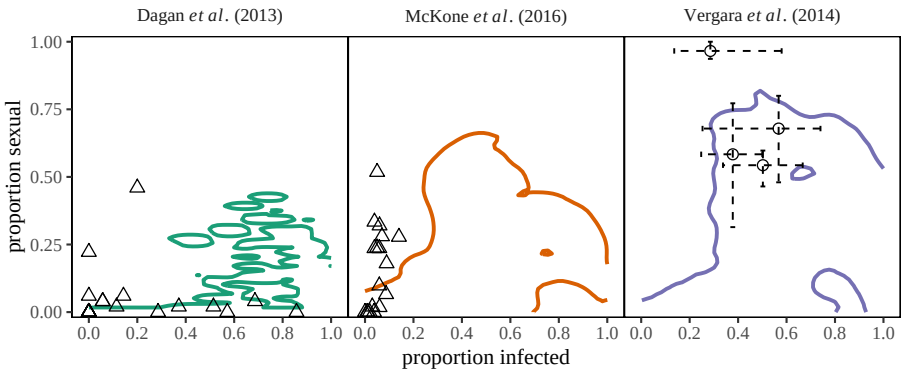

Figure 2: **Predicted relationship between mean infection prevalence and mean proportion of sexual hosts in each population.** For each posterior sample, 10 simulations are run. For each population within a simulation, mean infection prevalence and mean proportion of sexual hosts is calculated by averaging across last 100 generations. Each population is assigned equal weight as the parameter that simulated the population. Colored contour lines show 95% weighted highest posterior density region. Open triangles represent observed data; proportion of sexual hosts is computed from proportion of male hosts. Open circles represent observed mean proportions averaged across years. Dotted lines around open circles represent ranges of proportion of sexual and infected hosts observed in each site.

We find that there is a region (around 30% infection prevalence) in which proportion of infected hosts remains almost constant while proportion of sexual hosts increases (most clearly visible in the fits to McKone et al. (2016) and Vergara et al. (2014b)). As transmission rate (β) increases, selection for sexual hosts increases but increasing number of resistant offsprings prevents further infection from occuring and can decrease overall infection prevalence. Such a trend is consistent with previous results by Lively (2001) who noted that there is a region in which both sexual and asexual reproduction can be selected exclusively under same infection prevalence. We also find that proportion of sexual hosts decreases when infection prevalence is very high. Decrease in fitness

of sexual hosts associated with increase in prevalence was predicted by Ashby and King (2015); it can also be found in an earlier work by Lively (2010b) although it was not discussed in the paper.

[SWP: *You haven't read anything after this point:*] Parameter estimates are presented in Fig. 3. Even though we do not obtain good fits to data from Dagan et al. (2013a) and McKone et al. (2016), we find that high virulence and low asexual to sexual genetic diversity is necesary to partially explain the observed dynamics. Moreover, observed differences in mean and variation in infection prevalence among studies are captured in estimates of transmission rate parameters (β_{mean} and β_{CV}). Surprisingly, our fits to **?** suggest that scale parameter for the cost of sex, c_b, should be higher than our assumption based on Gibson et al. (2017) that estimated cost of sex (95% CI) to be 2.14 (1.81 - 2.55). Ashby and King (2015) defined c_b as additional costs and benefits of sex, where $c_b = 1$ corresponds the two fold cost. Under their interpretaion, our estimate of c_b corresponds to the following mean (95% CI) cost of sex: 1.95 (1.68 - 2.4). We propose an alternate interpretation to this parameter estimate in the discussion.

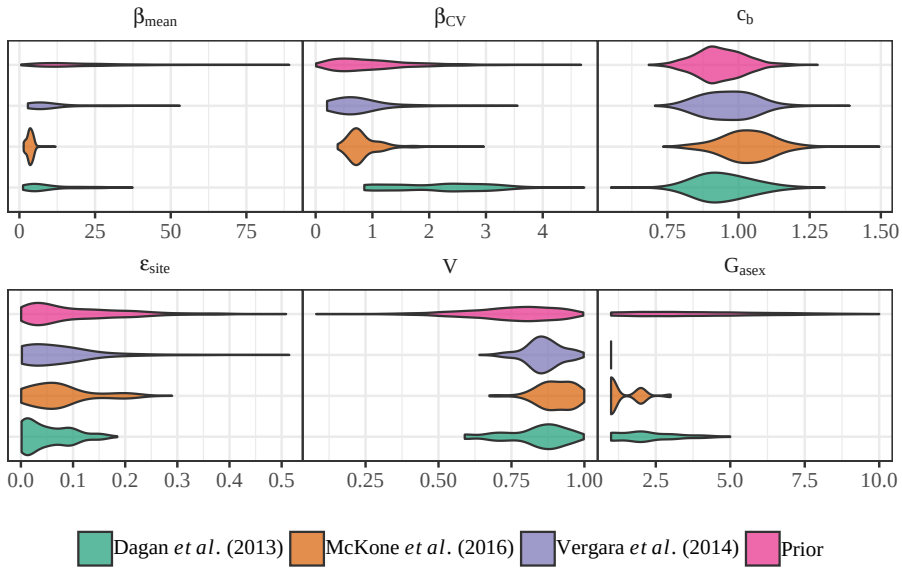

Figure 3: **Parameter estimates from Sequential Monte Carlo Approximate Bayesian Computation.** Violin plots represent weighted distribution of 100 posterior samples obtained from ABC. Violin plots for prior distribution is obtained by drawing 10000 random parameter samples from the prior distribution. G_{asex} is a discrete variable but is drawn on a continuous scale for convenience.

Finally, our power analyses reveal that there is high power to detect a positive

correlation between infection prevalence and frequency of sexual hosts in both systems studied by Dagan et al. (2013a) and McKone et al. (2016) (Fig. 4). Such high power predicted for Dagan et al. (2013a) is particularly surprising given that they were not able to observe the expected correlation. This discrepancy implies that the snail populations studied by Dagan et al. (2013a) show sufficient variation in infection prevalence to encompass the correlation under pure Red queen selection but other underlying factors, for which our model does not account, may have caused the populations to move away from their expected behaviours. On the other hand, our model predicts low power for detecting the positive correlation for the system studied by Vergara et al. (2014b) (Fig. 3). Overall, increasing number of sites is a more effective way to increase power than increasing number of samples per site.

While we originally planned to perform power analysis using Spearman's rank correlation, we repeated the analysis using Pearson's correlation after applying arcsine square root transformation [CITE] to see whether there is any change in power. Surprisingly, using Pearson correlation gives slightly higher power to detect the positive correlation bewteen frequency of sexual hosts and infection prevalence (see Appendix).

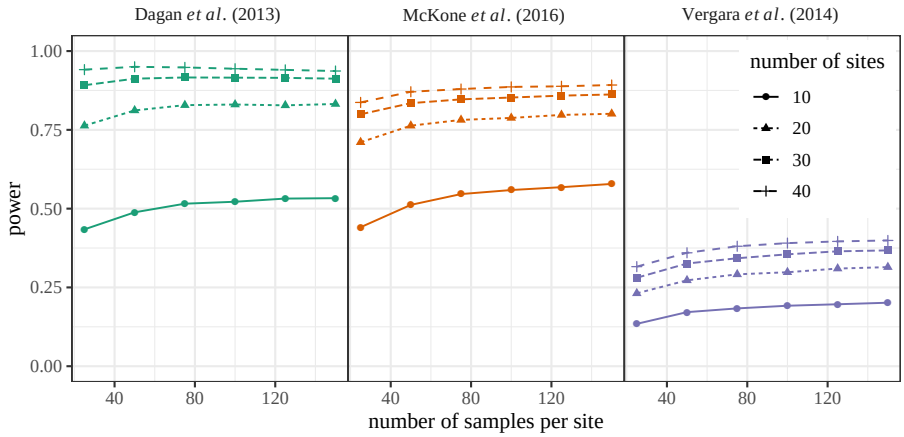

Figure 4: **Power to detect a statistically significant positive correlation between infection prevalence and frequency of sexual hosts.** Spearman's rank correlation was used to test for correlation between infection prevalence and frequency of sexual hosts in simulated data from the posterior distributions.

4 Discussion

Our study provides a useful direction for studying the Red Queen Hypothesis for sex. Many modeling studies have relied on assumed parameter values

to understand the role of host parasite coevolution in maintaining sexual reproduction; such method allows us to learn about the model and not so much about the nature. Instead, we tried to fit a simple Red Queen model to three different data sets from similar snail trematode systems. We show that (1) model parameters can be estimated from data and (2) biologically meaningful predictions can be made from the model. However, discrepancy between model prediction and observed data suggests that a simple host-parasite coevolution model is not sufficient to explain maintanence of sexual reproduction observed in snail populations.

A model that does not fit well can sometimes tell us more about a biological system than a model that fits well. For example, there was a clear mismatch between the model prediction and the data presented by Dagan et al. (2013a) (Fig. 2). The snail populations studied by Dagan et al. (2013a) live in intrinsically different environments from two other snail populations that we considered. For example, some habitats are subject to seasonal flash floods, which can affect reproductive strategies of snails (Ben-Ami and Heller, 2007) and interfere with the host parasite coevolution. As a result, positive correlation between infection prevalence and frequency of sexual reproduction could not be detected from the system even though high power is predicted. We caution against performing statistical tests that were purely designed under the Red Queen hypothesis when other mechanisms that may affect reproduction mode are present in the system.

The model fit to McKone et al. (2016) suggests that cost of sex can be overcome and sexual reproduction can be maintained only if infection prevalence is much higher than the observed prevalence (Fig. 2). In other words, benefit of producing offspring with novel genotype is small when infection prevalence is low. Therefore, benefit of sex must be greater or other mechanisms must compensate for the difference in order to support sexual reproduction at lower infection prevalence. As our model relies on a simple structure and strong parametric assumptions, additional benefit of sex can only be provided by lowering the cost of sex (i.e., increasing the scale parameter, c_b).

The simple structure of the model and limited genetic diversity provides an explanation for the discrepancy observed in model prediction and the observed data by McKone et al. (2016). Here, we assumed that host resistance to infection is deteremined entirely by two biallelic loci, which result in 10 genotypes, but it is unlikely that such simple model can capture genetic interaction between hosts and parasites observed in nature. Although exact genetic architecture that determines trematode infecion in snails (e.g., number of loci involved in parasite resistance) is not known **[SWP:** *How do I even cite this?*], genetic diversity of snails that have been documented is far greater than what we have assumed (King et al., 2011; Dagan et al., 2013a). In addition, increasing genetic diversity of the model would have allowed sexual hosts to escape infection more easily and maintained sexual reproduction at lower prevalence of infection (Lively, 2010a; King and Lively, 2012; Ashby and King, 2015).

While a simple model cannot

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