Systematic review: Red queen hypothesis elucidates evolution of sexual reproduction

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Abstract

Sexual reproduction is an energetically costly process for organisms to accomplish in contrast to asexual reproduction. It requires organisms to compete for mates, exhibit pre-copulatory behaviors, and engage in the act of copulation, all of which are arduous behaviors that are not required in asexual reproduction. Nonetheless, sexual reproduction is evolutionarily conserved. The high prevalence of sexual reproduction among organisms remains unknown. Current literature supports the conservation of sexual reproduction due to its creation of genetic variation between organisms, which is particularly favored in unpredictable environments. One model which supports this is the Red Queen Hypothesis (RQH). The RQH states that organisms and their co-evolving parasites continually undergo genetic recombination in a positive-frequency dependent selection manner, to counter-adapt one another. Whereas, the parasite acts to evade the immune system of the host, the host's immune system acts to evade the entry and virulence of the parasite. As a result of the necessity for genetic variation in this evasion process, this parasite-host relationship reinforces sexual reproduction. In this review, I first introduce the theory of the Red Queen and the type of selection that it models. I then tested the validity of the RQH against various models including computer-simulated bacterium such as Pseudomonas fluorescens SBW25 and their parasitic hosts, and ancestral genomes of Denisovans and Homo sapiens. Lastly, I will conclude whether there are limitations to the Red Queen. While this review will not begin to cover the breadth of possible benefits to sexual reproduction, it will uncover real-world applications for how genetic variation is beneficial in combating pathogens.

Introduction

Living organisms reproduce via two mechanisms, including asexual and sexual reproduction. Both modes achieve the same result, the passing down of genetic material to offspring and increasing fitness within an individual. However, they differ in the percentage of genetic material that is passed along per parental genome, and the conditions necessary for each type of reproduction to occur. Asexual reproduction describes a parent cell duplicating its DNA to produce a genetically identical offspring. Asexually reproducing organisms will not yield genetic variation within a population's gene pool, unless in the case of random mutation. Modes of asexual reproduction typically include the duplication of the parental genome and cytoplasm within the cell, followed by a breaking away of the duplicate cell. Such modes include binary fission, snapping division, and budding (Bauman, 2016).

Alternatively, sexual reproduction is the generation of progeny via the gametic combination of two individuals, thereby creating genetically diverse offspring. This typically requires two haploid gametes fusing and fertilizing one another to create a diploid cell that is genetically diverse from the parental genomes. Recombination and crossing over of the parental chromosomes during fertilization allow for the zygote to remain genetically distinct from its parents' genomes (Bauman, 2016). However, because the zygote's DNA was yielded from the parent's DNA, parent and daughter cells are genetically similar. Overall, asexual reproduction only requires one parent cell for the formation of progeny and guarantees the full genome of the parent cell will be duplicated and passed down for generations. Whereas sexual reproduction requires two separate parent cells and assures only half of each parental genome will be passed down to progeny. Sexual reproduction is viewed as an energetically costly process compared to that of asexual reproduction. Organisms that engage in sexual reproduction must outwardly exert energy seeking a mate, engaging in both pre- and post-copulatory behaviors, and engaging in the actual act of copulation. Furthermore, these acts themselves do not ensure the organism will be successful in yielding a fertile and viable offspring. Whereas organisms that reproduce via asexual reproduction need not contribute energy to the mating process, rather can delegate energy into rapid growth and replication. This then begs the question as to why sexual reproduction evolved if it displays decreased rates of parental fitness than asexual reproduction. It remains unknown as to why sexual reproduction is so common among living organisms, despite the large energy consumption it requires and the lack of assurance that progeny will be formed (Salathé et al., 2009). Some literature argues that sexual reproduction allows for the breaking down of detrimental allele combinations that may otherwise diminish an organism's fitness (Neiman and Schwander, 2011; Salathé et al., 2009). Furthermore, sexual reproduction creates heritable variation within an individual, which can be beneficial for populations within an unstable environment (Case and Bender, 1981). Along this line of thought exists the Red Queen Hypothesis (RQH). The RQH states that species within predator-prey, or parasite-host associations are in a coevolutionary arms race with another, coevolving to counter-adapt the other organism. Because sexual reproduction yields high genetic variation within offspring, it may prevent both species from fully optimizing the weaknesses of their competitor, acting as "moving targets," and thereby increasing fitness (Ashby and King, 2015). Sexual reproduction allows this counter-adaption to continue in a continual feedback loop. In totality, the benefits of counter-adapting to parasites and hosts may outweigh the energetic costs of sexual reproduction.

This review article aims to investigate whether the RQH can account for the evolution and persistence of sexual reproduction. We will begin by investigating the validity of the RQH and whether it can be applied to real-life systems. This will allow us to evaluate models by which the validity of the RQH was supported and can be used to explain the evolution of sexual reproduction. We will transition to examining parasite-host models that do not support the RQH as a driving force for the evolution of sexual reproduction. Lastly, we will advance our understanding of the RQH by determining if this theory holds true for non-parasite-host or prey-predator models, such as cancer-host relationships.

Investigating the Validity of the RQH with Computer-Simulated Models

Computer-simulated models are a nimble way of modeling parasite-host interactions under a brisk timeline. Stochastic individual-based models can be used to determine the population dynamics between genetic variability and parasite contraction. Most stochastic individual-based models abide by the theoretical assumption that population sizes of both the host and parasite must remain constant over time, an idea that cannot hold true for populations within the real-world, due to extrinsic factors that may impact population growth or mortality (Ashby and King, 2015). Furthermore, they argue that virulence of the parasite must remain high, and genetic specificity between host and parasite organisms must be present (Auld et al., 2012). However, modern models have formulated calculations that allow these computer-simulated models to be more representative of real-world dynamics, not necessarily needing to abide by these intangible assumptions.

To account for parasitic infection, researchers have calculated the probability of epidemics and secondary infections impeding on population growth of hosts (Ashby and King, 2015). These calculations require the probability of an epidemic to be inversely correlated with genetic diversity of a host population. If these calculations are true, as genetic host diversity increases, the likelihood of contracting a parasite decreases (Ashby and King, 2015). One could argue that on a short-term scale, if host genetic variability is too high, then parasite prevalence will decrease to zero, rendering the parasite population extinct (Ashby and King, 2015). If the parasite population goes extinct, then there is no need for sexual reproduction to create further variation. Therefore, selection for sexual reproduction is primarily driven by delayed short-term effects (Salathé et al., 2009). Simulated models must then account for genetic diversity within the host population. Ashby and King (2015) did just that, measuring sexual diversity by the number of loci per haplotype within the host genome. They find that an intermediate level of diversity within sexually reproducing organisms is most favored in environments where parasites have low transmission rates (Fig. 1) (Ashby and King, 2015). Furthermore, sexual reproduction persisted in more simulations as the mean number of sexual haplotypes increased. If diversity within sexually reproducing organisms is too high, and transmission rates are decreased, then asexual reproduction will be more favored, as organisms are unlikely to encounter parasites and prioritize variation. Conversely, if diversity within sexual organisms is low, and transmission rates are high, then sexual organisms are likely to die and be driven to extinction, thereby eradicating sexual reproduction (Ashby and King, 2015). Ashby and King's model of sex by parasites was more holistic than older

models, as they incorporated density-dependent mortality, fluidity of recombination rates, and parasite immigration, all factors which may reflect population dynamics within the real-world (Ashby and King, 2015). They also properly addressed the idea that genetic variation of sexual individuals may differ in the real-world, a factor that has been held constant within previous models, but most surely is variable in actuality. Overall, their findings support the RQH, suggesting that intermediate genetic diversity does correspond with decreased parasite contractility, which also promotes the evolution of sexual reproduction. Because their parameters so highly reflect that of the real-world, this study may accurately demonstrate the RQH in effect today in parasite-host relationships. Furthermore, their results can be applied to all genetically diverse species that are involved in coevolving relationships, where hosts have intermediate genetic variability, rather than high or low.

As presented in the Ashby and King study, variance in transmission of the parasite must be modeled for a simulation to mimic real parasite-host relationships. However, variance in virulence (severity of the infection by the parasite) must also be modeled for the RQH to be upheld, because many factors such as temperature and resource availability may impact virulence of parasites in the real-world (Gibson et al., 2018). This is contradictory to previous RQH studies, which thought that virulence must remain high for the RQH to be upheld (Auld et al., 2012). Using a simulated parasitic model and female hosts that produced both sexually and asexually, Gibson et al (2018) found that variance in virulence promotes the evolution and maintenance of sexual reproduction in hosts (Gibson et al., 2018). This aligns with modern-day infection data, where not all parasites or microbes will yield the same severity of infection. These results support the RQH, suggesting that when parasitic virulence varies, which is seen between and within microbial species, then sexual reproduction will be most beneficial to adopt, allowing an individual to counter-adapt these microbes via their immune system.

Overall, modern-day computer-simulated models account for variables that may be infringed on real-life populations, but also variability within population dynamics. Such models have been able to vouch for the validity of the RQH, suggesting it is a driving force for the evolution of sexual reproduction. Despite computer models being useful tools for studying coevolution, some literature cautions when a simpler model is used, because the reality of biology cannot be easily quantified (Ochoa and Jaffé, 2002). Upon the entry of diploidy, non-random mate selection, variable population densities, and density-dependent selection into these mathematical models, the RQH is not supported (Ochoa and Jaffé, 2002). Researchers find that sexual reproduction in diploid hosts under nonrandom mating does not promote the acceleration of “defensive allele” mutations against parasitic infections (Ochoa and Jaffé, 2002). One strength of this study is that they incorporated three models of mating, random, assortative (choose mates like oneself) and distortive (choose mates dissimilar to oneself). They found that when sexually reproducing individuals choose mates dissimilar to themselves, fitness is increased (Ochoa and Jaffé, 2002). This does support the RQH, as organisms do not necessarily choose alike mates, and mating is not random within most organisms. However, one limitation of this study is that they allow parasite larvae to “infect” host individuals, which does not typically lead to disease in real-world application (Ochoa and Jaffé, 2002). This shows that despite computer-simulated models being a strong tool in studying coevolutionary biology, their limit truly resides behind the programmer. Nonetheless, most models have been able to model the Red Queen Hypothesis, demonstrating that as host diversity increases to an extent, then parasite infection decreases.

Investigating the Validity of the RQH With Empirical Data

Despite the convenience in modeling the RQH using artificial intelligence, it is important to note that these models are dependent on mathematical assumptions that may place constraints on applying them to real-life scenarios. Therefore, when validating the RQH, we must observe real-life relationships between parasites and their hosts. I will begin by discussing literature that supports the RQH as a driving force of sexual reproduction and follow up with literature that opposes this idea.

One of the best portrayals of a parasite-host relationship is between humans and the multitude of microbes we encounter daily. Researchers compared genomic hotspots between modern-day Homo sapiens and their ancestral sister species, the Denisovans (Lesecque et al., 2014). Hotspots are locations within the genome that recombination is most likely to occur and hypothesized to be conserved throughout the human lineage (Lesecque et al., 2014). However, genomic comparisons have found that recombination rates between Denisovans and Homo sapiens were not conserved, suggesting a selective pressure to switch to new targets (Lesecque et al., 2014). These genomic comparisons provide support for the RQH, as exposure to microbes, among other selective pressures, could have accounted for hotspot turnover and targets to change. In simple terms, high hotspot turnover is evidence of previously enacting parasite-host relationships. These genomic studies may act to contribute evidence towards the support of the RQH, but do not draw a direct cause-and-effect relationship between parasite infection and sexual reproduction. Measuring present host-parasite relationships provides the best insight as to whether the RQH is valid. Researchers measured microbial presence in vaginal and seminal fluid in 23 couples before and after sexual intercourse (Ma, 2022). They found the transmission of microbes during sex is random, and the populations of microbes between seminal and vaginal fluids are similar (Ma, 2022). This serves to directly display that sexual reproduction promotes transmission of microbes during sexual intercourse. Consequently, because sexually reproducing organisms are exposed to infection, they require the ability to counter-adapt the parasites they encounter. Thus, sexual reproduction would be favored to counter-adapt the ever-present microbes.

Animals are not the only organisms that can experience parasite-host relationships. Plants participate in numerous parasite-host relationships and reproduce sexually via outcrossing (Busch, 2007). Busch et al (2007) measured outcrossing rate and fungal parasitic infection occurrence in plants. They found that plants that reproduce sexually are infected with a higher number of pathogens than plants that reproduce asexually (Busch, 2007). Comparing prevalence of sexual organisms and parasite/infection susceptibility is by far a common method to determine if the RQH is acting on two species. The key to relating such studies to the RQH, is that the two organisms must be demonstrated to coevolve with another. Proximity between two organisms may be able to suggest coevolution, such was the case when comparing a population of freshwater snails, Potamopyrgus antipodarum, to local trematode parasites, Microphallus, that shared residence within a lake (Gibson et al., 2016). Over a three-year period, researchers found that sexually reproducing snails were more susceptible to trematode parasitism than their asexually reproducing counterpart snails (Gibson et al., 2016). These results reaffirmed Gibson’s studies in previous years, where sexual reproduction was more likely to arise in parasitic lineages, likely due to exposure to coevolving pathogens (Gibson and Fuentes, 2014).

Viruses and bacteria are two common asexually reproducing organisms. However, when left to coevolve, they can promote genetic variation between one another (Paterson et al., 2010). Researchers found that when the Pseudomonas fluorescens SBW25 bacteria and a viral phage were allowed to coevolve with one another, the genetic variation of the phage increased (Paterson et al., 2010). Furthermore, variation between bacterial generations increased as a function of infecting diverse hosts (Paterson et al., 2010). This suggests that coevolution between a host and a parasite promotes genetic variation. Overtime, genetic variation can be increased by evolving sexual reproduction, directly supporting the RQH.

Nonetheless, there is evidence of parasite-host models that refute the RQH, suggesting it is not a mechanism by which sexual reproduction could evolve. Tobler and Schlupp (2005) evaluated two different related fish species, one asexually reproducing Poecilia formosa and one sexually reproducing Poecilia latipinna. They measured the number of parasites that each organism hosts (Tobler and Schlupp, 2005). Nearly 200 fish from both fish species were collected in Texas and analyzed for parasitic infection. Researchers found there was no difference in parasitic load between the asexually reproducing and sexually reproducing relatives (Tobler and Schlupp, 2005). It is important to note that researchers did not adjust alpha levels, which is standard procedure when accounting for multiple ran tests (Tobler and Schlupp, 2005). One strength of this study is that fish were sampled from four different sites within Texas, and compared to parasites within those areas, distinguishing geographical area as a limiting factor (Tobler and Schlupp, 2005).

In totality, these studies discern that when two species are allowed to coevolve with one another, typically interacting in a parasite-host manner, then genetic variation increases among both species in a positive frequency-dependent manner. This variation is what allows the organisms to counter-adapt one another, thereby favoring sexual selection as means of genetic variation. This, in essence, is the RQH acting in real-time. Therefore, the RQH can be deemed as a valid mechanism which drives the evolution of sexual selection.

Advancing Our Understanding of the RQH in Non-Predator-Prey or Parasite-Host Relationships

While the RQH surely acts on parasite-host and predator-prey models, evolutionary biologists questioned whether it can be observed between genetically similar parasite-host models. For example, cancer cells which feed off living hosts for nutrition (Aubier et al., 2020). This is a unique way of viewing the RQH because cancer cells are derived from host cells but mutate and replicate at faster rates (Aubier et al., 2020). In other words, cancer and host cells are one in the same. This is unlike a parasite-host relationship, as parasites and hosts are two different domains that interact with one another. Nonetheless, host cells have been shown to have anticancer defenses, including but not limited to natural killer cells, cytotoxic lymphocytes, macrophages, and self-recognizing antibodies (Skrajnowska and Bobrowska-Korczak, 2019). Therefore, cancer cells and host cells should hypothetically be able to coevolve with one another. However, researchers found that because cancers are genetically similar to their hosts', fluctuating selection is rarely seen between the multicellular organisms and their cancers (Aubier et al., 2020). Therefore, sexual reproduction is difficult to maintain between these models.

As previously mentioned, the body has natural defenses to parasites and some cancers. What then happens when these defenses are heightened with modern technology, such as vaccines? Stockmann et al (2016) investigated the evolution of pneumococcal serotype in children with Invasive Pneumococcal Disease (IPD) from 1997 to 2014, before and after the introduction of pneumococcus conjugate vaccines (PCVs) (Stockmann et al., 2016). Pneumococcus, or Streptococcus pneumoniae is a bacterium that causes a range of infections but is most famously known for causing pneumonia in children and adults (Drijkoningen and Rohde, 2014). Researchers found the introduction of the PCVs was positively correlated with diversity of the pneumococcal serotype (Stockmann et al., 2016). Whereas these serotypes were not seen nearly to the same extent prior to vaccine introduction (Stockmann et al., 2016). While this research supports the RQH, it is interesting to see, in a vaccine-promoted society, the effects of modern technology on parasite-host relationships. This shows that the era of vaccines may reinforce the necessity for sexual reproduction as the arms-race between host and parasite is vastly quickening. In any case, modern advancements in technology have forced researchers to evaluate where and when the RQH can be applied, and how it may be impacted in a world where hosts are now consciously attempting to out-think their coevolving parasites.

Discussion

In conclusion, the RQH argues that coevolving organisms, such as those in parasite-host relationships, will favor greater genetic variation to counter-adapt one another. This review article sought to determine whether the RQH is a valid mechanism by which sexual reproduction could be favored. By investigating the RQH through the lens of computer-simulated models and empirical data, we have demonstrated the RQH is a plausible explanation for why sexual reproduction would be so common in living organisms, despite its energy and parental fitness costs. Mathematical models simulating parasite-host relationships may not necessarily illustrate the complexity of open systems. More factors, such as diploidy and mate selection need to be accounted for. Nonetheless, repeatedly, we have seen that host variation is positively correlated with contraction frequency of parasites or other microbes within the host, both in simulation and real-life models. Such real-life models have involved plants, humans, and nematodes. Moreover, we have seen that parasite-host relationships demonstrate positive-frequency dependent selection of their genomes. However, the RQH cannot be upheld for parasite-host-mimicking relationships, such as those concerning cancer and host species, suggesting that both participants must be genetically different enough from another.

Sexual reproduction is essential for creating genetic diversity among organisms. Most importantly, it allows for coevolving organisms to gain beneficiary genes that may be used to optimize their fitness against one another. Therefore, although the high prevalence of sexual reproduction in organisms cannot be indisputably defined, it is highly supported that the RQH allows the race between parasites and hosts to remain ongoing.

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