Suicidal Red Queen: Population dynamics and genetic drift accelerate diversity loss

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Abstract

Long term oscillations of genotype abundances in host-parasite systems are difficult to confirm experimentally. Therefore, much of our current understanding of these dynamics is based on theoretical concepts explored in mathematical models. However, the same biological assumptions can lead to very different mathematical models with diverging properties. The precise model can depend on the level of abstraction from reality, on the educational background and taste of the modeler, and on the current trends and conventions in the field. Here, we first review the current literature in the light of mathematical approaches. We then propose and compare our own framework of biologically similar, yet mathematical very different models that can all lead to host-parasite Red Queen dynamics. We highlight the different mathematical properties and use analytical and numerical tools to understand the long term dynamics. We focus on (i) the difference between deterministic and stochastic models and (ii) how ecological aspects, in our case population size, can influence the evolutionary dynamics. Our results show not only that stochastic effects can lead to extinction of subtypes, but that a changing population size speeds up this extinction. The loss of strain diversity can be counteracted with random mutations which then allow the populations to recurrently undergo fluctuating selection dynamics and selective sweeps.

1 Introduction

Van Valen (1973) first introduced the term Red Queen Hypothesis in an abstract verbal model explaining constant extinction as a result of biotic selection pressure. Today, Red Queen dynamics are interpreted as oscillations in genotype abundances induced by antagonistic co-evolution

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between host and parasite populations (Woolhouse et al., 2002). Since other associations with the term Red Queen are common in the literature (Salathé et al., 2008; Brockhurst et al., 2014; Neiman et al., 2017; Strotz et al., 2018; da Silva, 2018), it may be useful to think of Red Queen Dynamics as oscillating selection dynamics (sometimes also called fluctuating selection dynamics), in contrast to arms race dynamics. The intense interaction with often catastrophic impacts on either population strongly determines the genotype distributions over time and evolutionary parameters like the diversity within a population and the virulence or resistance of certain strains. Although a well known hypothesis, there is only little evidence for the ubiquitous prevalence of long term Red Queen oscillations in nature – empirical challenges preclude the observation of more than a few subsequent oscillations, as these require an impressive degree of experimental ingeniousness Koskella and Lively (2009); Buckling and Rainey (2002); Decaestecker et al. (2007). Thus, most work on the actual long term temporal dynamics is theoretical. Here, we examine several mathematical models all based on the same verbal models, which all assume a very simple form of antagonistic interactions and can verbally be described in exactly the same way. While most models so far produce and analyse the oscillations under various aspects and foci, only few assess their occurrence and show under what assumptions the oscillations do not occur (Gokhale et al., 2013; Schenk et al., 2017).

Many mathematical models have been formulated in order to address the impact of different assumptions like diverse infection matrices, population structure, few/many genotypes, different virulence dependencies, sexual vs. asexual reproduction, spatial structure, infection and recovery patterns, etc. Other assumptions are often not mentioned, as they are often implicit or not of further interest to the scientist. As these models are strong abstractions, there are typically numerous such assumptions. Examples are the commonly assumed Markov property, continuous time or discrete generations, a constant environment, no influence of life history and continuous density due to high population sizes. Finally, certain additional assumptions would make a model much too complicated to analyse which is circumvented by collapsing several cascades or complex dependencies into one parameter or simple function. We have summarised some of the literature and their assumptions in Table 1.

One (sometimes hidden) property of a model is determinism. This makes a model much easier to handle – but makes it impossible to address some important aspects. Coming back to the underlying stochastic process is our first main focus. By allowing genetic drift to influence the dynamics we enable strains to die out or take over the population. Our second focus is the comparison between fixed, constrained, and free population size. Population size is seemingly unimportant because Red Queen dynamics are oscillations of genotype abundances within a population, a change in the composition of the population's gene pool. To keep the model simple and to the point, infinite or constant population size can therefore be asummed by default. But in reality, the effect of a changing population size can enhance the influence of genetic drift, especially when population size is small (Papkou et al., 2016). These two aspects have been examined crudely before (Gokhale et al., 2013). Here, we explore a wider range of possible assumptions in seven models to obtain a more general understanding of the influence of population size and stochasticity on co-evolutionary dynamics. To measure this influence we use the time to extinction. In stochastic population models extinction or fixation of a type is often the only absorbing state and therefore inevitable, yet the time to extinction varies. The time to extinction is an informative measure, because extinction of one type implies that Red Queen dynamics are terminated and that genetic variation is reduced. Another important read-out is the stability of an internal fixed point in the analogous deterministic model. Amplitude size and frequency can also be of interest, yet in many models these measures vary greatly in the course of the dynamics.

We start by introducing the specificities of the models, then all models are examined via individual based simulations, supported by analytical calculations or approximations. The most pronounced effect is that Red Queen oscillations survive for a shorter time in models with a freely changing population size. A second result is that the strength of selection usually, but not always increases the time to extinction in some models. Finally, we include more types and argue that species diversity declines based on our assumptions, however, reviving subtypes from a reservoir of previously extinct types (by recombination, mutation or immigration) can lead to cascades of arms race and oscillating selection dynamics.

Table 1: **Literature overview.** Mathematical models and properties discussed in this paper sorted by publication year. Many models deal with relative (allele) abundances without considering ecological dynamics – these have been categorised as constant population size models. Those models that include a changing population size and stochastic effects focus on completely different aspects than the possible extinction that are the focus of this paper.

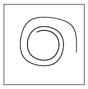
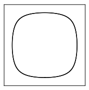
Authors (year)	focus	deterministic/ stochastic	equations/method	time	population size
Schaffer and Rosenzweig (1978)	CSS	deterministic	ODE	continuous	constrained[4]
Seger (1988)	many genotypes, chaos	deterministic	recursion equation	discrete	constant
Nee (1989)	co-evolution, recombination	deterministic	recursion equation	discrete	constant
Dybdahl and Lively (1998)	time lag, experiment	deterministic	recursion equation	discrete	constant
Boots and Sasaki (1999)	infection on lattice	both	ODE, IBM, AD	continuous	variable
Peters and Lively (1999)	fluctuating epistasis	deterministic	recursion equation	discrete	constant
Sasaki (2000)	multilocus GfG	deterministic	ODE	continuous	infinite
Agrawal and Lively (2001)	selfing vs outcrossing	deterministic	recursion equation	discrete	infinite
Agrawal and Lively (2002)	GfG vs MA	deterministic	recursion equation	discrete	constant
Gandon (2002)	local adaptation (spatial)	deterministic	recursion equation	discrete	infinite, constant
Gandon (2004)	multihost parasites	deterministic	ODE, AD	continuous, discrete	constant
Kouyos et al. (2007)	oscillations in stochastic model	both[7]	ODE	discrete, continuous	constant[5]
Alizon and van Baalen (2008)	multiple infections	deterministic	ODE, AD	continuous	
Agrawal (2009)	sex vs recombination	deterministic	recursion equation	discrete	constant
Best et al. (2009)	transmission, susceptibility	deterministic	ODE, AD	continuous	constant
Lively (2010b)	sex (long term persistance)	both[6]	recursion equation	discrete	variable
Gilman et al. (2012)	multiple host traits, resistance	stochastic	IBM	discrete	constant, constrained[4]
Gokhale et al. (2013)	population size	stochastic	IBM	continuous	variable, constrained
Luijckx et al. (2013)	MA, Daphnia	deterministic	recursion equation	discrete	constant
Abou Chakra et al. (2014)	plastic behaviour	both	ODE, IBM	discrete, continuous	constant
Taylor et al. (2014)	virus of virus	deterministic	ODE	continuous	constrained
Ashby and King (2015)	diversity, transmission, sex	stochastic	IBM	continuous	variable
Engelstädter (2015)	infection matrices	deterministic	recursion equation	discrete	constant
Rabajante et al. (2015)	many types	deterministic	ODE	continuous	carrying capacity
Song et al. (2015)	population size, GfG MA	deterministic	ODE	continuous	constant, variable
Hesse et al. (2015)	environment, specialisation	deterministic	ODE, AD	continuous	variable
Rabajante et al. (2016)	rare types	deterministic, noise[1]	ODE, SDE	continuous	constrained
Nordbotten and Stenseth (2016)	RQ vs stasis	deterministic	PDE	continuous	variable
Best et al. (2017)	no specificity	deterministic[3]	ODE, AD	continuous	constrained[4]
Bonachela et al. (2017)	crossfeeding	deterministic[2]	ODE and mutants	continuous	variable
Greenspoon and Mideo (2017)	relatedness, transmission	deterministic	ODE	contiunous	constant
Lively (2017)	allopatric, sympatric parasites	deterministic[2]	recursion equation	discrete	constrained
Nuismer (2017)	local, global adaptation	deterministic[2]	recursion equation	discrete	constant
Veller et al. (2017)	speed of evolution (RQ, RK)	stochastic	IBM	discrete	constant
Current paper	population size, extinction	stochastic	IBM	discrete, continuous	constant, constrained, variable

ODE/PDE/SDE: ordinary/partial/stochastic differential equation, IBM: individual based model (stochastic simulations), AD: adaptive dynamics (most often ODE with added mutants), MA: matching alleles, GfG: gene for gene, RQ: Red Queen (oscillations in genotype abundances or in trait space), RK: Red King (slow evolution favoured), CSS: coevolutionary stable strategy. [1] not intrinsic stochasticity [2] stochastic mutants added [3] adaptive dynamics simulations (no intrinsic stochasticity) [4] via carrying capacity [5] but discussed [6] some randomness in infection (+/- 1 in next generation) [7] when time discrete, only host stochastic

2 Models and properties

The mean population dynamics is ultimately driven by events on the individual level. These individual based models can be written in the form of chemical reactions with a certain reaction rate. All our stochastic processes are based on these individual interactions, where parasites have negative fitness effects on the hosts, but beneficial effects on the parasite. Although our models can be explained with the same words and biological relevance, the mathematics behind them can be completely different. A verbal summary of the model is given in Table 2, for mathematical details we refer to the supplementary material (Section S1 and Table S1). Whether parasites can successfully infect a host or not is controlled by specificities. Parasites are often highly specific to certain host subtypes (Carius et al., 2001; Schulte et al., 2011). We define the mathematical subtypes by their infectivity/susceptibility to another type. Then we can describe the infection in a simple table which records the impact of each parasite type (columns) upon a host type (rows). For example, in the simplest case of only two host phenotypes and two parasite phenotypes, we have $M^H = \left(\begin{smallmatrix} a & b \\ c & d \end{smallmatrix}\right)$. For equally virulent parasite types and strict specificity we obtain $a = d = -1$ and $b = c = 0$, which is the matching allele model where P_1 can infect H_1 and P_2 can infect H_2.

Table 2: **Model overview.** Model names and their main assumptions. Models are ordered by population size constraint.

Model	reactions	time	population size	fixed point	dimension
discrete time Moran (dtMoran)	reactions within host (host Birth death*) or within parasite population (parasite Birth death), or simultaneously in both, global competition	discrete	constant	attractive 	2D
Moran	as above, but with continuous time and no simultaneous reactions	continuous	constant	attractive	2D
Discrete time Pairwise Comparison (dtPC)	like dtMoran but with local competition	discrete	constant	neutral 	2D
Pairwise Comparison (PC)	like Moran but with local competition	continuous	constant	neutral	2D
Self controlling population size (SCPS)	reactions between two subtypes of different populations, single birth of parasite and death of host by dynamically adjusted rates.	continuous	nearly constant	neutral	4D
Logistic independent reactions (logIR)	reactions between two subtypes of different populations, or competition in hosts, also single birth of parasite and death of host	continuous	constrained	attractive	4D
Independent reactions (IR)	like logIR but with no competition	continuous	unconstrained	neutral	4D/2×2D

* we write Birth death (Bd) when selection is on birth and death is random

We propose seven models ranging between stochastic Game Theory and original models of antagonism based on individuals. The most constrained models are the Birth-death processes taken from Evolutionary Game Theory and Population Genetics (see Supplement S1.1, Table

S2). Every time an individual duplicates (gives birth to the same type), another random one dies, keeping population size constant, e.g. $H_1 + H_2 \xrightarrow{\text{rate(fitness)}} 2H_2$. The birthrate is proportional to the individual's fitness, i.e. the payoff gained from this particular antagonistic interaction, which depends on the relative abundances of matching or non-matching types of the other population (host vs parasite). In the Moran process, fitness of a subtype depends on the average fitness of it's own population over all subtypes. A similar model is the Pairwise Comparison (PC) process, where the difference in fitness between two rival types flows into the reproduction rate. Both models can be implemented with discrete time (dtMoran, dtPC) or continuous time (Gillespie algorithm, see Supplement S1.2). On the other end of the spectrum (and unrelated to Evolutionary Game Theory) is the completely free independent reactions (IR) model (Supplement S1.3). Here, an interaction between matching host-parasite pairs directly results in parasite birth, e.g. $H_2 + P_2 \overset{\lambda}{\to} H_2 + 2P_2$ or host death $H_2 + P_2 \overset{\lambda}{\to} P_2$. The dynamics can be slightly constrained by introducing competition in the hosts, equivalent to logistic growth around a carrying capacity (logIR, Supplement S1.3). Finally, an intermediate model with self controlled, but not fixed, population size (SCPS, see Supplement S1.4) is built from the individual interactions model, but with reaction rates taken from Game Theory. We implement all models using the matching allele interaction matrix, as described above. We could work with any other interaction matrix, but as we are interested in a comparison of different dynamical process, it is simpler to focus on a particular interaction mode.

In total, these considerations define a microscopic process describing individual deaths and births. To analyse these models, we can in some cases directly analyze the stochastic process, but often we have to resort to deterministic limits or numerical simulations.

3 Results

The distribution of many independent simulations can be approximated by the stochastic process, described by a Fokker Planck equation derived from the individual "chemical" reactions (Master equation, see Supplementary Material S2 and Table S3). The Fokker Planck equation has a drift term (mean deterministic dynamics) and a diffusion term (affecting the variance) and can be solved only for simpler models than ours. In addition, the Fokker Planck equation can be used to derive a stochastic differential equation (SDE). An SDE describes, like individual simulations, a single realisation of the process. Yet while population size is an inherent property of the stochastic simulations, it is only a technical parameter affecting the noise in the SDE. Importantly, the Fokker Planck equation, or the SDE, provide detailed information on the noise, which is not simply white noise added to the deterministic part, but dependent on the variables of host and parasite abundance.

For the deterministic description, we can calculate the fixed points and analyse their stability (Table 2 and Supplement S3). A population only departs from fixed points under the influence of stochastic fluctuations. An internal coexistence fixed point exists in all models described here. Yet, whether this stationary state is reached is another issue and determined by its stability (also recorded in Table 2). Attractive fixed points pull the dynamics inward, this produces damped oscillations which finally reach the stable state. Neutral fixed points do not excert this pulling force; When starting away from the coexistence fixed point, dynamics oscillate around this point indefinitely.

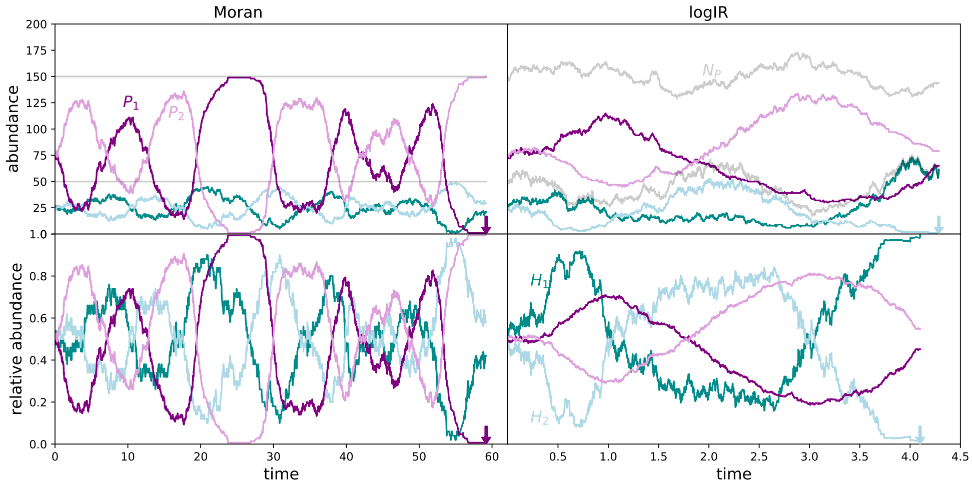


Figure 1: **Oscillations of host and parasite genotype abundances with drift for constant and changing population size**. The Moran Process (Gillespie algorithm) with constant population size and logistic independent reactions (logIR) are simulated until one subtype dies out (arrow). Note that the time axis is not the same, the logIR oscillations are sustained for much shorter times. Top: actual abundances of subtypes and total population size, bottom: relative abundances (densities) within the population. The simulations start with equal abundance of both types $H_1(0) = H_2(0) = N_H/2$ and $P_1(0) = P_2(0) = N_P/2$, which coincides with the deterministic attractive fixed point. Parameters: $N_H = 50$, $N_P = 150$, $w_H = 0.6$, $w_P = 0.9$, $\alpha = 1$, $\beta = 0$, $d_P = 1$, $b_H = 6$, $K = 100$, $\lambda_0 = 4$, $\lambda = \frac{\lambda_0}{K}$, $\mu = \frac{b_H}{K}$

Yet, under the influence of stochasticity (diffusion/genetic drift), the dynamics are always perturbed. In models with attractive coexistence, the opposing forces can balance the dynamics such that oscillations can persist (McKane and Newman, 2005), but in neutrally stable models the dynamics are pushed further outwards (oscillations become larger, amplitudes increase) and extinction occurs faster. These observations are intuitive and well known in the field of stochastic dynamical systems. What is also quite clear is that populations with low total abundances (population sizes) a prone to extinction more than large populations, simply by the fact that minima in the oscillations of relative abundances refer to lower absolute abundances of subtypes when population size is small.

While a variable population size does not necessarily speed up extinctions, we show in our case that it does. In other words, genetic drift (stochastic diffusion) is much more influential when population size is not constant. As an example with two host strains and two parasite types (Fig. 1), we pick the Moran process and the logistic independent reactions (logIR), which both have a pulling force as described above, but in the independent reactions model population size is not fixed, merely constrained.

These single simulations are only a snapshot and one specific realisation of the process. Ideally, we would analytically derive extinction times depending on the parameters of the model. Yet, to derive an exact analytical solution for this problem is extremely challenging. In addition to, simulations, we have calculated the numerical (but exact) sojourn times and provide an approximative method based on the averaged drift (see Supplementary material S4 for further

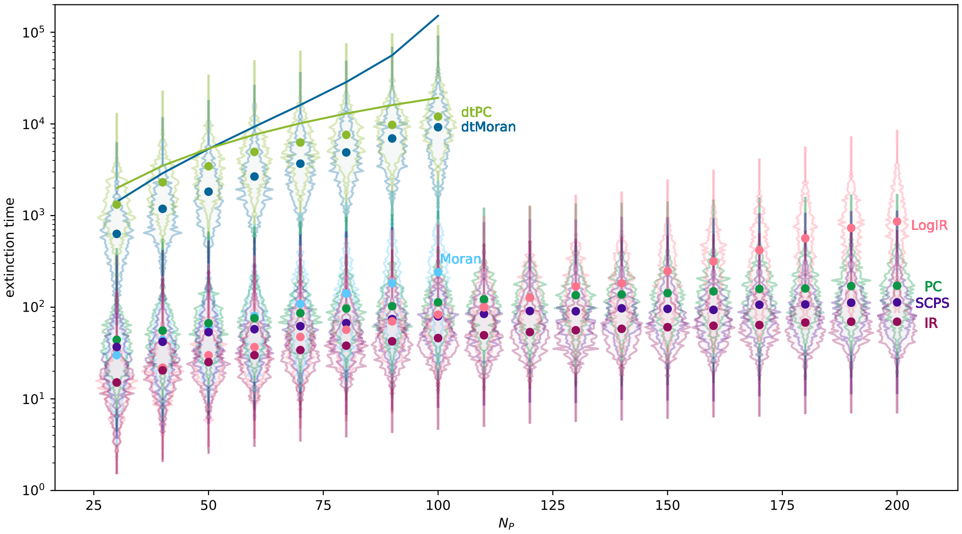


Figure 2: **Extinction time** of one type of host or parasite for different average population size of the parasite N_P and six different models. We show the mean extinction time over 1000 independent simulations (dots) and the distribution of those extinction times (shaded area around the mean). The simulations start with equal abundance of both types $H_1(0) = H_2(0) = N_H/2$ and $P_1(0) = P_2(0) = N_P/2$. Lines denote approximative results from the constant of motion drift method (see Supplement S4). Parameters: $N_H = 250$, $w_H = 0.5$, $w_P = 1$, $\alpha = 1$, $\beta = 0$, $d_P = 1$, $K = 500$, $\lambda_0 = 4$, $\lambda = \frac{\lambda_0}{K}$, $\mu = \frac{b_H}{K}$ but $\mu = 0$ for the IR model. The birthrate b_h in the logIR model is chosen $b_h \in \{0.24, 0.32, ..., 1.6\}$ and with $\mu = 0$ in the IR model without competition $b_h \in \{0.12, 0.16, ..., 0.8\}$ to achieve the population sizes N_P displayed.

details). These methods are limited to a subset of the seven models and can thus not be used for a comparison of all models, but only to support the computationally costly simulations which provide our now following main result.

We simulate 1000 replicates for several parameter combinations and show that the more constrained a population size is (upper models in Table 2), the longer oscillations survive (higher extinction times in Figure 2). Thus, as a rule of thumb, the more flexible the population size is in a model, the more likely it is that classic Red Queen oscillations of genotype abundances subside in the long run. The lines for the discrete time processes in Figure 2 are results from an approximate average drift method using a constant of motion (Supplement S4), inspired by Claussen (2007); Claussen and Traulsen (2008). The error of this approach cannot be neglected, but the qualitative trend is clearly visible and the result is fully analytical. Counterintuitively, the population size freedom seems to have a stronger influence on extinction times than the stability of the coexistence fixed point, at least in the parameter region tested here. Due to the challenges of employing an exact analytical approach, we cannot analytically tune the models for the same amplitudes, fluctuations and frequencies/periods of oscillations. The specific choice of the parameters is not necessarily directly comparable, but we have made an effort to choose them in a meaningful way, such that the fixed points are exactly the same and amplitudes comparable. We choose strong selection for the parasite $w_P = 1$ and weaker selection for the

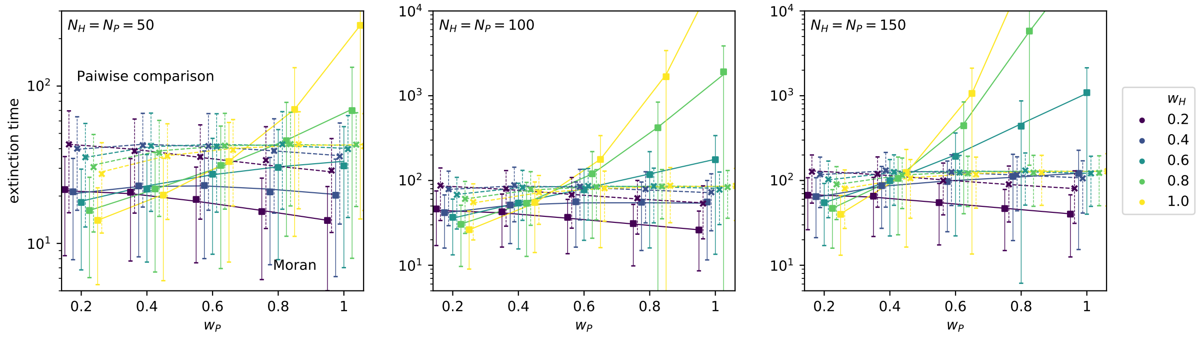


Figure 3: **Average extinction time for constant population sizes and different selection intensities.** The dtMoran and dtPC process are compared by the mean (■, ×) extinction times and the standard deviation from simulations with the exact sojourn times (—, - -) calculated analytically. The simulations start with equal abundance of both types $H_1(0) = H_2(0) = N_H/2$ and $P_1(0) = P_2(0) = N_P/2$. Parameters: $N_H = 250$, $w_H = w_P = 1$, $\alpha = 1$, $\beta = 0$. Note the log scale and different ranges on the y-axis.

host $w_H = 0.5$ in the models derived from Game Theory, because the logIR model is built in a similar way: Parasite birth can only occur through the antagonistic interaction, but host mortality is also influenced by the competition term. While the parasite is obligate and thus completely dependent on the host, the host possibly only suffers mildly from an infection. (The predator-prey "run for dinner vs. run for life" is reversed here: In predator-prey interactions the exploiter can choose a different dinner or hunt later, while in the host-parasite interaction the exploiter is an obligate and specialised parasite. One would thus expect a higher selection pressure on the prey, but a higher selection pressure on the parasite.)

Although our focus lies on comparing the variability of the population size, other interesting features can be explored in the models we have chosen. We briefly provide some insight into global vs. local competition, the influence of selection intensity, and what happens when we increase the number of types and add an option for mutation. It would be beyond the scope of the paper to provide a complete analysis for all these extensions, thus we limit the results to some exemplary set-ups.

We now go back to a constant population size and turn to the impact of selection intensity (in the Moran and PC process from Game Theory), which modulates the pulling force in models with an attractive fixed point. For a more robust result we compare the simulations (lines in Figure 3) with sojourn times (Supplement S5) calculated for the discrete time dtMoran and dtPC processes. Since only discrete time and discrete state processes can be represented by a transition matrix, we can only apply this approach to the discrete time constant population size processes.

Although the Moran process has an attracting fixed point, intuitively making extinction times longer than in the PC process, for low population sizes and weak selection we see the opposite – fast extinction. Furthermore, while the extinction time increases exponentially with strong selection in the Moran process, the PC extinction times stay comparably constant, which is not surprising considering the neutral stability. One interesting and unexpected result is that extinction time is lower for increasing selection intensity of one species while keeping the other

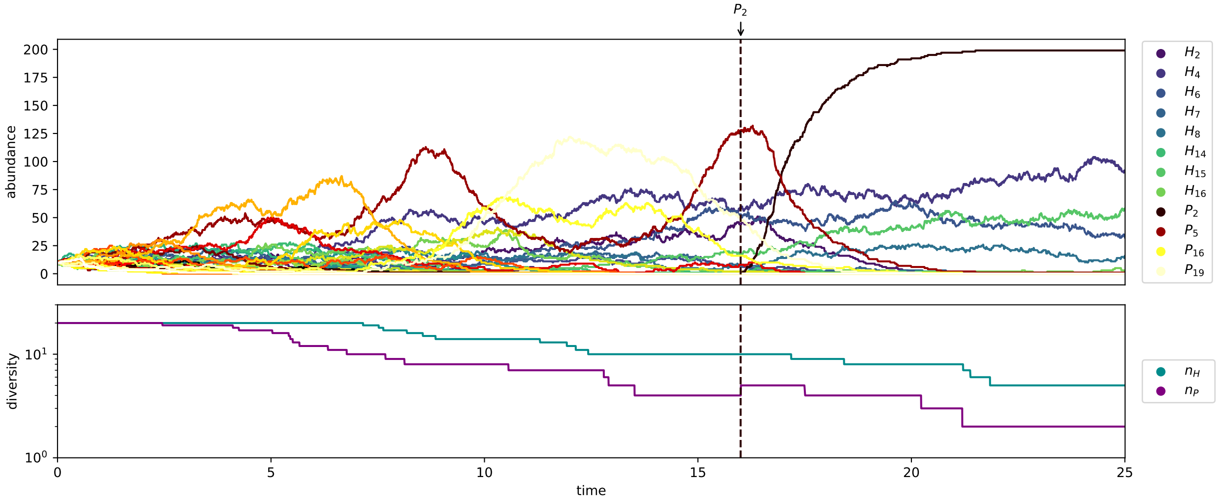


Figure 4: **Diversity decline** of subtypes of hosts and parasites. Example of a Moran process implemented with a Gillespie algorithm. The simulations start with equal abundance of all 20 types $H_i(0) = N_H/20$ and $P_i(0) = N_P/20$. At time point $t = 16$ a well adapted but extinct $P_2 = 1$ is reintroduced manually, while P_5 is reduced by one individual to keep N_P constant. Parameters: $N_H = 200$, $N_P = 200$, $w_H = w_P = 1$, $\alpha = 1$, $\beta = 0$.

constant. This occurs when one of the selection intensities is very low (some lines are decreasing, especially for example $w_H = 0.1$ and colours are reversed for fixed low values of w_P).

So far we have compared models with two types in each species. We now provide an outlook of how diversity can decline for many types. The Moran process simulated with a Gillespie algorithm is updated such that the interaction matrix is normalised depending on the number of strains (otherwise there is an imbalance between matching and non-matching pairs which results in change of selection strength). Strains are constantly lost from the population with a constant rate as shown by the exponential decline in diversity (Figure 4).

Oscillating selection can give an advantage to any type, but at different time points. A previously extinct parasite type (P_2) is reintroduced manually at time point 16, where the abundance of the corresponding host is especially high. Allowing the possibility for a re-introduction or mutation thus gives some types an extreme advantage if they are revived at the right time in which they are adapted perfectly.

In reality, subtypes are not as static in their traits as described here, but one of our types can be seen as an average of several individuals with slightly different traits. We can now add a form of mutation or recombination to the model so that reproduction does not necessarily result in a clonal daughter, but a new individual with different traits. For example, parasites could evolve fast by allowing (beneficial) mutations to produce other (even extinct) genotypes. Depending on the model system, a sexually reproducing host could also store genetic material to revive long extinct phenotypes by recombination. We abstract both of these processes by starting with many pre-defined genotypes and inserting a conversion rate μ from one type to the neighbouring type. For example with five types, $H_1 \xrightarrow{\mu/2} H_5$ and $H_1 \xrightarrow{\mu/2} H_2$, etc.. The dynamics we now

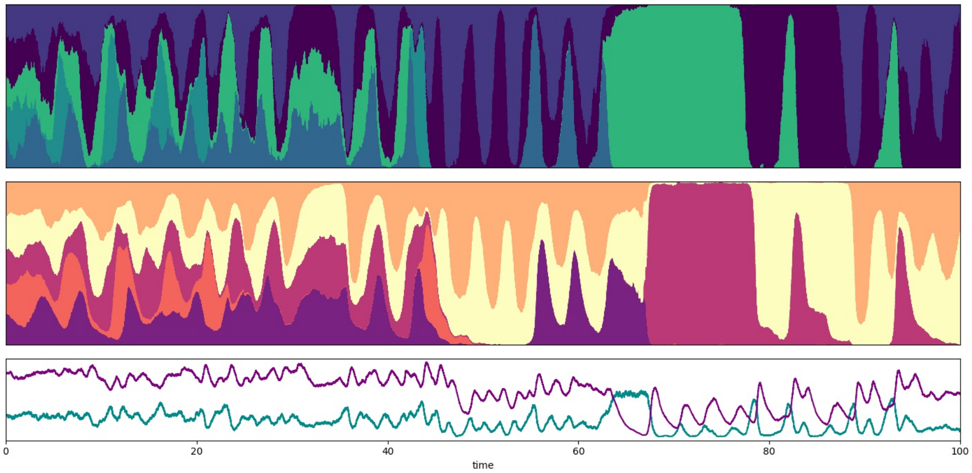


Figure 5: **Revival of types and evolution of diverse strains** of hosts (top) and parasites (middle) with conversion rate $\mu_H = 0.005$ and $\mu_P = 0.01$ to neighbouring types. Stacked plots: the area covered by one colour is proportional to the relative abundance of that subtype of host (top) or parasite (middle panel). Lower panel: total abundance of hosts and parasites. Example of a logistic Independent Reaction (logIR) process implemented with a Gillespie algorithm. The simulations start with equal abundance of all 5 types $H_i(0) = N_H/5$ and $P_i(0) = N_P/5$. Parameters: $N_H = 300$, $N_P = 900$ (each initially), $b_H = 6$, $d_P = 1$, $K = 600$, $\lambda_0 = 10$.

observe (Figure 5) are not pure Red Queen oscillations, but a mixture of oscillations and arms race dynamics, where selective sweeps can make a population monoclonal in a very short time, but a re-introduction of extinct times allows for short term Red Queen oscillations.

4 Discussion

We here provide a systematic comparison of seven related host-parasite co-evolution models and the resulting interaction dynamics. We demonstrate that the presence of stochastic effects and limited population size, which are likely common in nature, yet usually ignored in mathematical models, have a significant effect on evolutionary dynamics, often leading to rapid loss of genotypes and thus termination of Red Queen dynamics. In detail, the seven models are all based on the same widely used biological assumptions, but with differences in their mathematical properties: discrete and continuous time models with attractive or neutral deterministic dynamics in different dimensions. Instead of analysing only the deterministic versions, we have allowed genetic drift (intrinsic stochasticity) to govern the dynamics. We have found that flexible population sizes lead to a faster extinction of subtypes when genetic drift is allowed (Figures 1 and 2). We see that global competition stabilises the coexistence of types and leads to a prolonged period of oscillations when selection is strong. This effect is greater for large population sizes (Figure 3). Diversity (the number of types or strains present in the population) declines exponentially with time at a constant rate (Figure 4), but can be stabilised when types are allowed to mutate or recombine (Figure 5).

The models suggested here differ in many aspects, for example in the stability of the inner fixed point. Throughout the paper we discuss the flexibility of population size as the most influential factor, but as population sizes increase, the stochastic models become more like their deterministic analogues, as intuitively expected. When the stability of the fixed point gains in importance, the dynamics are pulled more towards the inner equilibrium state, making stochasticity less influential. It is challenging to find the parameters that determine the tipping point from which drift becomes less influential and the pulling force of stable fixed points take over. An estimate can be made from the average drift method. Our results are mostly based on simulations owing to the complexity of stochastic models, but we have compared them with numerical results and even analytic approximations where possible. The infection pattern is restricted to the matching alleles model, yet other zero-sum infection matrices would not gain more qualitative insight into the outcome of extinction studied here.

The term Red Queen has been used to explain several different phenomena, always following the metaphor describing co-evolution derived from Lewis Caroll's children's book 'Through the looking glass': you have to run to stay in the same place (because your surroundings are also running). Originally Van Valen (1973) observed that over millions of years taxa go extinct with a constant rate. In the Red Queen Hypothesis, he proposed that biotic forces, especially antagonistic interactions, are a source of changing selection pressure which can explain the law of constant extinction. He further envisioned a zero-sum game theory approach, at a time when Evolutionary Game Theory was being developed (Maynard Smith and Price, 1973). Bell (1982) then used the term Red Queen dynamics to describe oscillations of genotype relative abundances over time, without extinction. Since parasites are selected to target the most common resource and thus the most abundant host genotype, being a rare strain is advantageous for the host. This temporary high fitness makes the subtype grow in relative abundance, but before it can take over the whole population, it is severely diminished by new evolved parasites, which now target this common host type. Bell also put the spotlight on host-parasite interactions (rather than predator-prey or other victim-exploiter interactions) as the most influential antagonistic association, as they are common, often inter-dependent and exert the required high selective pressures on the interacting organisms. These dynamics are now often called fluctuating selection dynamics (oscillations of genotype abundances), to distinguish them from arms race dynamics (selective sweeps of new types taking over the population), but both are often referred to as Red Queen dynamics. The most prominent usage of the term Red Queen, is probably the Red Queen Hypothesis for the maintenance of sex (see reviews (Lively, 2010a; Neiman et al., 2017; Ashby and King, 2015; West et al., 1999)), which uses persistent changes of selection pressure (induced by parasites) to justify otherwise costly sexual reproduction.

We propose here, that Red Queen dynamics are not as regular and ongoing as previously believed and often illustrated. Even in the most simple and pure form of antagonistic interactions, as implemented in all models discussed here, oscillating selection dynamics cannot withstand a loss in diversity in the long run. The more complete picture includes all possibilities discussed in the Red Queen literature: there can be constant extinction, as suggested by Van Valen on a taxonomic level and there can be oscillations and arms race dynamics as suggested by host-parasite interactions and the resulting co-evolution. With our preliminary results we might be going too far if we also justify sexual reproduction, yet, without recombination or mutation, diversity decline is inevitable. If parasites can evolve more quickly due to shorter generation times and larger numbers, then hosts are given an advantage by being able to store genotypes through recombination. See Neiman et al. (2017) for a comprehensive connection to the Red Queen Hypothesis for sexual reproduction. Here, we merely wish to show that under simple mathematical models, arising from the same verbal biological description, many possible dynamics can occur. Our most important point remains an increased extinction under a variable population size, which we believe should be considered in modelling and when discussing the underlying co-evolutionary mechanisms of two antagonistic organisms.

These model predictions may also apply to the real world. Bottlenecks are likely more common in natural host-parasite associations (Papkou et al., 2016) than usually assumed and, therefore, the interaction dynamics are likely shaped by genetic drift and, thus, stochastic effects. For example, seasonal epidemics in influenza are characterised by changes in diversity in the pathogen (Rambaut et al., 2008). While in *Daphnia* the epidemic size changes diversity in the host (Auld and Brand, 2017). Yet, cyclic oscillations of population sizes also occur on smaller time scales (Bjørnstad et al., 2001). In consideration of model results, it would thus be of particular importance to assess the occurrence of bottlenecks, drift and stochasticity in natural host-parasite associations and relate them to the resulting allele frequency dynamics. Such empirical data would help us to obtain a more general understanding of host-parasite co-evolution and the importance of Red Queen dynamics in this context.

References

Abou Chakra, M., Hilbe, C., and Traulsen, A. (2014). Plastic behaviors in hosts promote the emergence of retaliatory parasites. *Scientific Reports*, 4:4251.

Agrawal, A. and Lively, C. M. (2002). Infection genetics: gene-for-gene versus matching-alleles models and all points in between. *Evolutionary Ecology Research*, 4:79–90.

Agrawal, A. F. (2009). Differences between selection on sex versus recombination in red queen models with diploid hosts. *Evolution: International Journal of Organic Evolution*, 63(8):2131–2141.

Agrawal, A. F. and Lively, C. M. (2001). Parasites and the evolution of self-fertilization. *Evolution*, 55(5):869–879.

Alizon, S. and van Baalen, M. (2008). Multiple infections, immune dynamics, and the evolution of virulence. *The American Naturalist*, 172(4):E150–E168. PMID: 18702601.

Ashby, B. and King, K. C. (2015). Diversity and the maintenance of sex by parasites. *Journal of evolutionary biology*, 28(3):511–520.

Auld, S. K. and Brand, J. (2017). Simulated climate change, epidemic size, and host evolution across host–parasite populations. *Global Change Biology*, 23(12):5045–5053.

Bell, G. (1982). *The Masterpiece of Nature: The Evolution and Genetics of Sexuality.* CUP Archive.

Best, A., Ashby, B., White, A., Bowers, R., Buckling, A., Koskella, B., and Boots, M. (2017). Host–parasite fluctuating selection in the absence of specificity. *Proc. R. Soc. B*, 284(1866):20171615.

Best, A., White, A., and Boots, M. (2009). The implications of coevolutionary dynamics to host-parasite interactions. *The American Naturalist*.

Bjørnstad, O. N., Sait, S. M., Stenseth, N. C., Thompson, D. J., and Begon, M. (2001). The impact of specialized enemies on the dimensionality of host dynamics. *Nature*, 409(6823):1001.

Bonachela, J. A., Wortel, M. T., and Stenseth, N. C. (2017). Eco-evolutionary red queen dynamics regulate biodiversity in a metabolite-driven microbial system. *Scientific reports*, 7(1):17655.

Boots, M. and Sasaki, A. (1999). 'small worlds' and the evolution of virulence: infection occurs locally and at a distance. *Proceedings of the Royal Society of London B: Biological Sciences*, 266(1432):1933–1938.

Brockhurst, M. A., Chapman, T., King, K. C., Mank, J. E., Paterson, S., and Hurst, G. D. D. (2014). Running with the Red Queen: the role of biotic conflicts in evolution. *Proceedings of the Royal Society B: Biological Sciences*, 281(1797):1797.

Buckling, A. and Rainey, P. B. (2002). Antagonistic coevolution between a bacterium and a bacteriophage. *Proceedings of the Royal Society B*, 269:931 –936.

Carius, H. J., Little, T. J., and Ebert, D. (2001). Genetic variation in a host-parasite association: potential for coevolution and frequency-dependent selection. *Evolution*, 55(6):1136–1145.

Claussen, J. C. (2007). Drift reversal in asymmetric coevolutionary conflicts: influence of microscopic processes and population size. *European Physical Journal B*, 60:391–399.

Claussen, J. C. and Traulsen, A. (2008). Cyclic dominance and biodiversity in well-mixed populations. *Physical Review Letters*, 100:058104.

da Silva, J. (2018). Red queen theory. *eLS*, pages 1–7.

Decaestecker, E., Gaba, S., Raeymaekers, J. A. M., R. Stoks, L. v. K., Ebert, D., and Meester, L. D. (2007). Host–parasite 'Red Queen' dynamics archived in pond sediment. *Nature*, 450:870–873.

Dybdahl, M. F. and Lively, C. M. (1998). Host-Parasite Coevolution: Evidence for Rare Advantage and Time-Lagged Selection in a Natural Population. *Evolution*, 52(4):1057–1066.

Engelstädter, J. (2015). Host-parasite coevolutionary dynamics with generalized success/failure infection genetics. *The American Naturalist*, 185:E117–E129.

Gandon, S. (2002). Local adaptation and the geometry of host–parasite coevolution. *Ecology Letters*, 5(2):246–256.

Gandon, S. (2004). Evolution of multihost parasites. *Evolution*, 58(3):455–469.

Gilman, R. T., Nuismer, S. L., and Jhwueng, D.-C. (2012). Coevolution in multidimensional trait space favours escape from parasites and pathogens. *Nature*, 483(7389):328.

Gokhale, C. S., Papkou, A., Traulsen, A., and Schulenburg, H. (2013). Lotka-Volterra dynamics kills the Red Queen: population size fluctuations and associated stochasticity dramatically change host-parasite coevolution. *BMC Evolutionary Biology*, 13:254.

Greenspoon, P. B. and Mideo, N. (2017). Parasite transmission among relatives halts red queen dynamics. *Evolution*, 71(3):747–755.

Hesse, E., Best, A., Boots, M., Hall, A. R., and Buckling, A. (2015). Spatial heterogeneity lowers rather than increases host–parasite specialization. *Journal of Evolutionary Biology*, 28(9):1682–1690.

Koskella, B. and Lively, C. M. (2009). Evidence for negative frequency-dependent selection during experimental coevolution of a freshwater snail and sterlizing trematode. *Evolution*, 63:2213–2221.

Kouyos, R. D., Salathé, M., and Bonhoeffer, S. (2007). The red queen and the persistence of linkage-disequilibrium oscillations in finite and infinite populations. *BMC Evolutionary Biology*, 7(1):211.

Lively, C. M. (2010a). A Review of Red Queen Models for the Persistence of Obligate Sexual Reproduction. *Journal of Heredity*, 101(suppl 1):S13–S20.

Lively, C. M. (2010b). An epidemiological model of host-parasite coevolution and sex. *Journal of Evolutionary Biology*, 23(7):1490–1497.

Lively, C. M. (2017). Habitat heterogeneity, host population structure, and parasite local adaptation. *Journal of Heredity*, 109(1):29–37.

Luijckx, P., Fienberg, H., Duneau, D., and Ebert, D. (2013). A Matching-Allele Model Explains Host Resistance to Parasites. *Current Biology*, 23(12):1085–1088.

Maynard Smith, J. and Price, G. R. (1973). The logic of animal conflict. *Nature*, 246:15–18.

McKane, A. J. and Newman, T. J. (2005). Predator-prey cycles from resonant amplification of demographic stochasticity. *Physical Review Letters*, 94:218102.

Nee, S. (1989). Antagonistic co-evolution and the evolution of genotypic randomization. *Journal of Theoretical Biology*, 140(4):499–518.

Neiman, M., Lively, C. M., and Meirmans, S. (2017). Why sex? a pluralist approach revisited. *Trends in ecology & evolution*, 32(8):589–600.

Nordbotten, J. M. and Stenseth, N. C. (2016). Asymmetric ecological conditions favor Red-Queen type of continued evolution over stasis. *Proceedings of the National Academy of Sciences USA*, 113:1847–1852.

Nuismer, S. L. (2017). Rethinking conventional wisdom: Are locally adapted parasites ahead in the coevolutionary race? *The American Naturalist*, 190(4):584–593.

Papkou, A., Gokhale, C. S., Traulsen, A., and Schulenburg, H. (2016). Host-parasite coevolution: why changing population size matters. *Zoology*, 119:330–338.

Peters, A. and Lively, C. (1999). The red queen and fluctuating epistasis: a population genetic analysis of antagonistic coevolution. *The American Naturalist*, 154(4):393–405.

Rabajante, J. F., Tubay, J. M., Ito, H., Uehara, T., Kakishima, S., Morita, S., Yoshimura, J., and Ebert, D. (2016). Host-parasite red queen dynamics with phase-locked rare genotypes. *Science advances*, 2(3):e1501548.

Rabajante, J. F., Tubay, J. M., Uehara, T., Morita, S., Ebert, D., and Yoshimura, J. (2015). Red Queen dynamics in multi-host and multi-parasite interaction systems. *Scientific Reports*, 5:10004.

Rambaut, A., Pybus, O. G., Nelson, M. I., Viboud, C., Taubenberger, J. K., and Holmes, E. C. (2008). The genomic and epidemiological dynamics of human influenza a virus. *Nature*, 453(7195):615.

Salathé, M., Kouyos, R. D., and Bonhoeffer, S. (2008). The state of affairs in the kingdom of the Red Queen. *Trends in Ecology & Evolution*, 23(8):439–445.

Sasaki, A. (2000). Host-parasite coevolution in a multilocus gene-for-gene system. *Proceedings of the Royal Society B: Biological Sciences*, 267(1458):2183–2188.

Schaffer, W. M. and Rosenzweig, M. L. (1978). Homage to the red queen. i. coevolution of predators and their victims. *Theoretical Population Biology*, 14(1):135 – 157.

Schenk, H., Traulsen, A., and Gokhale, C. S. (2017). Chaotic provinces in the kingdom of the Red Queen. *Journal of Theoretical Biology*, 431:1–10.

Schulte, R. D., Makus, C., Hasert, B., Michiels, N. K., and Schulenburg, H. (2011). Host–parasite local adaptation after experimental coevolution of caenorhabditis elegans and its microparasite bacillus thuringiensis. *Proceedings of the Royal Society of London B: Biological Sciences*, 278(1719):2832–2839.

Seger, J. (1988). Dynamics of Some Simple Host-Parasite Models with More than Two Genotypes in Each Species. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 319(1196):541–555.

Song, Y., Gokhale, C. S., Papkou, A., Schulenburg, H., and Traulsen, A. (2015). Host-parasite coevolution in populations of constant and variable size. *BMC Evolutionary Biology*, 15:212.

Strotz, L. C., Simões, M., Girard, M. G., Breitkreuz, L., Kimmig, J., and Lieberman, B. S. (2018). Getting somewhere with the red queen: chasing a biologically modern definition of the hypothesis. *Biology Letters*, 14(5).

Taylor, B. P., Cortez, M. H., and Weitz, J. S. (2014). The virus of my virus is my friend: Ecological effects of virophage with alternative modes of coinfection. *Journal of Theoretical Biology*, 354:124 – 136.

Van Valen, L. (1973). A new evolutionary law. *Evolutionary Theory*, 1:1–30.

Veller, C., Hayward, L. K., Hilbe, C., and Nowak, M. A. (2017). The Red Queen and King in finite populations. *Proceedings of the National Academy of Sciences of the United States of America*, 114(27):E5396–E5405.

West, S. A., Lively, C. M., and Read, A. F. (1999). A pluralist approach to sex and recombination. *Journal of Evolutionary Biology*, 12(6):1003–1012.

Woolhouse, M. E. J., Webster, J., Domingo, E., Charlesworth, B., and Levin, B. (2002). Biological and biomedical implications of the co-evolution of pathogens and their hosts. *Nature Genetics*, 32(4):569–577.

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Hinrich and Arne designed the research question. Hanna and Arne developed/adapted the models. Hanna conducted the analysis. All authors discussed and interpreted the results. Hanna wrote the initial draft. All authors revisited the manuscript critically and approved the final version.

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