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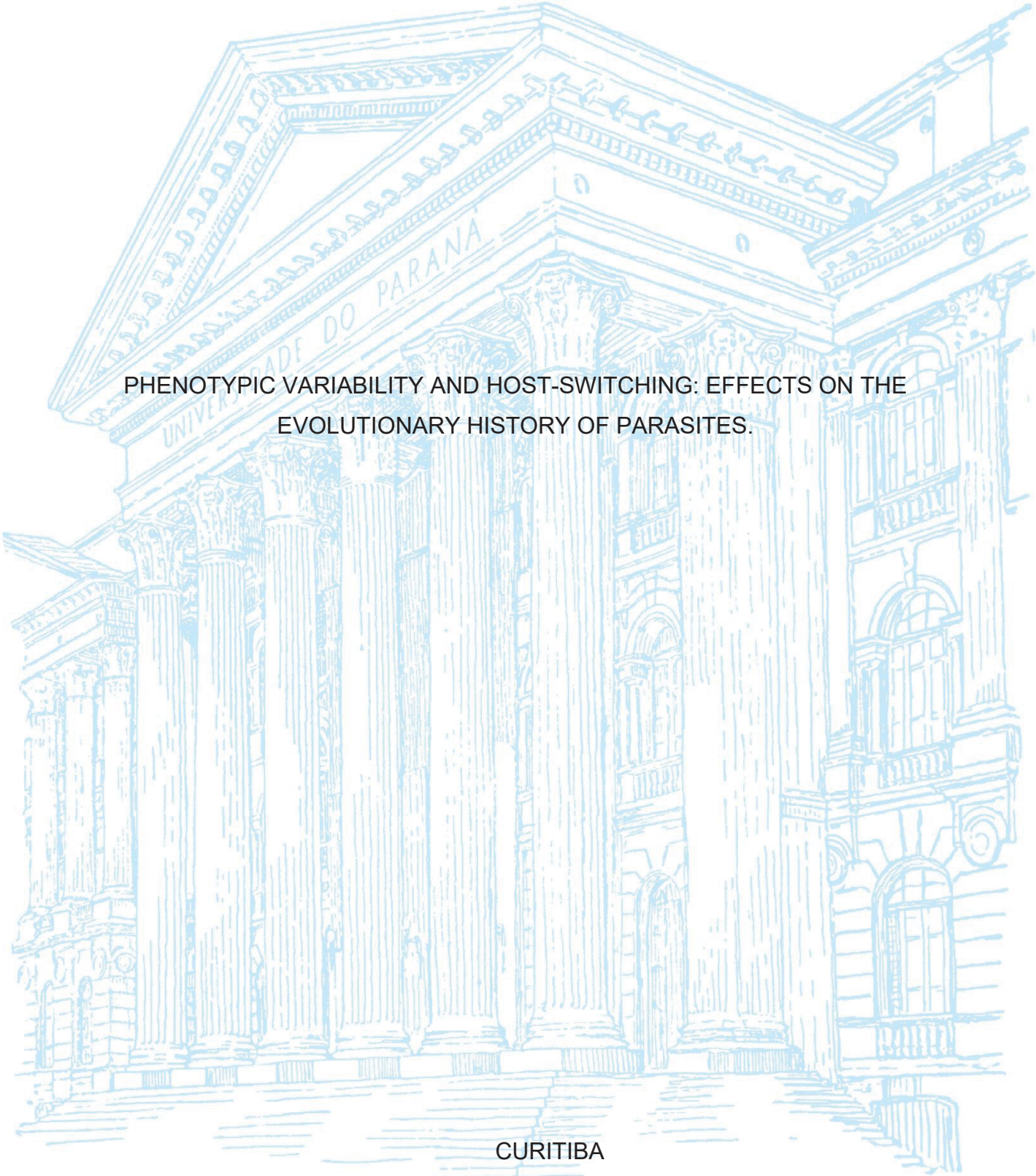

PHENOTYPIC VARIABILITY AND HOST-SWITCHING: EFFECTS ON THE EVOLUTIONARY HISTORY OF PARASITES.

CURITIBA

2024

ANGIE THAISA DA COSTA SOUZA

PHENOTYPIC VARIABILITY AND HOST-SWITCHING: EFFECTS ON THE EVOLUTIONARY HISTORY OF PARASITES.

Tese apresentada ao curso de Pós-Graduação em Ecologia e Conservação, Setor de Ciências Biológicas, Universidade Federal do Paraná, como requisito parcial à obtenção do título de Doutora em Ecologia e Conservação.

Orientadora: Prof.ª Dra. Sabrina Borges Lino Araujo

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Os membros da Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação ECOLOGIA E CONSERVAÇÃO da Universidade Federal do Paraná foram convocados para realizar a arguição da tese de Doutorado de **ANGIE THAISA DA COSTA SOUZA** intitulada: **Phenotypic variability and Host-Switching: effects on the evolutionary history of parasites** , sob orientação da Profa. Dra. SABRINA BORGES LINO ARAÚJO, que após terem inquirido a aluna e realizada a avaliação do trabalho, são de parecer pela sua APROVAÇÃO no rito de defesa.

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Dedico aos que acreditam na ciência e não fecham os olhos a ela por conveniência. Também dedico aos que lutam por um ensino público de qualidade, e à todas as mulheres que vieram antes de mim e abriram caminho para que eu pudesse estar aqui.

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“Ciência é a disposição para aceitar fatos, mesmo quando eles se opõem aos desejos.”

“Science is a willingness to accept facts even when they are opposed to wishes.”

(Skinner, 1953)

RESUMO GERAL

Doenças infecciosas emergentes (EIDs) são, além de uma questão de segurança alimentar e saúde pública, uma questão ecológica e evolutiva. O reconhecimento dessa condição aliado ao acúmulo de evidências de que os patógenos não são especialistas em seus hospedeiros evidencia a necessidade de compreender como ocorre a dinâmica de interação entre patógenos e hospedeiros. Enquanto a produção e análise de dados empíricos oferecem oportunidades para estudar sistemas complexos, modelos computacionais que simulam sistemas biológicos fornecem importantes insights para a compreensão dos processos ecológicos e evolutivos emergentes. Na primeira parte deste trabalho, Capítulo 1, revisamos modelos associados a dinâmica de EIDs, integramos seus resultados em uma suposta dinâmica de doenças infecciosas e fornecemos sugestões sobre como integrar esses achados em um protocolo de prevenção de EIDs (DAMA). Para a sequência do trabalho, Capítulo 2, analisamos o efeito da variabilidade fenotípica no sucesso de estabelecimento de parasitos em hospedeiros que representam diferentes distâncias filogenéticas hospedeiro original. Através de simulações *in silico*, contrastamos cenários com e sem variabilidade fenotípica entre os indivíduos presentes no propágulo e testamos três tamanhos de propágulos. Os parâmetros avaliados se mostraram positivamente relacionados com a incorporação de hospedeiros distantes ao repertório original dos parasitos. Além disso, demonstramos que variantes de parasitos pouco frequentes em suas populações originais e, portanto, possivelmente desconhecidas por nós, podem ser as responsáveis pela colonização e posterior estabelecimento em hospedeiros bastante distintos dos seus originais. Por fim, Capítulo 3, buscamos por evidências de eventos de troca de hospedeiros na evolução dos parasitas, e se estes sinais diferem de acordo com o aumento da diferença de pressão seletiva imposta pelos hospedeiros utilizados. Avaliamos alterações nas frequências de mutação, número de eventos de diversificação, extinção, número de linhagens, balanço da filogenia e aceleração da diversificação de populações de parasitas simuladas. Nós encontramos assinaturas temporárias da troca de hospedeiros em todas as métricas avaliadas, com efeito da distância entre hospedeiros apenas nas

medidas feitas a partir dos parasitas presentes exclusivamente no hospedeiro recém colonizado. Os estudos dessa tese contribuem com a compreensão de aspectos ecológicos e evolutivos entre parasitos e hospedeiros.

Palavras-Chave: Evolução, modelo baseado no indivíduo (IBM), padrões macroevolutivos, Paradigma de Estocolmo.

GENERAL ABSTRACT

Emerging infectious diseases (EIDs) are, besides food security and public health issues, an ecological and evolutionary issue. The recognition of this condition, combined with the accumulation of evidence that pathogens are not specialists in their hosts, highlights the need to understand how the dynamics of interaction between pathogens and hosts occur. While the production and analysis of empirical data give opportunities to study complex systems, computational models that simulate biological systems provide important insights for understanding emerging ecological and evolutionary processes. In the first part of this work, Chapter 1, we review models associated with EIDs' dynamics, integrate their results into a putative dynamic of infectious disease, and provide suggestions on how to integrate these findings into an EID prevention protocol (DAMA). In the workflow sequence, Chapter 2, we analyzed the effect of phenotypic variability on the success of establishment in hosts that represent different phylogenetic distances from the original host. Through in silico simulations, we contrasted scenarios with and without phenotypic variability between individuals in the propagule and tested three propagule sizes. The evaluated parameters were positively related to the incorporation of distant hosts into the parasites' original repertoire. Furthermore, we demonstrated that variants with low frequency phenotypes in their original populations and, therefore, possibly unknown to us, may be responsible for colonization and subsequent establishment in hosts that are phylogenetically quite different from their originals. Finally, in Chapter 3, we looked for signatures of host switching events in parasites' evolution, and whether these signatures vary according to how different the selective pressures imposed by the hosts involved. We evaluated changes in mutation frequencies, number of diversification events, extinction, number of lineages, phylogeny balance, and acceleration of diversification of simulated parasite populations. We found temporary signatures of host-switching in all metrics assessed, and the effect of distance between hosts had affected only measurements made from parasites present exclusively in the newly colonized host. These studies contribute to the understanding of ecological and evolutive aspects between parasites and their hosts.

Key-words: Evolution, host colonization, individual-based model (IBM), macroevolutionary patterns, Stockholm Paradigm

SUMÁRIO

1.1 INTRODUÇÃO GERAL

A ecologia evolutiva estuda como as linhagens biológicas se transformam ao longo do tempo, isto é, a história da origem e da extinção de espécies, bem como as suas causas. Para tal, ela leva em conta tanto processos ecológicos quanto processos evolutivos, buscando entender como eles agem simultaneamente transformando as linhagens biológicas e determinando os padrões de distribuição das mesmas (Mayhew, 2006; Wiens and Donoghue, 2004). Uma das áreas de estudo dentro da ecologia evolutiva são os sistemas de interação parasita-hospedeiro.

Por muito tempo acreditou-se que parasitas são extremamente especializados e, portanto, presos as espécies hospedeira que utilizam (por exemplo: Gioti et al., 2013; Rychener et al., 2017). No entanto, essa crença tem sido refutada por diversos estudos que avaliaram interações em diferentes grupos biológicos e também pelo aprimoramento de metodologias para reconstrução de filogenias que, como uma alternativa a coespeciação, apontam a troca de hospedeiros como um mecanismo comum de diverificação de parasitas (Charleston and Robertson, 2002; Hoberg and Brooks, 2008; Agosta et al., 2010; Giraud et al., 2010; Longdon et al., 2014; Doña et al., 2017; D'Bastiani et al., 2023).

A introdução de parasitos em novas áreas/hospedeiros gera a possibilidade de uso de recursos que anteriormente estavam indisponíveis. Alguns estudos sugerem que a disponibilidade de recursos/hospedeiros variados pode gerar um rápido aumento da diversificação de seus consumidores/parasitas (De Vienne et al., 2007; Braga et al., 2018; Freitas et al., 2022). Segundo a Hipótese da Oscilação (Janz and Nylin, 2008), uma espécie teoricamente especialista, ao ter oportunidade de interagir com novos hospedeiros pode tornar-se generalista. A expansão da sua distribuição devido aos novos recursos (hospedeiros) utilizados é seguida pelo processo de adaptação local, tornando-a novamente especializada e, com o fluxo gênico suficientemente diminuído em relação a sua população fonte, a especiação pode ocorrer. Tais eventos podem ser cíclicos, oscilando entre momentos de generalização e especialização.

A origem de novas interações entre parasitas e hospedeiros é explicada pelo conceito de *ecological fitting* (Janzen, 1985) que, aplicada ao parasitismo, implica na possibilidade de utilizar um novo hospedeiro (mudança ecológica) uma vez que exista *capacidade pré-existente* de utilizar os recursos que fornece, bem como a de superar as barreiras (físicas e/ou fisiológicas) que ele impõe. Adicionalmente, a mortalidade na população hospedeira causada por essa associação não deve comprometer a sobrevivência das espécies envolvidas. Além disso, para que associação persista a longo prazo, ambas as espécies (parasita e hospedeira) devem ser capazes de resolver conflitos que possam surgir ao longo do tempo (co-acomodação/co-adaptação) (Agosta and Klemens, 2008; Araujo et al., 2015). Obviamente, além da capacidade pré-existente, para que novas associações entre parasitas e hospedeiros aconteçam é necessário que ocorra a *oportunidade* de encontro entre as espécies, isto é, sua coocorrência espaço temporal, bem como a dos mecanismos de transmissão necessários. Infelizmente, o atual cenário em que vivemos, com o crescimento descontrolado da população humana, alterações climáticas, deslocamento de espécies e a conectividade incomensurável entre as mais diversas regiões do mundo, é um cenário perfeito para que esses encontros ocorram (Gubler, 2010).

Uma das formas que parasitas podem incorporar novas espécies ao seu repertório de hospedeiros é por colonização de hospedeiros que representem um recurso similar ao hospedeiro ancestral (Agosta and Klemens, 2008). Espécies próximas tendem a possuir características mais semelhantes entre si do que quando comparamos espécies mais distantes (Agosta and Klemens, 2008; Gilbert and Webb, 2007; Gómez et al., 2010). Neste contexto, filogenias podem funcionar como um *proxy* das características biológicas dos organismos. Pensando no sistema parasita/hospedeiro, o conservadorismo filogenético das características das espécies hospedeiras podem agir como um facilitador para que parasitas incorporem espécies filogeneticamente próximas ao seu repertório de hospedeiros, como já demonstrado por diversos estudos (Charleston and Robertson, 2002; De Vienne et al., 2007; Faria et al., 2013; Doña et al., 2017).

Ainda que a similaridade dos hospedeiros seja um facilitador, espécies mais distantes podem ser incorporadas ao repertório do parasita. Além da possibilidade de ocorrer convergência evolutiva de recursos, Araujo et al. (2015) demonstraram que a colonização de hospedeiros distantes pode ocorrer por um

processo de "*stepping-stone*". Neste processo a colonização de um novo hospedeiro é seguida pelo acúmulo de variabilidade sob a nova pressão seletiva e, a partir dessas novas características é possível alcançar hospedeiros que representem um recurso/pressão seletiva ainda mais distintos do que seria possível anteriormente.

Outro facilitador para que a colonização de novos hospedeiros ocorra é a variabilidade, fenotípica e genotípica, presente entre os indivíduos que compõe o propágulo. Quando uma espécie é introduzida em uma nova área/hospedeiro, em teoria, apenas uma amostra da sua diversidade é levada para a nova população (Efeito gargalo). A intensidade deste gargalo desempenha um papel importante na dinâmica ecológica e evolutiva das associações parasita-hospedeiro (McCrone and Lauring, 2018). Gargalos pouco severos, geralmente relacionados a um tamanho de propágulo (número de indivíduos) relativamente grande, permitem uma melhor amostragem da variabilidade da população doadora e aumentam a probabilidade de estabelecimento quando comparado a propágulos menores. Além disso, os gargalos pouco severos têm maior probabilidade de conter variantes raras, que podem ser essenciais para a colonização de novos hospedeiros (Brooks et al., 2019). Por outro lado, propágulos com poucos indivíduos podem limitar a diversidade da população fundadora (gargalo rigoroso), alterando drasticamente a frequência de variantes em relação à população doadora e agindo como um catalisador para a diferenciação entre populações (McCrone and Lauring, 2018).

Diferentes processos ecológicos, como os dois cenários apresentados acima, podem deixar registros na história evolutiva das espécies envolvidas. Entretanto, não é claro até que ponto o estudo de eventos de especiação pode recuperar o(s) processo(s) ecológico(s) que os determinaram. Neste trabalho, discutiremos como os modelos teóricos são ferramentas essenciais para entender a dinâmica entre parasitas e hospedeiros. Na primeira parte, Capítulo 1, revisamos modelos associados a dinâmica de EIDs, integramos seus resultados em uma suposta dinâmica de doenças infecciosas e fornecemos sugestões sobre como integrar esses achados em um protocolo de prevenção de EIDs (DAMA). Na sequência, Capítulo 2, analisamos o efeito da variabilidade fenotípica no sucesso de estabelecimento de parasitos em hospedeiros que representam diferentes distâncias filogenéticas hospedeiro original. Por fim,

Capítulo 3, buscamos por evidências de eventos de colonização de novos hospedeiros na evolução dos parasitas, e se estes sinais diferem de acordo com o aumento da diferença de pressão seletiva imposta pelos hospedeiros utilizados.

1.2 GENERAL INTRODUCTION

Evolutionary ecology studies how biological lineages changes over time, that is, the history of the origin and extinction of species, as well as their causes. To this end, it considers both ecological and evolutionary processes, seeking to understand how they act simultaneously transforming biological lineages and determining their distribution patterns (Mayhew, 2006; Wiens and Donoghue, 2004). One of the areas of study within evolutionary ecology is parasite-host interaction systems.

For a long time, it was believed that parasites are extremely specialized and, therefore, restricted to the host species they use (e.g., Gioti et al., 2013; Rychener et al., 2017). However, this belief has been refuted by several studies that have evaluated interactions in different biological groups, and also by the improvement of methodologies for reconstructing phylogenies, which, as an alternative to cospeciation, point to host-switching as a common mechanism of parasite diversification (Charleston and Robertson, 2002; Hoberg and Brooks, 2008; Agosta et al., 2010; Giraud et al., 2010; Longdon et al., 2014; Doña et al., 2017; D'Bastiani et al., 2023).

The introduction of parasites into new areas/hosts generates the possibility of using resources that were previously unavailable. Some studies suggest that the availability of varied resources/hosts can lead to a rapid increase in the diversification of their consumers/parasites (De Vienne et al., 2007; Braga et al., 2018; Freitas et al., 2022). According to the Oscillation Hypothesis (Janz and Nylin, 2008), a theoretically specialist species, when given the opportunity to interact with new hosts, can become a generalist. The expansion of its distribution due to the new resources (hosts) used is followed by the process of local adaptation, making it specialized again and, with sufficiently reduced gene flow in relation to its source population, speciation can occur. Such events can be cyclical, oscillating between moments of generalization and specialization.

The origin of new interactions between parasites and hosts is explained by the concept of *ecological fitting* (Janzen, 1985), which, when applied to parasitism, implies the possibility of using a new host (ecological change) as long as there is a *pre-existing capacity* to use the resources it provides, as well as the ability to overcome the barriers (physical and/or physiological) that it imposes.

Additionally, the mortality in the host population caused by this association should not compromise the survival of the species involved. Furthermore, for the association to persist in the long term, both species (parasite and host) must be able to solve conflicts that may arise over time (co-accommodation/co-adaptation) (Agosta and Klemens, 2008; Araujo et al., 2015). Obviously, in addition to pre-existing capacity, for new associations between parasites and hosts to occur, there must be an *opportunity* for the species to meet, i.e., their spatiotemporal co-occurrence, as well as the necessary transmission mechanisms. Unfortunately, the current scenario in which we live, with uncontrolled human population growth, climate change, species displacement, and the immeasurable connectivity between the most diverse regions of the world, is a perfect scenario for these encounters to occur (Gubler, 2010).

One way that parasites can incorporate new species into their host repertoire is by colonizing hosts that represent a resource similar to the ancestral host (Agosta and Klemens, 2008). Closely related species tend to have more similar characteristics to each other than when we compare more distant species (Agosta and Klemens, 2008; Gilbert and Webb, 2007; Gómez et al., 2010). In this context, phylogenies can function as a proxy for the biological characteristics of organisms. In the host-parasite system, the phylogenetic conservatism of the characteristics of host species can act as a facilitator for parasites to incorporate phylogenetically close species into their host repertoire, as already demonstrated by several studies (Charleston and Robertson, 2002; De Vienne et al., 2007; Faria et al., 2013; Doña et al., 2017).

While host similarity can facilitate host switching, more distant species can also be incorporated into a parasite's repertoire. In addition to the possibility of convergent resource evolution, Araujo et al. (2015) demonstrated that colonization of distant hosts can occur through a "stepping-stone" process. In this process, the colonization of a new host is followed by the accumulation of variability under the new selective pressure, and from these new characteristics, it is possible to reach hosts that represent a resource/selective pressure even more distinct than was previously possible.

Another facilitator for the colonization of new hosts is the phenotypic and genotypic variability present among the individuals that make up the propagule. When a species is introduced into a new area, in theory, only a sample of its

diversity is carried to the new population (bottleneck effect). As a consequence, adaptive responses to new selective regimes can limit colonization success. The intensity of this bottleneck plays an important role in the ecological and evolutionary dynamics of parasite-host associations (McCrone and Lauring, 2018). Loose bottlenecks, generally related to a relatively large propagule size, allow for better sampling of the variability of the donor population and increase the probability of establishment compared to smaller propagules. In addition, loose bottlenecks are more likely to contain rare variants, which may be essential for the colonization of new hosts (Brooks et al., 2019). On the other hand, propagules with few individuals can limit the diversity of the founding population (stringent bottleneck), drastically altering the frequency of variants in relation to the donor population and acting as a catalyst for differentiation between populations (McCrone and Lauring, 2018).

Different ecological processes, such as the two scenarios presented above, can leave signatures in the evolutionary history of the species involved. However, it is unclear to what extent the study of speciation events can recover the ecological process(es) that determined them. In this work, we will discuss how theoretical models are essential tools for understanding the dynamics between parasites and hosts. In the first part, Chapter 1, we review models associated with the dynamics of EIDs, integrate their results into a hypothetical dynamics of infectious diseases and provide suggestions on how to integrate these findings into an EID prevention protocol (DAMA). Next, in Chapter 2, we analyze the effect of phenotypic variability on the success of establishment of parasites in hosts that represent different phylogenetic distances from the original host. Finally, in Chapter 3, we seek evidence of colonization events of new hosts in the evolution of parasites, and whether these signatures differ according to the increase in the difference in selective pressure imposed by the hosts used.

2. CAPÍTULO 1

Chapter 1

Souza, A. T. C., Araujo, S. B. L., & Boeger, W. A. Modeling the Stockholm Paradigm: Insights for the Nature and Dynamics of Emerging Infectious Diseases. *An Evolutionary Pathway for Coping with Emerging Infectious Disease*, 78.

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Modeling the Stockholm Paradigm: Insights for the Nature and Dynamics of Emerging Infectious Diseases

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2.1 Abstract

Emerging infectious diseases (EIDs) are, besides a question of food safety and public health, an ecological and evolutionary issue. The recognition of this condition combined with the accumulation of evidence that pathogens are not specialists in their original hosts evidences the need for understanding how the dynamics of interaction between pathogens and hosts occurs. The Stockholm Paradigm (SP) provides the theoretical foundation to understand the dynamics of emergence of diseases and design proactive measures to avoid both the emergence and various reemergence of infectious diseases. In this review, we revisit the models that evaluate several aspects of the proposed dynamics of the SP, including the complex nature of the elements that have been associated with this new framework for the evolution of associations. We integrate the results from these studies into a putative dynamic of infectious diseases, discuss subordinate elements of this dynamic, and provide suggestions on how to integrate these findings into the DAMA (Document, Assess, Monitor, Act) protocol.

Keywords: individual-based model (IBM), agent-based model (ABM), computer modeling, evolution, emergent infectious diseases, DAMA (Document, Assess, Monitor, Act) protocol.

2.2 Introduction

Among the most worrisome consequences of the changes we are presently subjected to on Earth is the alarming increase in both emergence and reemergence of infectious diseases (EIDs) (Brooks and Ferrao, 2005; Fauci and Morens, 2012). Although many did not recognize it, emergences have accumulated in the recent and distant past, with serious consequences to humans, crops, and livestock (Morens et al., 2004; Brooks and Hoberg, 2007; Fauci and Morens, 2012; Brooks et al., 2014, 2019; Hoberg and Brooks, 2015; Brooks and Boeger, 2019; Trivellone et al., 2022).

We struggle to understand the dynamics of pathogens, having assumed they were a special and unique part of the biosphere. This has not allowed us to anticipate and prevent the emergence of new infirmities in the human-associated ecological network, and we remain greatly dependent on reactive measures following the establishment of a disease (Brooks et al., 2014). However, we are learning that biology is not fragmented in relatively independent systems (e.g., hosts and pathogens; plants and insect; predator and prey) that follow their own rules (Nylin et al., 2018). Since the beginning, life has been linked in a single, vast, and complex network that evolves under the influence of the interactions of its elements and the environment. Darwin was one of the first to recognize this and expressed it in his metaphor of an “entangled bank” (Darwin, 1872). He also recognized that the complex association among the involved actors was driven by independent elements—the nature of the organism and the nature of the conditions—and that this interaction results in common and universal properties of the entire biological system: evolution and ecology (Brooks and Agosta, 2012; Agosta and Brooks, 2020).

For a long time, we have ignored these most fundamental elements of evolution posed by Darwin, especially for pathogens. Pathogens are usually thought to be specialists to their hosts species and, hence, trapped in a single lineage of hosts (Haldane, 1951; Gioti et al., 2013; Rychener et al., 2017; Scheiner and Mindell, 2019). However, pathogens are resource specialists (Agosta et al., 2010), and specific sets of resources may be widespread among distinct host species. Often what has been assumed to be coadaptation or coevolution actually reflects ecological fitting (EF; see Janzen, 1985; Brooks and

McLennan, 2002; Agosta, 2006; Agosta and Klemens, 2008). More than a characteristic of antagonistic associations, EF is widely common relative to ecological changes in general (Wilkinson, 2004; Le Roux et al., 2017; Cipollini and Peterson, 2018) and influences the dynamics of ecological networks on this planet. EF is the most basal element of an emerging paradigm, the Stockholm Paradigm (SP) (Brooks et al., 2019), a theorical framework that accommodates Darwinian theory into the ecology and evolution of antagonistic associations. This paradigm provides a strong explanatory structure for the understanding of the present emergent infectious diseases crisis (Brooks and Hoberg, 2013).

For the SP, the most significant factors that drive the present crisis are the opportunities generated by changes in species distribution, of both or either hosts and pathogens, and the capacity of pathogens to exploit new hosts (Hoberg and Brooks, 2015; Brooks and Boeger, 2019). On Earth—with unchecked human population growth, climate change, and unmeasurable connectivity associated with human travel and commerce—we have generated a perfect scenario for the emergence of new associations among pathogens and compatible hosts to occur (Gubler, 2010). We introduce species in new areas through socioeconomic interests, force species to move because of habitat loss caused by landscape changes, and even carry them through geographic space both intentionally and unintentionally (Ribeiro Prist et al., 2022). Like numerous Trojan horses, actively or passively translocated host individuals may contain parasites that, once inserted in a new locality, can establish new associations with compatible resident species and cause diseases previously unknown (Hulme, 2014) or become hosts of local symbionts (Steward et al., 2022).

The SP recognizes that the interaction between actors that compose host-pathogen networks is complex (Brooks and Boeger, 2019). While the production of new or available empirical data provides opportunities to study complex systems (Patella et al., 2017), computer models simulating biological scenarios provide important insights for understanding the emerging ecological and evolutionary processes (Dieckmann and Doebeli, 1999; Giacomini, 2007). Models can also provide adequate testing for pure theoretical proposals; integrate empirical results and theory; simulate future scenarios; and explore putative solutions to minimize, mitigate, or even avoid the emergence of new antagonistic associations (Giacomini, 2007; Altizer et al., 2013; Christaki, 2015).

One set of models that can handle adequately the simulation of complex interactions that are expected in the biological system is known as the agent-based model (ABM), also known as the individual-based model (IBM) (Dada and Mendes, 2011). In this approach, individuals that compose the system are explicitly modeled. The characteristics of individuals can be freely defined by the modeler along with their behavioral rules of interaction with other individuals and with the environment in which they are inserted. It is from this set of rules of behavior, limitations, and individual needs that the system dynamics emerge (Giacomini, 2007). Thus, in this chapter, we revisit the models that evaluate several aspects of the proposed dynamics of the SP, including the complexity nature of the elements that have been associated with this new framework for the evolution of associations. We integrate the results from these studies into a putative dynamic of diseases, discuss subordinate elements of this dynamics, and provide suggestions on how to integrate these findings into the DAMA protocol.

2.3 Synthesis of the Models Developed under the Stockholm Paradigm

Since 2015, the time of publication of the first model that simulated theoretical assumptions associated with the SP (Araujo et al., 2015), several papers have been published that test many elements of this theoretical framework (see Table 4.1). Among other outcomes, subsequent models explored the accumulated evidence that the different elements of the SP represent emergent properties in a complex system that are directly linked to the ability of biological systems (e.g., molecules, species, communities) to realize EF (Janzen, 1985; Agosta, 2006).

Within the framework of the SP, pathogens (and all other consumer species) continuously explore their environments for associated host (resource species for consumers in general) at reach. Successful exploration may result in colonization by EF and, if successful, in the exploitation of new hosts (when the new association persists, and the evolutionary path of the pathogen is subjected to the new selective regime imposed by the new host). These steps compose what is widely called “host switching,” a term inadequate to the process of emergence of new symbiotic associations because there is no switch of hosts but

rather the expansion of the host repertoire (Braga and Janz, 2021) by the pathogen or parasites (or any consumer species). The interaction between opportunity and compatibility determines the possibility and the extent of exploration and exploitation (Araujo et al., 2015; Braga et al., 2018; Brooks et al., 2019). Compatibility defines the possibility of realizing EF and is the symmetrical expression of the capacities of the actors in the association (in this case, pathogen and host). Opportunity is the chance of encounter among potential actors of an association, and thus opportunity is determined by ecology, time, and space (Figure 1) (see also Combes, 2001; Araujo et al., 2015). The entire process of host-repertoire expansion triggers emergences or reemergences of new infectious diseases.

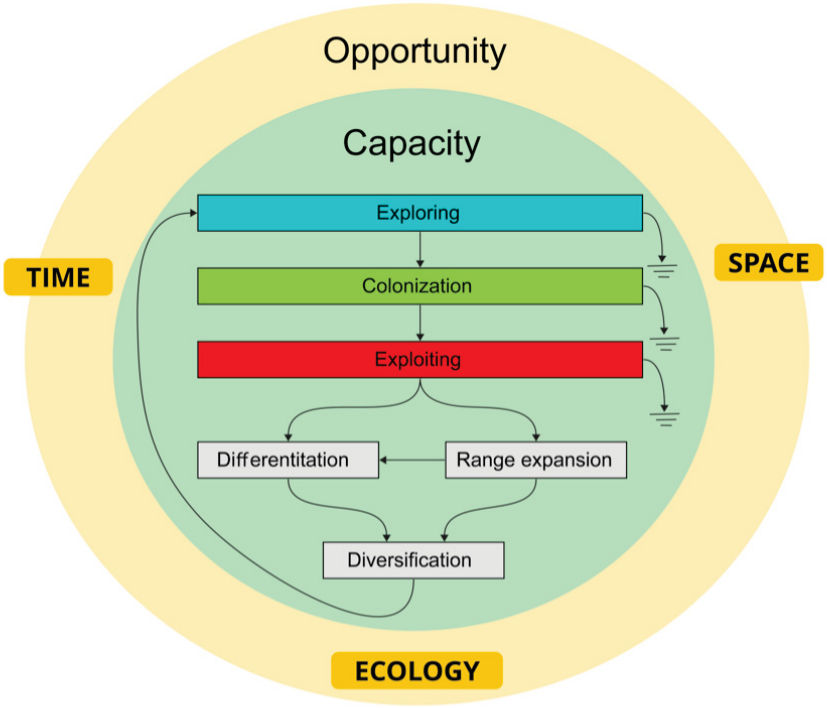

Figure 1. Pathogens explore, colonize, and exploit hosts according to their capacity and opportunity (determined by space, time, and ecology).

Table 4.1. Synthesis of models created from the theoretical assumptions associated with SP.

Article	Goals	Methods	Main results
Araujo et al. (2015)	To explore the potential of host-switches for a parasite species with variable phenotype amplitudes (expression of the fitness space).	- Pathogen individual is characterized by a phenotype value that was exposed to new host resources at each generation. - Hosts do not evolve but are characterized by a carrying capacity and an optimum phenotype value (p_r) imposed on pathogen. - At each pathogen generation, a new host, whose p_r value is randomly defined, is available. - Each individual pathogen has the same probability of dispersing to a new random host. - The model dynamics is composed of the cycles of sexual reproduction, dispersion to new hosts, and selection.	- Cyclical changes in the phenotype amplitude – colonization results in reduction and exploitation, in increase. - Colonization of a new host does not require prior evolutionary novelty - Survival of pathogen populations in sub-optimal adaptive regions. - Exploiting host increases the FS and the chance of host-switching to hosts more distant. - Host-switching between hosts representing highly divergent resources occurs by a stepping-stone process.
Braga et al. (2018)	To offer a mechanistic basis for the origins of macroevolutionary patterns of pathogen diversity and host range that emerges from a heterogeneous fitness landscape.	- Pathogen individuals are characterized by the species identity, a genotype (a binary string whose sum corresponds to individual phenotype). - Hosts do not evolve but are characterized by a carrying capacity and an optimum phenotype value (p_r) imposed on pathogen. - The phylogenetic distance between hosts is represented by the difference between p_r values imposed by each one. - Each individual pathogen has the same probability of dispersing to any other host. - The model dynamics are composed of the cycles of sexual reproduction, dispersion to new hosts and selection. As the model explicitly describes the individuals' genotype, speciation events are also recorded.	- Colonization of a new host increases phenotypic variation. - Use of multiple hosts facilitates speciation (divergent selection by including a new fitness peak). - Pathogen's species richness and phenotypic range are mainly affected by "mutation" rate. - Host range negatively affected by distance between hosts. - Phenotypic amplitude was positively correlated with species richness. - Host range oscillates through the time (specialists, generalist).

Feronato, Araujo & Boeger (2021)	To explore the significance and the interaction of the reproduction rate, the rate of novelty emergence and the propagule size for the success of colonization of new host species and its consequences to the phenotypic profile evolution of the new population.	- Pathogen individuals are characterized by the genotype (a binary string whose sum corresponds to individual phenotype). - The model considers a unique host, characterized by a carrying capacity and an optimum phenotype value (p_r) imposed on pathogens. - At the beginning of simulations, the host is not parasitized, and *n* pathogens individuals (with phenotype p_0) are allowed to attempt colonization the host. - Each time step represents a new cycle of asexual reproduction, and selection.	-Maximization of all parameters (evolutionary novelty rate, reproduction rate, and propagule size) results in a synergetic facilitation of the colonization. - The evolutionary novelty rate has the smallest effect on the establishment success in the new host. - Higher evolutionary rates accelerate population growth. - Population size stabilizes (reaches maximum) before phenotypic stabilization. - Even in the absence of evolutionary novelty, and in a suboptimal condition, population size reaches carrying capacity. - Small evolutionary novelty rates ($<10^{-3}$) result in a smaller phenotypical range, the loss of ancestral phenotypes, and a delay for the population to stabilize around the new optimum imposed by the newly colonized host when compared to larger evolutionary novelty rates.
D'Bastiani et al. (2022)	To understand how host-switching intensity affects parasite evolution.	- Pathogen individuals are characterized by their used host species and genetic identity. - Hosts evolve through time without being influenced by the presence of the pathogens (based on empirical phylogenies). - Each host species has the same carrying capacity. - Sexual reproduction. - Continuous host-switching, with probability of success inversely proportional to evolutionary distance between hosts. - Comparison with nine empirical interaction networks using Sackin Index (balance of phylogenetic trees) and beta diversity.	- The model was able to reproduce ecological and evolutionary patterns of the parasites (beta diversity and Sackin Index) of all communities analyzed, suggesting that host-switching is determinant in parasite evolution. - Beta diversity is inversely proportional to host-switching intensities, suggesting that this metric can be proxy for host-switching intensity. - The variation in the Sackin Index reveled that stochastic host-switching events can change the evolutionary trajectory of parasites.

The first three models (Araujo et al., 2015; Braga et al., 2018; Feronato et al., 2021) have the following elements in common: (1) they explicitly describe each pathogen individual, characterized by a phenotype (zi); (2) the resources impose selection pressure on parasite individuals around an optimum phenotype (zh); and (3) individuals that survive this selection can reproduce, and the offspring inherits the parental phenotype with a probability of incorporating a variation due to the random origin evolutionary novelties (e.g., mutation). These elements essentially follow Darwin's theory of evolution (Darwin, 1872) (Figure 2)—surviving organisms reproduce according to their frequency within the parental generation. The fitness space (FS) in the model is assumed to be correlated to the phenotypic amplitude of a population in each generation (PA in Figure 2b), since the greater the phenotype amplitude, the wider is the range of possible hosts with which the pathogen could interact.

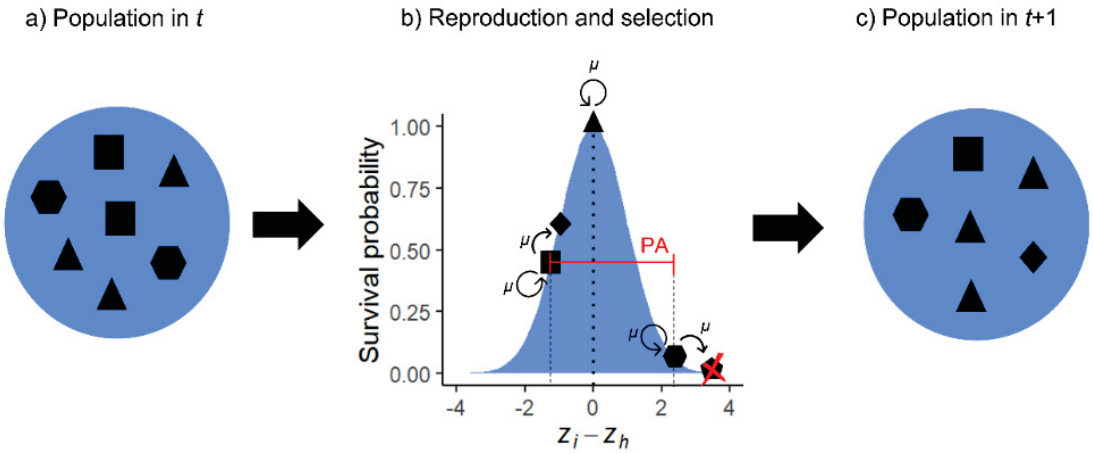

Figure 2. Population dynamics common to IBMs of Araujo et al. (2015); Braga et al. (2018); Feronato et al. (2021). a) In time *t*, the parasite population inhabiting a given host (blue circle) is composed of three different phenotypes (triangle, square and hexagon). b) All phenotypes survive and reproduce in the host, however, the probability of survival decreases with the increase in the distance between the phenotype expressed by the individual (z_i) and the optimal phenotype value imposed by the host (z_h). Reproduction can occur in a sexual (Araujo et al., 2015; Braga et al., 2018) or asexual way (Feronato et al., 2021), the offspring inherits the parental phenotype with a μ probability of incorporating evolutionary novelties and c) individuals who survive the selection imposed by the host form the population present in *t* +1. The phenotype amplitude indicated by PA (in graph b) is correlated to the concept of Fitness Space.

The first model (Araujo et al., 2015) evaluated the relationship between the historical fluctuations of the FS and the potential for pathogens to colonize

new hosts by EF. At each time step, a reproductive cycle occurs, and a new host is available to be colonized (see Figure 3). A fraction of the pathogen individuals explores the available host and, when colonization is successful, only the evolution of this new population is subsequently recorded. Due to the model dynamics, the phenotypic amplitude (i.e., the FS) can vary and evolve by accumulating evolutionary novelties through time. The simulations showed that (1) successful host colonization does not require “adaptive” evolutionary novelties emerging immediately before colonization, (2) that the FS varies in amplitude (i.e., it oscillates), (3) that pathogen populations can survive for long periods under suboptimal conditions, and (4) that host colonization can occur by a “stepping-stone” process (subsequent colonization of hosts depicting different nature of resources).

Subsequently, Braga et al. (2018) extended the previous model (Araujo et al., 2015) by allowing the evolution of the pathogens in more than one host to coinhabit the same community and by monitoring the evolution of all pathogen populations simultaneously. During one generation, a certain proportion of the pathogens can migrate to a randomly chosen host. When the exploration of the new host results in its colonization by the pathogen, the same lineage of pathogens exploits this host and evolves under different selective regimes. The model describes the pathogen genome and restricts mating to a minimal genotypic similarity. This approach determines the possibility of gene flow among individuals and was used as a proxy to delimit species. When gene flow is reduced between populations of pathogens (imposed by the limits of phenotypic similarity), a speciation event occurs. The model shows that the exploitation of new hosts increases phenotypic and genotypic variation of the pathogen population, which, with reduction in reproductive exchange, may result in speciation of the pathogen, generating host range cycles through time (= oscillations).

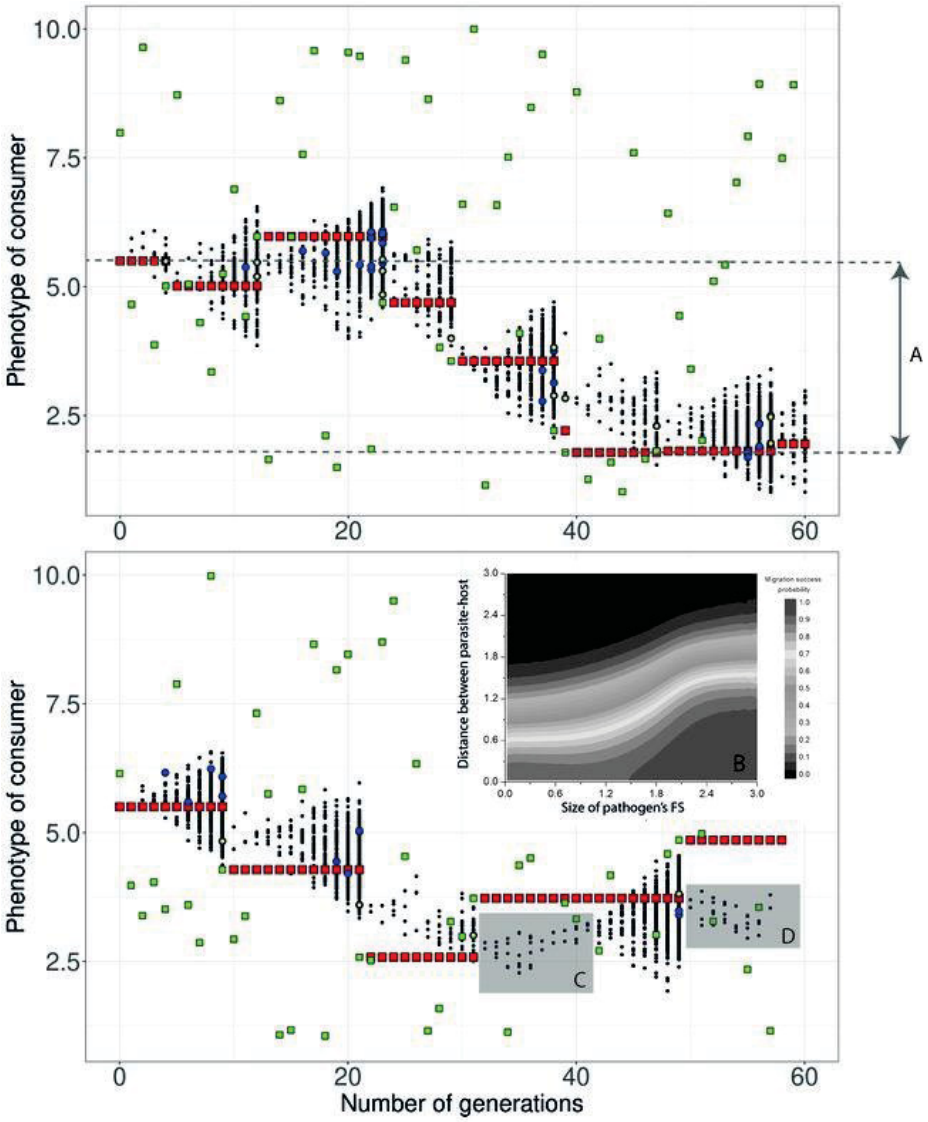

Figure 3. Two independent simulations of temporal evolution of the phenotype of the pathogen population (consumer). This graph was generated from "HostSwitch" package (Trivellone et al., 2021) based on the model of Araujo et al. (2015). The green squares represent the optimum phenotype of the pathogen to survive on that specific host resource; red squares are host resources in use at that moment; black dots = pathogen's phenotype. A = distance between the first and final host in a stepping-stone chain of host expansion; B = mean values of successful colonization of new host resources according to the distance pathogen-host and the size of the pathogen's Fitness Space; C and D. individual parasite phenotypes surviving for many generations of a no-ideal host.

The model by Feronato et al. (2021) challenged pathogens to explore new host resources and evaluated the influence of demographic parameters of pathogens (reproduction rate, rate of novelty emergence, and propagule size) on the success of colonization. In the beginning of the simulation, the pathogen population had a single opportunity to colonize a predetermined host resource;

following successful colonization, subsequent steps represented new cycles of asexual reproduction and selection. Supporting the model by Araujo et al. (2015) and contrary to the prevailing belief, the rate of novelty emergence (e.g., mutations) depicted a secondary contribution to the success of colonization—even in the absence of emergence of evolutionary novelties, pathogens could survive under suboptimal conditions and reach the carrying capacity imposed by the host.

Finally, motivated by the empirical suggestions that host expansion of a pathogen lineage is common among closely related host species (Braga et al., 2015), D'Bastiani et al. (2021) designed a model to estimate the intensity of host-switching observed in nature and how this parameter affects the phylogenetic history of parasites. In this model, the evolution of a parasite occurs freely along preestablished phylogenies of hosts, with the possibility of migration among hosts at any time. Based on the idea that phylogenetically close hosts present more similar resources (Gilbert and Webb, 2007; Streicker et al., 2010; Imrie et al., 2021), D'Bastiani et al. (2021) assume that the probability of success in the exchange of pathogens between closely related hosts is high and that this probability decays as the hosts diversify and differentiate. The model reproduced the ecological and evolutionary patterns of all nine empirical studies analyzed, suggesting that host-switching is a strong determinant in parasite evolution and diversification. The ecological and evolutionary patterns were measured by the dissimilarity of parasite composition per host species (beta diversity— Baselga, 2010, 2013) and the balance of the phylogenetic tree (Sackin index—Blum and François, 2005), respectively. The variation in the Sackin Index revealed that stochastic host-switching events (leading to host range expansion) can change the evolutionary trajectory of parasites. Beta diversity was inversely proportional to host-switching intensities, suggesting that this metric can represent a proxy for host-switching intensity.

Although the mathematical models presented here enable a good understanding of resource-pathogen dynamics, the code of all these models does not provide a user-friendly interface, restricting many potential users from manipulating the model with their own data sets. Recently, Trivellone and collaborators created an R package, "HostSwitch" (Trivellone et al., 2023), that provides several accessible functions to explore host-switching dynamics. The

authors implemented and expanded the original model by Araujo et al. (2015). Users can easily change model parameters and plot the outputs (see Figure 3 as an example). They also indicate a method to parameterize the model using three real-world scenarios drawn from selected ecology, agriculture, and parasitology literature. This publication is an effort to facilitate the use of theoretical tools, helping the users build hypotheses of pathogens' evolution.

2.4 Insights derived from the simulations

2.4.1 Connecting the elements of the Stockholm Paradigm through complexity levels

The series of models developed under the framework of the SP strongly suggest the recognition that the eco-evolutionary dynamics of infectious diseases represent a complex system. Species of such associations are never playing in pairs but in a network of interactions among many other species, something that creates a level of complexity such that its behavior cannot be understood nor predicted easily. The rules of the "game" of interactions may be simple, but complexity comes from interaction among multiple agents. Published models (Araujo et al., 2015; Braga et al., 2018; D'Bastiani et al., 2021) indicate that at least one of the elements of the SP, oscillation, is a putative emergent property of communities in which interactions are driven by EF. Taxon pulse is the interaction between the increased opportunity associated with environmental disruptions, and thus it likely also represents an emergent property in this chain of complexity—an emergent property resulting from the interaction of communities with potential for oscillation and an unstable environment.

By exploring the available capacity represented by sloppy fitness space (SFS) (Agosta and Klemens, 2008; Agosta et al., 2010), a pathogen can colonize new hosts, exploiting new elements of a community (i.e., the resources offered by hosts). In the simulation presented in Araujo et al. (2015), some of the individuals in the pathogen population try to colonize a new host, but just a fraction succeeds. Consequently, the FS of the population in this new host is reduced compared to the original host. During exploitation of the new host, the accumulation of evolutionary novelties often resulted in an increase of the FS but

presented a distinct nature according to the influence of the new host-associated selection. This oscillatory nature of the simulated FS in Araujo et al. (2015) strongly suggested the emergence of oscillations (Janz and Nylin, 2008) in host repertoire, another fundamental element of the SP (Brooks et al., 2019). To test for the evidence that evolution under EF may generate oscillations as an emergent property, in the following model, the opportunity to colonize variable hosts was constant and all pathogen populations were followed over time. The simulations of Braga et al. (2018) replicated the pattern expected from the hypothesis of oscillation proposed by Janz and Nylin (2008), in which pathogens' lineages oscillate between generalists and specialists through time. Hence, the result supports the observation that host oscillation is an emergent property of a community of interacting species that change their ecology by EF, and that oscillation does not necessarily require the geographic vector suggested by Janz and Nylin (2008).

The evidence that the SP is composed of elements defined as fundamental (EF) and emergent properties (oscillation and taxon pulse) reveals the flexibility of the many levels of complexity of biological systems. This flexibility is far greater than that expected under the prevailing paradigm of evolutionary theory (i.e., maximum adaptation/specialization). That includes greater than expected flexibility at the metabolic (Khersonsky et al., 2006; Carbonell et al., 2011), cellular (Margulis, 1971; Alison et al., 2002), organism, population (Schradin et al., 2012), and community levels (Wilkinson, 2004; Malcicka et al., 2015; Hui and Richardson, 2018). Hence, this property of life, replicated at all levels of complexity, is certainly a fundamental element of evolution that favors the survival of life on an unstable planet and biosphere (Brooks and Agosta, 2012; Agosta and Brooks, 2020). This relatively great flexibility of the actors involved in the complex system and the instability of the planet also increases the capacity of pathogens to explore, colonize, and exploit available hosts. That is the fundamental reason for the ongoing emerging infectious disease crisis on a planet greatly interconnected by human activities and under climate change.

2.4.2 The dynamics of infectious diseases under the SP

Modeling has allowed recognition of ecological and evolutionary patterns of pathogens during processes of exploration, colonization, and exploitation of host species in a continuously changing community caused by geographical, geological, climatological, and inherent biological processes (Brooks et al., 2019). Evolution is, despite anecdotal knowledge, a highly conservative process (Gómez et al., 2010), and this most likely reflects conservatism of resources (of the host) and capacity (of the pathogen). Closely related hosts have a greater possibility of sharing the same characteristics (e.g., biochemistry, physiology, morphology) that are required by pathogens as resources. Correspondingly, closely related species of pathogens likely depict similar capacities to utilize these hosts that share traits (especially those representing the fundamental resources for the maintenance of a pathogen's infrapopulations). Combining these elements, it is evident that the history of any association is about compatibility (and potential compatibility) between the actors involved (Gilbert and Webb, 2007; De Vienne et al., 2009). However, the fit between phylogeny and compatibility is not perfect nor equally effective in determining the extent of the arena of possible host incorporation by pathogens (Gilbert and Webb, 2007) since capacity of the pathogen and the nature of the resource (a host property) can be homoplasious (e.g., subjected to convergent evolution) (Brooks and McLennan, 2002).

The IBM simulations of host repertoire expansion performed by D'Bastiani et al. (2021) assumed host phylogeny as a proxy for pathogens' colonization. They assumed that the closer the phylogenetic relationship between the donor and the recipient host species, the greater the probability of successful host expansion by the simulated parasite species. Simulated relationships resulted in scenarios compatible with empirical studies when host repertoire increase is considered (i.e., host-switching). Moreover, the authors recovered the expected pattern that host-repertoire expansion is higher on a local than regional scale. This supports the conclusion that intense exploration favors new associations. This is an expected result for a group of closely related host species—and the putative intensity of host repertoire expansion should be smaller for an entire community composed by variably related hosts. The study also supports the

conclusion of Braga et al. (2018) that although evolution of pathogens within a community may generate cycles of oscillation in host repertoire (i.e., specialization), and that these tend to stabilize as closely related hosts, that is, those bearing a similar nature of resources are colonized and exploited (Brooks et al., 2019).

This scenario of multihost dynamics is compatible with the accumulated knowledge on the ecology of associations (Nylin et al., 2018; Brooks et al., 2019; Agosta and Brooks, 2020), and it recently became more conspicuous in the ongoing SARS-CoV-2 pandemic (Fenollar et al., 2021; Boeger et al., 2022; Hoberg et al., 2022; Kuchipudi et al., 2022). SARS-CoV-2 further exposed the importance of opportunity, especially those derived from human activities, in the dynamics of antagonistic associations (Hoberg et al., 2022).

Temporal variation in the presence or in the levels of permeability of barriers among communities can result in changes in species distributions and, as a consequence of this variability, large- or small-scale changes can occur in the structure of ecological networks, which offer new opportunities for the emergence of new ecological interactions (Hoberg and Brooks, 2010). This scenario can facilitate and even enable an unmeasurable intensity of change in the opportunity of encounter—in time, space, and ecology—between pathogen and host species. However, species (including actual or potential hosts) in a community are usually not each other's closest relatives and, thus, communities present different combinations of pathogens and resources in both quality and quantity (Figure 4.1).

Whenever opportunity exists, pathogens are continuously probing the nature of the resource provided by different host species within a community (Figure 4.2). Some explorations (exploratory infections) are successful, resulting in colonization and exploitation (Figure 4.3), but most are likely not (Figure 4.3—extinction of the red circle in the dark pink host). Expected differences in the success of colonization of new hosts are dependent on a series of factors that influence compatibility among pathogens and hosts, and many of these have been revealed by the simulations generated with IBMs (Araujo et al., 2015; Braga et al., 2018; Feronato et al., 2021).

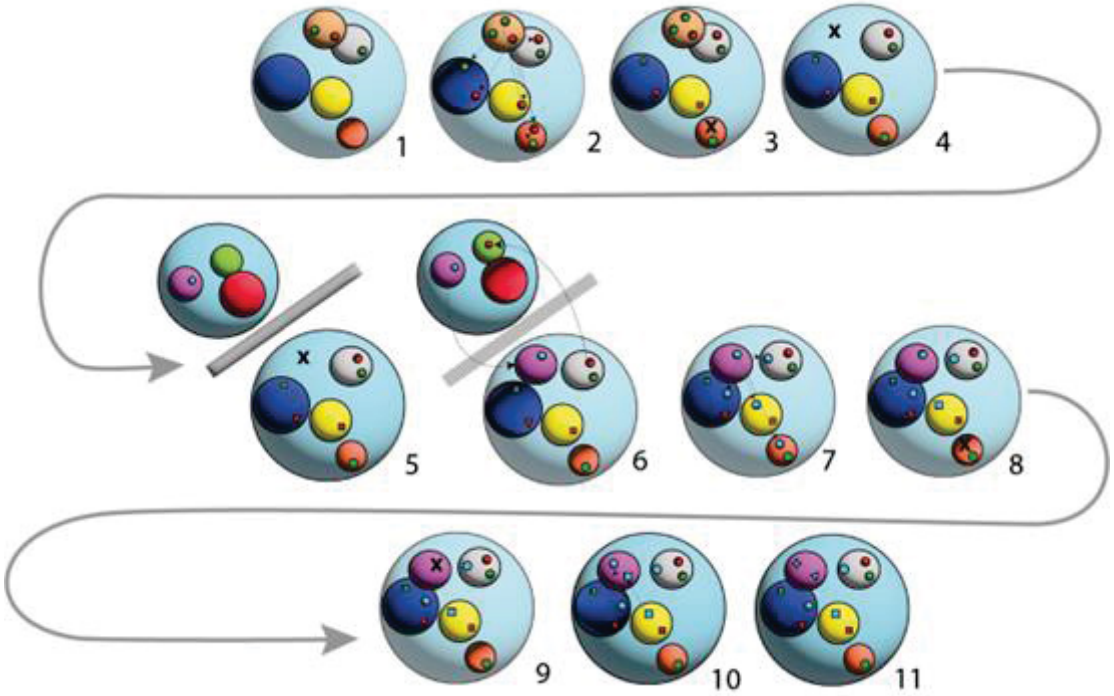

Figure 4. The putative dynamics of diseases under the perspective of the Stockholm Paradigm. 1. In an isolated community five host species are present, two of which are in association with pathogens (the orange species with two pathogen lines – green and red – and the ash also parasitized by the green pathogen. 2. Still in isolation, pathogens exploit the species available when the opportunity presents itself. 3. Exploration may result in successful or non-successful colonization (failure to establish the red pathogen represented by an X). The strains capable of surviving and reproducing in the new hosts eventually differ from their ancestors (pathogens with new shapes represent descendent strains of the ancestral forms with the same color). 4. The loss of a host (X) does not imply coextinction of the strains of pathogens with which it was associated, because the same pathogen lineage may be associated with more than one host species. 5. Two communities remain isolated by a barrier (grey bar). 6. The loss or increase of barrier permeability allows migration of hosts and pathogens between communities. 7. A new phase of exploration of new hosts takes place. 8. During the period of stability and exploitation of hosts whose association was established, new diversification events occur. 9. The loss (X) of pathogens, natural or human-mediated, can happen. However, 10. Retro-colonization from a descending variant (light blue square) present in the population and that has retained the ability to survive in the ancestral host can happen. 11. A new period of stability follows. No demography is represented here.

Both stochastic and deterministic processes are involved in shaping the success of each colonization attempt of compatible hosts (Araujo et al., 2015; Feronato et al., 2021). One of the most significant results of the simulation of Araujo et al. (2015) indicates that even when the phenotype amplitude of a pathogen population is null, colonization of other host species with the same or

slightly different compatibility (i.e., hosts presenting different resource quality and/or quality) is still possible (Figure 3). That same simulation also suggested that there is an upper limit to the extent of successful colonization—that is, hosts may represent a set of resources too distant from that of the original donor species to be successfully colonized. In this case, exploration occurs but colonization—and hence exploitation—is not achieved, and the pathogen cannot exploit the resource provided by the host (Figure 3, inset B).

However, empirical evidence and simulations have recovered a process that makes it possible for pathogens to indirectly colonize hosts bearing relatively distant resources. This is known as the host-repertoire expansion by steppingstone (Araujo et al., 2015; Braga et al., 2015). In fact, stepping-stone embraces distinct processes, involving either opportunity or capacity. Hosts, intermediary in the chain of transmission, may favor contact between compatible host species. For instance, while bats are important reservoirs for zoonotic viruses (Calderon et al., 2016), the opportunity of contact with humans is limited and transmission often occurs through other hosts that bridge ecological and spatial distances between viruses and humans (Hoberg et al., 2022). There is no logical reason to believe that this type of transmission involves only a single species intermediary in the expansion to new hosts. Given time, especially for microorganisms that depict fast evolutionary rates, stepping-stone may also facilitate colonization of distant host resources through changes in the nature of the capacity space (CS) and FS of the pathogen in response to gradual and sequential influence of the selection imposed by hosts intermediary in the process (Figure 3) (Araujo et al., 2015; Brooks et al., 2019).

Successful colonization is also strongly associated with inherent and demographic properties and processes of the pathogen attempting to populate the new hosts. Feronato et al. (2021) varied key demographic features — reproductive rate, rate of emergence of evolutionary novelties (e.g., mutations), and propagule pressure—for simulated pathogens and concluded that propagule pressure was the most important in determining the success of colonization of new hosts. Contrary to what is commonly assumed, the rate of emergence of new evolutionary novelties of the pathogen species was shown to be less important to ascertain the success of colonization. However, synergy among these simulated parameters maximizes the colonization and apparently provides

explanatory evidence for the observed success of microorganisms in expanding to new hosts. Maximizing the values of the evaluated parameters during simulation results in an unexpected increase in the success of colonization of hosts representing resources of variable compatibility by parasites that are prolific, present high mutation rates, and generate large propagule sizes, such as viruses.

Once the process of colonization of a new host species is successful, the pathogen population may have different outcomes, depending on the heterogeneity of the resources offered by the parasitized hosts (Braga et al., 2018), and it is strongly dependent on the lagload (Smith, 1976) imposed by the new host species. Lagload (Smith, 1976) originates by differences in the nature of the new resource being explored when compared to the donor host—the difference in selective pressure between the original and the newly colonized host species. Change in lagloads may result in the qualitative and quantitative accumulation of evolutionary novelties (mutations for viruses, for instance) in the pathogen (Bashor et al., 2021, 2022). If there are no significant differences between the nature of the resources, the pathogen may not diverge rapidly from its original profile (e.g., genetic, phenotypic) unless demographic processes take place (i.e., intense bottleneck following isolation in the new host). In this case, from the view of the observer, the pathogen has simply expanded its host repertoire (sensu Braga and Janz, 2021) (Figure 4.3—the green and red circles). However, if the pathogen can be subjected to a sufficiently strong lagload that may impose relocation of the realized fitness space (RFS) within the FS (Figure 5), the accumulation of evolutionary novelties (e.g., mutations in viruses) can generate new variants or even new species (Figure 4.3—red triangle and square, and green square). This scenario is also well represented by the dynamics of emergence of variants of SARS-CoV-2 (Boeger et al., 2022; Kuchipudi et al., 2022). Boeger et al. (2022) suggest that long branches in the phylogeny of selected SARS-CoV-2 sequences of the spike protein is evidence of faster evolutionary rates imposed by a larger lagload that originated from the virus colonization of new mammal host species.

From Figure 4.1 to Figure 4.4, pathogens are alternating between exploring, colonizing, and exploiting—under stable opportunity within an isolated community. The simulations (Araujo et al., 2015; Braga et al., 2018) strongly

suggest that this dynamic results from the cyclic variation of the capacity of the pathogen—that is, variation in FS—a consequence of demographic processes associated with colonization of new host resources. This fluctuation of diversity in the CS of pathogens is registered in species of viruses (Sacristán et al., 2003; Holmes, 2009; Ali and Roossinck, 2010), but the simulations suggest that this may be a common feature in the processes of host repertoire expansion for all other symbiotic species (Moxon and Kussell, 2017; Pérez et al., 2019; Techer et al., 2021).

Among other consequences of host expansion within a community, pathogens with a large host repertoire have a greater chance of survival even when the population of one or some of these hosts become locally extinct (Figure 4.4 — the X marks the extinction of the orange host population). Pathogens that exploit more than a single species of host may survive the extinction event by persisting in other host species (Figure 4.4—the red and green circles survived in the gray host), even if they are marginally fit to the surviving host. That entire process certainly is important to maximize permanence of pathogen species within a community, sometimes at expected low prevalence, often undetected by traditional sampling efforts.

However, we predict that cycles of oscillation within an isolated community stabilize through time. Most likely, pathogen exploration (i.e., probing) of new host species never ceases, but successful colonization decreases in rate through time as compatible hosts become colonized and are exploited by pathogens. Furthermore, evolution has generated enough diversity in the nature of the resource (i.e., hosts) in such magnitude that many hosts are never reached by or exposed to a specific lineage of pathogen, either directly or by a stepping-stone process (despite maximized opportunity) (see, for instance, Braga et al., 2014). These gaps in the nature of the resource within a biological community likely results from differences in the historical pathway of lineages of hosts and consequent historical constraints of the CS of the pathogens and community assemblage and composition. However, no community is perfectly isolated, and even during periods of considerable stability, the dynamics may be resumed through the introduction of new species from other communities (Figure 4.6). Hence, the special concern by health authorities with migratory birds, invasive

species, human traveling, and species translocations (Pinder et al., 2005; Peeler et al., 2006; Hoberg, 2010; Conn, 2014).

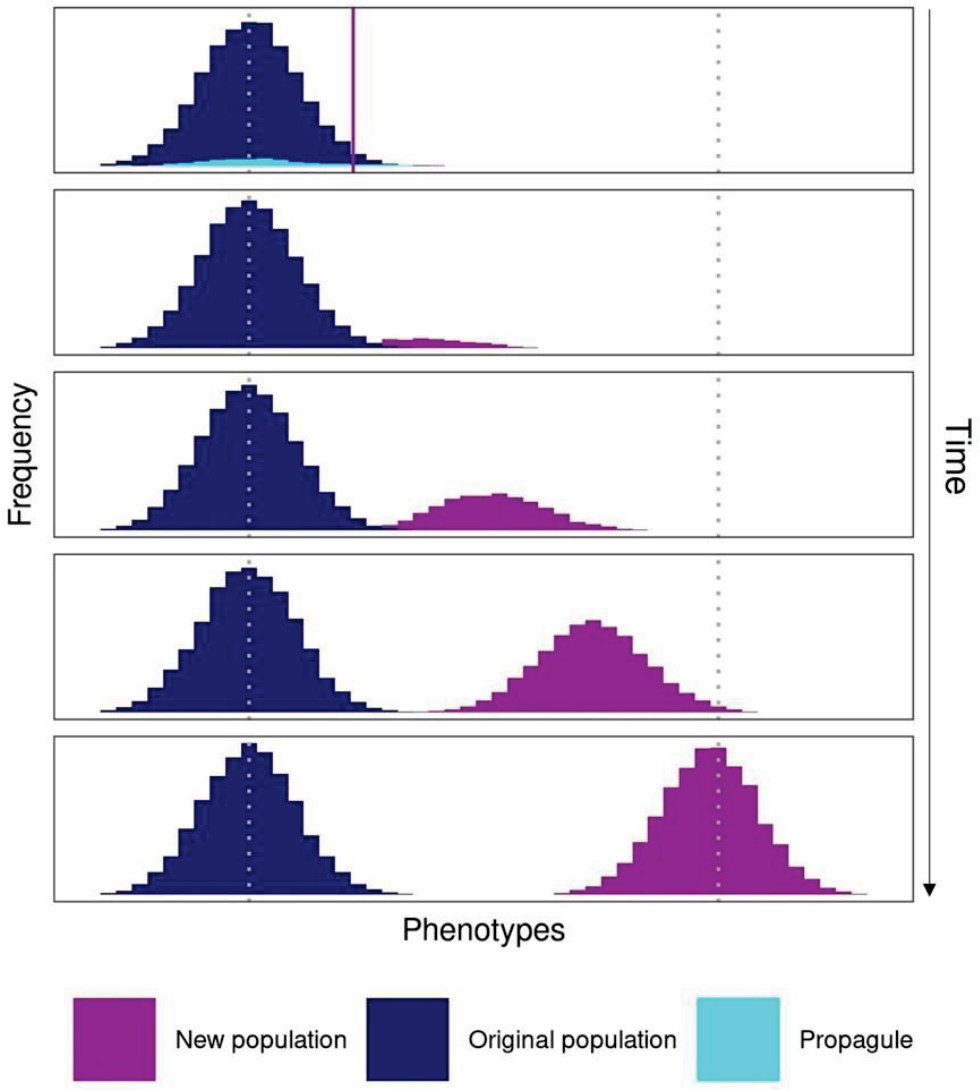

Figure 5. Evolution of the phenotypic profile of a population of pathogens after host switch. A portion (propagule) of the original population of pathogens can migrate to a new host. Only a fraction of these individuals survives the new selective pressure, and the mean phenotype of the survivors is identified by the pink vertical line. Over time the new population has an increase in the number of individuals and, due to the new selective pressure imposed by the new host (dotted line), the phenotypic population profile is directed to the optimal value imposed, stabilizing around it.

The simulations of Araujo et al. (2015) provide another alarming insight regarding pathogens breaking sanitary barriers. As previously mentioned, this model suggests that pathogens may survive for many generations on hosts that represent only marginally adequate resources (Figure 3, C and D; Figure 5). This result also suggests that even if evolutionary novelties that favor the exploitation

of the new resource never emerge, this does not preclude the continuous use of the host species by a small population of the pathogen (low prevalence and low intensity of infection) (see Figure 3, C and D). Under this scenario, pathogen populations may be small because of strong selective pressure within this host, and as a consequence, pathogen detection by sanitary inspections is hampered. However, Feronato et al. (2021) indicated that even in the absence of new evolutionary novelties (e.g., mutations)—hence, without the possibility of generating a more fit pathogen population—the pathogen population may, with time, reach similar populational size to those with greater fitness.

This same outcome of the simulations of Araujo et al. (2015) also provides a potential explanation for the fallacious conclusion that the emergence of new diseases is associated with the evolution of new genetic strains of the pathogen species. Although a common belief, emergence due to new mutations does not appear to be the case for many EID evaluated by Morse (2001); this study concluded that most emergences appear to be associated with increasing opportunity. As distribution of fitness of the pathogen strains in the original host is likely not uniform (Figure 5), by chance or because of selective differences, marginally fit, low-frequency strains may have a better opportunity to explore and exploit new host species, some of which may bear distinct but exploitable resources by EF. Since the probability of sampling marginal and low-frequency variants of the pathogen in its original host is comparatively smaller, an inadequate sampling scheme may conclude that the pathogen is absent in that host while it is present in larger frequencies in the new host species. This is likely the main reason for the fallacious assumption that emergences of new, or previously unknown pathogens in previously unutilized hosts are necessarily associated with the “right mutation” occurring just at the opportune time, which basically extends the question of Kellogg (1907) to parasites or pathogens in general.

Environmental and ecological disruptions can promote changes in the relative permeability of ecological barriers (Figure 4.6), creating or increasing interfaces among communities (or systems)—opportunity for encounters between symbionts previously not in sympatry. This process may increase the probability of contact among previously isolated potential hosts and pathogens that had been maintained in geographic separation in different communities or

habitats. New opportunity drives new cycles of exploration, colonization, and exploitation (Figure 4.6–4.10). Currently, humans are likely the most significant and consistent agent of ecological disruption, transporting pathogens throughout the planet, directly or indirectly (Boeger et al., 2022). Besides humans themselves, inserting populations in literally all biomes on Earth, SARS-CoV-2 is perhaps the most convincing example of this process, and it is clear that we are super-spreaders of diseases (Hoberg et al., 2022).

In recent time, even before the COVID-19 pandemic, we had hints of our great influence on the spreading of diseases—including the contemporary emergence of ZikaV, dengue, and chikungunya in distinct geographical areas. However, the spatial and temporal behavior of SARS-CoV-2 revealed an unexpected dynamic of host use. While the involvement of other mammal species in the epidemiology of SARS-CoV-2 has been reported since the beginning of the COVID-19 pandemic, most researchers ignored it, assuming a more traditional perspective on the evolution of pathogens—that is, that pathogens are highly specialized and incapable of crossing host barriers easily, except when releasing mutations occur (CDC, 2022). The SP predicted (Agosta et al., 2010; Brooks et al., 2014, 2019; Hoberg and Brooks, 2015), and it is recently becoming empirically evident (Fenollar et al., 2021; Bashor et al., 2022; Kuchipudi et al., 2022; Mallapaty, 2022), that nonhuman mammals (at least) likely play a significant role not only as reservoirs for the virus in urban, peri-urban, and wildlife systems but also in the origin of new variants (Boeger et al., 2022; Hoberg et al., 2022). The above-proposed dynamics for SARSCoV-2 was likely replicated in many regions of the planet, involving a much larger number of species than we presently know (Boeger et al., 2022).

While allopatry is often considered the most common mode of differentiation—the generation of new species or variants (Fitzpatrick et al., 2009)—mathematical models have shown that other processes are also likely to occur (de Aguiar et al., 2009; Yamaguchi and Iwasa, 2017; Princepe et al., 2022). Princepe et al. (2022), for instance, using a neutral model for two islands, demonstrated that migration promotes species diversification through two processes: (1) the founding population has no ability (similarity) to reproduce with resident species/variant, creating a new population with, at least in the beginning, independent evolution; (2) the founding population can reproduce with resident

species/variant, introducing new genetic variability in the resident population. In this latter case, sympatric speciation is induced by migration. These results highlight the fact that the contact between variants increases the probability of new variants emerging and should be considered seriously during the management of pandemics. The proposed generalized model for the dynamics of antagonistic associations (Figure 4)—such as diseases—are dependent on both historical (time) and spatial (distribution) processes. Unfortunately, because of tradition, we have not approached the problem of epidemiology of diseases by integrating all these elements. This has hampered the way we understand and deal with emerging and reemerging diseases.

For instance, the question whether biodiversity influences amplification or dilution (Clay et al., 2009; Keesing et al., 2010; Ostfeld and Keesing, 2012; Rohr et al., 2019) of pathogens, thus affecting the emergence or reemergence of diseases in humans, has been in discussion for some time now. Ecological factors are often assumed to influence the observed patterns (Luis et al., 2018), but at least part of the answer may be associated with the dynamics of pathogens through time and under the influence of environmental disruptions, as synthesized in Figure 4. It is intuitive to recognize that the dilution effect may result from the early process of oscillation when species are exploring hosts within the limits of opportunity and capacity—presenting larger host-range but low levels of parasitism. Otherwise, during exploitation, pathogens specialize and diverge, each lineage occupying now one or a limited number of hosts within the community at higher prevalence levels (see, for instance, Patella et al., 2017), maximizing the number of propagules and amplifying exploration and, hence, the emergence of diseases in species newly introduced in the community (i.e., us, new crop or livestock). Hence, the answer to the dilution/amplification paradox may be eco-evolutionary and needs to be evaluated in this way in the future.

2.5 Putting the insights to work

These insights derived from the models and supported by empirical data also provide important elements that should be considered when applying the DAMA protocol (Brooks et al., 2014, 2019; Boeger et al., 2022; Hoberg, 2022; Molnár et al., 2022; Trivellone et al., 2022). For instance, it is not enough to

document (D of DAMA) the biodiversity of pathogens associated with known host species. As suggested by the models and in consonance with accumulated empirical data, pathogens may reach us and species of our direct (and indirect) interest by several ways, including stepping-stone, recolonization, convergent or plesiomorphic nature of the resource, or simply by historically changing its own capacity to explore new and more distant host species. Hence, prospective efforts should not be limited to pathogens nor to a group of species closely related to the focal host species (e.g., us) within a community but expanded to all those that may be involved in the previously described processes of colonization.

The theoretical and empirical evidence that stepping-stone host expansion occurs shows a necessity of a more comprehensive knowledge on the composition of potential host species of a pathogen. Hence, the need to also recognize the composition of potential hosts within a community since these may provide the conditions (either associated to capacity or opportunity) for pathogens to reach focal host species. This is a counterintuitive conclusion contrasting with the proposal that biodiversity constrains the emergence of infectious disease (see Keesing et al., 2010). In fact, it is not the richness of species that may facilitate the emergence of diseases but the composition of phylogenetically close species of hosts in a community that may result in a slow but effective process for pathogen lineages to reach distant host resources by stepping-stone (Braga et al., 2014).

For instance, mammal species living in a same geographic area in the same or close communities may represent elements in the chain toward colonization of ecologically distant mammal hosts. Indeed, the origin of the Omicron variant (and likely of many others—Boeger et al., 2022) is thought by many to have been the result of exploring and exploiting of different host mammals (Wei et al., 2021; Kuchipudi et al., 2022).

Increased capacity to reach new hosts within a community may also be a matter of increasing the pathogen's FS through time (Araujo et al., 2015). For microorganisms, especially those with large mutation rates, this may signify a short period of time as erroneously perceived by us (Manrubia, 2012; Sprouffske et al., 2018). The putative cycle of reduction and increase in FS of such pathogens is expectedly fast, and exploration of available hosts should result in many cases of serial and successful colonizations and exploitations by EF.

Monitoring the ecological and evolutionary dynamics of change of pathogens is, thus, fundamental.

The recent crisis generated by the SARS-Cov2 virus is an excellent example of the potential that successful encounters between a pathogen and compatible hosts can generate (Boeger et al., 2022). Most likely, access to a susceptible individual triggered colonization of humans followed by a quick spreading throughout the world catalyzed by demographics and connectivity of our species (Hoberg et al., 2022). We highlight two lessons from the SARS-CoV-2 pandemic: (1) humans are not detached from nature; we are at the mercy of ecological and evolutionary processes like any other species in the biosphere; and (2) technology did not allow us to react efficiently when a threat of this magnitude presented itself. This is the first major pandemic in an era of high technology and communication, and even with scientists around the world working to develop ways to minimize its effects, we were unable to save 6.28 million lives (WHO, 2022). However, studies of COVID-19 generated an enormous amount of data that can provide a more comprehensive understanding of the dynamics of diseases (emergent and reemergent) through testing of theoretical developments proposed recently, such as the SP.

Indeed, SARS-CoV-2 revealed how the evolutionary dynamics of the virus influenced the epidemiological characteristics of the disease. Substantial evidence shows that SARS-CoV-2 can expand into other mammal species by EF in spite of minor differences in the nature of the membranebound angiotensin-converting enzyme 2 (ACE2) receptor (Damas et al., 2020). Under different lagloads (i.e., selective pressure), the virus population may change, but it likely retains the ability to rapidly recolonize humans (Boeger et al, 2022; Hoberg et al., 2022) supporting the suggestion that rapidly evolving pathogens, such as viruses, can augment their capacity to reach more diverse resources (Araujo et al., 2015; Braga et al., 2018) (and hosts) but still preserve the ability to return to the original host species (Feronato et al., 2021).

Hence, the document step of the DAMA protocol needs to be continuous, combined with the equally continuous monitoring step (the M of DAMA) since the scale of evolution of many pathogens is many times faster than that of their actual and potential host species within a community. Exploration and exploitation are thought to continuously renew the risk space (i.e., the sum of all potential

pathogens of the focal species in a community) through evolution. In this scenario of variable lagloads (i.e., selective scenarios), pathogens may rapidly change and be recognized, upon return to the focal species, as a new variant or even as a new species (Boeger et al., 2022).

Sampling schemes for documenting and monitoring should use effective and sensitive sampling protocols to reveal the total variability of pathogens and its distribution in a community. The simulations have revealed the significance of low-frequency variants of pathogens in the colonization of new host resources (Araujo et al, 2015). These variant pathogens are often greatly concealed within local hosts until opportunity favors colonization of other hosts species, often causing the emergence of new diseases. Finally, monitoring of pathogens and hosts demographics are fundamental due to the evidence that propagule pressure represents the most influential characteristic of pathogens to accomplish colonization of new host resources (Feronato et al., 2021).

While assessing (Assess = first A of DAMA) the potential of pathogens to cause emergences, all these factors just mentioned need to be considered. These same factors will determine the compatibility and probability of encounter and emergence of new antagonistic associations. Thus, Assess is not as simple as analyzing the phylogenetic relationship of unknown pathogens with their known relatives to determine their zoonotic potential—although this is an important part of this process.

Using an analogy to illustrate the potential zoonoses we live with: we are living in a minefield in which new mines are being installed and replaced continuously. We predict that the risk space for focal species will never reduce, and the pathogen capacity to colonize new hosts will increase over time and as evolution continues. The DAMA protocol provides the continuous feedback for adjustments of the Act element of DAMA.

Models help us understand the dynamics of the diseases based on the elements of the SP. However, they may also represent important assets to provide anticipatory scenarios for specific pathogens under the opportunity provided by environmental and human-related disruptions. Hence, these models and future models may confer predictive capacity that will be key in the design of specific methodology associated with DAMA.

2.6 Literature Cited

Agosta, S.J. 2006. On ecological fitting, plant-insect associations, herbivore host shifts, and host plant selection. Oikos 114, 556–565.

Agosta, S.J.; Brooks, D.R. 2020. The Major Metaphors of Evolution: Darwinism Then and Now. Evolutionary Biology—New Perspectives on Its Development series, vol. 2. Springer, Cham, Switzerland. https://doi.org/10.1007/978-3-030-52086-1

Agosta, S.J.; Janz, N.; Brooks, D.R. 2010. How specialists can be generalists: resolving the “parasite paradox” and implications for emerging infectious disease. Zoologia (Curitiba) 27: 151–162. https://doi.org/10.1590/S1984-46702010000200001

Agosta, S.J.; Klemens, J.A. 2008. Ecological fitting by phenotypically flexible genotypes: implications for species associations, community assembly and evolution. Ecology Letters 11: 1123–1134. https://doi.org/10.1111/j.1461-0248.2008.01237.x

Ali, A.; Roossinck, M.J. 2010. Genetic bottlenecks during systemic movement of Cucumber mosaic virus vary in different host plants. Virology 404: 279–283. https://doi.org/10.1016/j.virol.2010.05.017

Alison, M.R.; Poulsom, R.; Forbes, S.; Wright, N.A. 2002. An introduction to stem cells. Journal of Pathology 197: 419–423. https://doi.org/10.1002/path.1187

Altizer, S.; Ostfeld, R.S.; Johnson, P.T.J.; Kutz, S.; Harvell, C.D. 2013. Climate change and infectious diseases: from evidence to a predictive framework. Science 341: 514–519. https://doi.org/10.1126/science.1239401

Araujo, S.B.; Braga, M.P.; Brooks, D.R.; Agosta, S.J.; Hoberg, E.P.; von Hartenthal, F.W.; Boeger, W.A. 2015. Understanding hostswitching by ecological fitting. PLOS ONE 10: e0139225. https://doi.org/10.1371/journal.pone.0139225

Baselga, A. 2010. Partitioning the turnover and nestedness components of beta diversity. Global Ecology and Biogeography 19: 134–143. https://doi.org/10.1111/j.1466-8238.2009.00490.x

Baselga, A. 2013. Separating the two components of abundance based dissimilarity: balanced changes in abundance vs. abundance gradients. Methods in Ecology and Evolution 4:552–557. https://doi.org/10.1111/2041-210X.12029

Bashor, L.; Gagne, R.B.; Bosco-Lauth, A.; Stenglein, M.; VandeWoude, S. 2022. Rapid evolution of SARS-CoV-2 in domestic cats. Virus Evolution: veac092. https://doi.org/10.1093/ve/veac092

Bashor, L.; Gagne, R.B.; Bosco-Lauth, A.M.; Bowen, R.A.; Stenglein, M.; VandeWoude, S. 2021. SARS-CoV-2 evolution in animals suggests mechanisms for rapid variant selection. Proceedings of the National Academy of Sciences 118: e2105253118. https://doi.org/10.1073/pnas.2105253118

Blum, M.G.B.; François, O. 2005. On statistical tests of phylogenetic tree imbalance: the Sackin and other indices revisited. Mathematical Biosciences 195, 141–153. https://doi.org/10.1016/j.mbs.2005.03.003

Boeger, W.A.; Brooks, D.R.; Trivellone, V.; Agosta, S.; Hoberg, E. 2022. Ecological super-spreaders drive host-range oscillations: Omicron and risk-space for emerging infectious disease. Illinois Experts reprint. https://doi.org/10.22541/au.164342794.41467213/v1

Braga, M.P.; Araujo, S.B.L.; Agosta, S.; Brooks, D.; Hoberg, E.; Nylin, S.; et al. 2018. Host use dynamics in a heterogeneous fitness landscape generates oscillations in host range and diversification. Evolution 72: 1773–1783. https://doi.org/10.1111/evo.13557

Braga, M.P.; Araújo, S.B.L.; Boeger, W.A. 2014. Patterns of interaction between Neotropical freshwater fishes and their gill Monogenoidea (Platyhelminthes). Parasitology Research 113: 481–490. https://doi.org/10.1007/s00436-013-3677-8

Braga, M.P.; Janz, N. 2021. Host repertoires and changing insect plant interactions. Ecological Entomology 46: 1241–1253. https://doi.org/10.1111/een.13073

Braga, M.P.; Razzolini, E.; Boeger, W.A. 2015. Drivers of parasite sharing among Neotropical freshwater fishes. Journal of Animal Ecology 84: 487–497. https://doi.org/10.1111/1365-2656.12298

Brooks, D.R.; Agosta, S.J. 2012. Children of time: the extended synthesis and major metaphors of evolution. Zoologia (Curitiba) 29: 497–514. https://doi.org/10.1590/S1984-46702012000600002

Brooks, D.R.; Boeger, W.A. 2019. Climate change and emerging infectious diseases: evolutionary complexity in action. Current Opinion in Systems Biology 13: 75–81.

Brooks, D.R.; Ferrao, A.L. 2005. The historical biogeography of co-evolution: emerging infectious diseases are evolutionary accidents waiting to happen. Journal of Biogeography 32: 1291–1299. https://doi.org/10.1111/j.1365-2699.2005.01315.x

Brooks, D.R.; Hoberg, E.P. 2007. How will global climate change affect parasite-host assemblages? Trends in Parasitology 23:571–574. https://doi.org/10.1016/j.pt.2007.08.016

Brooks, D.R.; Hoberg, E.P. 2013. The emerging infectious diseases crisis and pathogen pollution. In: The Balance of Nature and Human Impact. K. Rohde (ed.). Cambridge University Press, Cambridge, England. 215–230 p. https://doi.org/10.1017/CBO9781139095075.022

Brooks, D.R.; Hoberg, E.P.; Boeger, W.A. 2019. The Stockholm Paradigm: Climate Change and Emerging Disease. University of Chicago Press, Chicago.

Brooks, D.R.; Hoberg, E.P.; Boeger, W.A.; Gardner, S.L.; Galbreath, K.E.; Herczeg, D.; et al. 2014. Finding them before they find us: informatics, parasites, and environments in accelerating climate change. Comparative Parasitology 81: 155–164.

Brooks, D.R.; McLennan, D.A. 2002. The Nature of Diversity: An Evolutionary Voyage of Discovery. University of Chicago Press, Chicago.
Calderon, A.; Guzman, C.; Salazar-Bravo, J.; Figueiredo, L.T.; Mattar, S.; Arrieta, G. 2016. Viral zoonoses that fly with bats: a review. MANTER Journal of Parasite Biodiversity 6. https://doi.org/10.13014/K2BG2KWF

Carbonell, P.; Lecointre, G.; Faulon, J.-L. 2011. Origins of specificity and promiscuity in metabolic networks. Journal of Biological Chemistry 286: 43994–44004. https://doi.org/10.1074/jbc.M111.274050

CDC [Center for Disease Control and Prevention]. 2022. What you should know about COVID-19 and pets. [WWWdocument]. Accessed April 27, 2022. https://www.cdc.gov/healthypets/covid-19/pets.html

Christaki, E. 2015. New technologies in predicting, preventing and controlling emerging infectious diseases. Virulence 6:558–565. https://doi.org/10.1080/21505594.2015.1040975

Cipollini, D.; Peterson, D.L. 2018. The potential for host switching via ecological fitting in the emerald ash borer host plant system. Oecologia 187: 507–519. https://doi.org/10.1007/s00442-018-4089-3

Clay, C.A.; Lehmer, E.M.; Jeor, S.; Dearing, M.D. 2009. Sin Nombre virus and rodent species diversity: a test of the dilution and amplification hypotheses. PLOS ONE 4: e6467. https://doi.org/10.1371/journal.pone.0006467

Combes, C. 2001. Parasitism: The Ecology and Evolution of Intimate Interactions. University of Chicago Press, Chicago. Conn, D.B. 2014. Aquatic invasive species and emerging infectious disease threats: a One Health perspective. Aquatic Invasions 9: 383–390. https://doi.org/10.3391/ai.2014.9.3.12

Dada, J.O.; Mendes, P. 2011. Multi-scale modelling and simulation in systems biology. Integrative Biology 3: 86–96. https://doi.org/10.1039/c0ib00075b

Damas, J.; Hughes, G.M.; Keough, K.C.; Painter, C.A.; Persky, N.S.; Corbo, M.; et al. 2020. Broad host range of SARS-CoV-2 predicted by comparative and

structural analysis of ACE2 in vertebrates. Proceedings of the National Academy of Sciences 117: 22311–22322. https://doi.org/10.1073/pnas.2010146117

Darwin, C. 1872. The Origin of Species. 6th ed. John Murray, London.

D'Bastiani, E.; Princepe, D.; Marquitti, F.M.D.; Boeger, W.A.; Campião, K.M.; Araujo, S.L.B. 2021. Effect of host-switching on the eco-evolutionary patterns of parasites. bioRxiv preprint. https://doi.org/10.1101/2021.11.27.47014

de Aguiar, M.A.M.; Baranger, M.; Baptestini, E.M.; Kaufman, L.; Bar-Yam, Y. 2009. Global patterns of speciation and diversity. Nature 460: 384–387. https://doi.org/10.1038/nature08168

de Vienne, D.M.; Hood, M.E.; Giraud, T. 2009. Phylogenetic determinants of potential host shifts in fungal pathogens. Journal of Evolutionary Biology 22: 2532–2541. https://doi.org/10.1111/j.1420-9101.2009.01878.x

Dieckmann, U.; Doebeli, M. 1999. On the origin of species by sympatric speciation. Nature 400: 354–357. https://doi.org/10.1038/22521

Fauci, A.S.; Morens, D.M. 2012. The perpetual challenge of infectious diseases. New England Journal of Medicine 366: 454–461. https://doi.org/10.1056/NEJM1108296

Fenollar, F.; Mediannikov, O.; Maurin, M.; Devaux, C.; Colson, P.; Levasseur, A.; et al. 2021. Mink, SARS-CoV-2, and the humananimal interface. Frontiers in Microbiology 12: 745. https://doi.org/10.3389/fmicb.2021.663815

Feronato, S.G.; Araujo, S.; Boeger, W.A. 2021. 'Accidents waiting to happen'—insights from a simple model on the emergence of infectious agents in new hosts. Transboundary and Emerging Diseases 69: 1727–1738. https://doi.org/10.1111/tbed.14146

Fitzpatrick, B.M.; Fordyce, J.A.; Gavrilets, S. 2009. Pattern,process and geographic modes of speciation. Journal of Evolutionary Biology 22: 2342–2347. https://doi.org/10.1111/j.1420-9101.2009.01833.x

Giacomini, H.C. 2007. Sete motivações teóricas para o uso da modelagem baseada no indivíduo em ecologia [Seven theoretical reasons for using individual-based modeling in ecology]. Acta Amazonica 37: 431–445. https://doi.org/10.1590/S0044-59672007000300015

Gilbert, G.S.; Webb, C.O. 2007. Phylogenetic signal in plant pathogen–host range. Proceedings of the National Academy of Sciences 104: 4979–4983. https://doi.org/10.1073/pnas.0607968104

Gioti, A.; Stajich, J.E.; Johannesson, H. 2013. *Neurospora* and the dead-end hypothesis: genomic consequences of selfing in the model genus. Evolution 67: 3600–3616. https://doi.org/10.1111/evo.12206

Gómez, J.M.; Verdú, M.; Perfectti, F. 2010. Ecological interactions are evolutionarily conserved across the entire tree of life. Nature 465: 918–921. https://doi.org/10.1038/nature09113

Gubler, D.J. 2010. The global threat of emergent/reemergent vector-borne diseases. In: Vector Biology, Ecology and Control. P.W. Atkinson (ed.). Springer Netherlands, Dordrecht. 39–62 p. https://doi.org/10.1007/978-90-481-2458-9_4
Haldane, J.B.S. 1951. Everything Has a History. Routledge/Taylor & Francis Group, London.

Hoberg, E. 2022. The DAMA protocol, an introduction: finding pathogens before they find us. MANTER Journal of Parasite Biodiversity 21. https://doi.org/10.32873/unl.dc.manter21

Hoberg, E.P. 2010. Invasive processes, mosaics and the structure of helminth parasite faunas. Revue Scientifique et Technique—Office International des Épizooties 29: 255–272. https://doi.org/10.20506/rst.29.2.1972

Hoberg, E.P.; Boeger, W.A.; Brooks, D.R.; Trivellone, V.; Agosta, S.J. 2022. Stepping-stones and mediators of pandemic expansion—a context for humans as ecological superspreaders. MANTER Journal of Parasite Biodiversity 18. https://doi.org/10.32873/unl.dc.manter18

Hoberg, E.P.; Brooks, D.R. 2010. Beyond vicariance: integrating taxon pulses, ecological fitting, and oscillation in evolution and historical biogeography. In: The Geography of HostParasite Interactions. S. Morand and B. Krasnov (eds.). Oxford University Press, Oxford, UK. 7–20 p.

Hoberg, E.P.; Brooks, D.R. 2015. Evolution in action: climate change, biodiversity dynamics and emerging infectious disease. Philosophical Transactions of the Royal Society B—Biological Sciences 370: 20130553. https://doi.org/10.1098/rstb.2013.0553

Holmes, E.C. 2009. The Evolution and Emergence of RNA Viruses. Oxford Series in Ecology and Evolution. Oxford University Press, Oxford, UK.

Hui, C.; Richardson, D.M. 2018. How to Invade an ecological network. Trends in Ecology and Evolution 34: 121–131. https://doi.org/10.1016/j.tree.2018.11.003

Hulme, P.E. 2014. Invasive species challenge the global response to emerging diseases. Trends in Parasitology 30: 267–270. https://doi.org/10.1016/j.pt.2014.03.005

Imrie, R.M.; Roberts, K.E.; Longdon, B. 2021. Between virus correlations in the outcome of infection across host species: evidence of virus by host species interactions. Evolution Letters 5: 472–483. https://doi.org/10.1002/evl3.247

Janz, N.; Nylin, S. 2008. The oscillation hypothesis of host-plant range and speciation. In: Specialization, Speciation, and Radiation: The Evolutionary Biology of Herbivorous Insects. K. Tilmon (ed.). University of California Press. 203–215 p. https://doi.org/10.1525/california/9780520251328.001.0001

Janzen, D.H., 1985. On ecological fitting. Oikos 45: 308–310. https://doi.org/10.2307/3565565

Keesing, F.; Belden, L.K.; Daszak, P.; Dobson, A.; Harvell, C.D.; Holt, R.D.; et al. 2010. Impacts of biodiversity on the emergence and transmission of infectious diseases. Nature 468: 647–652.

Kellogg, V. 1907. Darwinism Today. Holt, New York. Khersonsky, O.; Roodveldt, C.; Tawfik, D.S. 2006. Enzyme promiscuity: evolutionary and mechanistic aspects. Current Opinion in Chemical Biology (Analytical Techniques/ Mechanisms special issue) 10: 498–508. https://doi.org/10.1016/j.cbpa.2006.08.011

Kuchipudi, S.V.; Surendran-Nair, M.; Ruden, R.M.; Yon, M.; Nissly, R.H.; Vandegrift, K.J.; et al. 2022. Multiple spillovers from humans and onward transmission of SARS-CoV-2 in white-tailed deer. Proceedings of the National Academy of Sciences 119: e2121644119. https://doi.org/10.1073/pnas.2121644119

Le Roux, J.J.; Hui, C.; Keet, J.-H.; Ellis, A.G. 2017. Co-introduction vs ecological fitting as pathways to the establishment of effective mutualisms during biological invasions. New Phytologist 215: 1354–1360. https://doi.org/10.1111/nph.14593

Luis, A.D.; Kuenzi, A.J.; Mills, J.N. 2018. Species diversity concurrently dilutes and amplifies transmission in a zoonotic host-pathogen system through competing mechanisms. Proceedings of the National Academy of Sciences 115: 7979–7984. https://doi.org/10.1073/pnas.1807106115

Malcicka, M.; Agosta, S.J.; Harvey, J.A. 2015. Multi-level ecological fitting: indirect life cycles are not a barrier to host switching and invasion. Global Change Biology 21: 3210–3218. https://doi.org/10.1111/gcb.12928

Mallapaty, S. 2022. How sneezing hamsters sparked a COVID outbreak in Hong Kong. Nature (News, February 4, 2022). https://doi.org/10.1038/d41586-022-00322-0

Manrubia, S.C. 2012. Modelling viral evolution and adaptation: challenges and rewards. Current Opinion in Virology 2: 531– 537. https://doi.org/10.1016/j.coviro.2012.06.006

Margulis, L. 1971. Symbiosis and evolution. Scientific American 225: 48–57. https://doi.org/10.1038/scientificamerican0871-48

Molnár, O.; Knickel, M.; Marizzi, C. 2022. Taking action: turning evolutionary theory into preventive policies. MANTER Journal of Parasite Diversity 28. https://doi.org/10.32873/unl.dc.manter28

Morens, D.M.; Folkers, G.K.; Fauci, A.S. 2004. The challenge of emerging and re-emerging infectious diseases. Nature 430:242–249.

Morse, S.S. 2001. Factors in the emergence of infectious diseases. In: Plagues and Politics. A.T. Price-Smith (ed.). Global Issues series. Palgrave Macmillan, London. 8–26 p. https://doi.org/10.1057/9780230524248_2

Moxon, R.; Kussell, E. 2017. The impact of bottlenecks on microbial survival, adaptation, and phenotypic switching in host-pathogen interactions. Evolution 71: 2803–2816. https://doi.org/10.1111/evo.13370

Nylin, S.; Agosta, S.; Bensch, S.; Boeger, W.A.; Braga, M.P.; Brooks, D.R.; et al. 2018. Embracing colonizations: a new paradigm for species association dynamics. Trends in Ecology and Evolution 33: 4–14. https://doi.org/10.1016/j.tree.2017.10.005

Ostfeld, R.S.; Keesing, F. 2012. Effects of host diversity on infectious disease. Annual Review of Ecology, Evolution, and Systematics 43: 157–182. https://doi.org/10.1146/annurev-ecolsys-102710-145022

Patella, L.; Brooks, D.R.; Boeger, W.A. 2017. Phylogeny and ecology illuminate the evolution of associations under the Stockholm Paradigm: *Aglaiogyrodactylus* spp.(Platyhelminthes, Monogenoidea, Gyrodactylidae) and species of Loricariidae (Actinopterygii, Siluriformes). Vie et Milieu 67: 91–102.

Peeler, E.; Thrush, M.; Paisley, L.; Rodgers, C. 2006. An assessment of the risk of spreading the fish parasite *Gyrodactylus salaris* to uninfected territories in the European Union with the movement of live Atlantic salmon (*Salmo salar*) from coastal waters. Aquaculture 258, 187–197. https://doi.org/10.1016/j.aquaculture.2005.07.042

Pérez, S.D.; Grummer, J.A.; Fernandes-Santos, R.C.; José, C.T., Medici, E.P., Marcili, A. 2019. Phylogenetics, patterns of genetic variation and population

dynamics of *Trypanosoma terrestris* support both coevolution and ecological hostfitting as processes driving trypanosome evolution. Parasites & Vectors 12: 473. https://doi.org/10.1186/s13071-019-3726-y

Pinder, A.C.; Gozlan, R.E.; Britton, J.R. 2005. Dispersal of the invasive topmouth gudgeon, *Pseudorasbora parva*, in the UK: a vector for an emergent infectious disease. Fisheries Management and Ecology 12: 411–414. https://doi.org/10.1111/j.1365-2400.2005.00466.x

Princepe, D.; Czarnobai, S.; Pradella, T.M.; Caetano, R.A.; Marquitti, F.M.D.; de Aguiar, M.A.M.; Araujo, S.B.L. 2022. Diversity patterns and speciation processes in a two-island system with continuous migration. Evolution 76: 2260–2271. https://doi.org/10.1111/evo.14603

Ribeiro Prist, P.; Reverberi Tambosi, L.; Filipe Mucci, L.; Pinter, A.; Pereira de Souza, R.; de Lara Muylaert, R.; Rhodes, J.R., et al. 2022. Roads and forest edges facilitate yellow fever virus dispersion. Journal of Applied Ecology 59: 4–17. https://doi.org/10.1111/1365-2664.14031

Rohr, J.R.; Civitello, D.J.; Halliday, F.W.; Hudson, P.J.; Lafferty, K.D.; Wood, C.L.; Mordecai, E.A. 2019. Towards common ground in the biodiversity-disease debate. Nature Ecology and Evolution 4: 24–33. https://doi.org/10.1038/s41559-019-1060-6

Rychener, L.; In-Albon, S.; Djordjevic, S.P.; Chowdhury, P.R.; Nicholson, P.; Ziech, R.E.; et al. 2017. *Clostridium chauvoei*, an evolutionary dead-end pathogen. Frontiers in Microbiology 8: 1–13. https://doi.org/10.3389/fmicb.2017.01054

Sacristán, S.; Malpica, J.M.; Fraile, A.; García-Arenal, F. 2003. Estimation of population bottlenecks during systemic movement of *Tobacco mosaic virus* in tobacco plants. Journal of Virology 77: 9906–9911. https://doi.org/10.1128/jvi.77.18.9906-9911.2003

Scheiner, S.M.; Mindell, D.P. (eds.). 2019. The Theory of Evolution: Principles, Concepts, and Assumptions. University of Chicago Press, Chicago. https://doi.org/10.7208/chicago/9780226671338.001.0001

Schradin, C.; Lindholm, A.K.; Johannesen, J.; Schoepf, I.; Yuen, C.-H.; König, B.; Pillay, N. 2012. Social flexibility and social evolution in mammals: a case study of the African striped mouse (*Rhabdomys pumilio*). Molecular Ecology 21: 541–553. https://doi.org/10.1111/j.1365-294X.2011.05256.x

Smith, J.M. 1976. What determines the rate of evolution? American Naturalist 110: 331–338. https://doi.org/10.1086/283071

Sprouffske, K.; Aguilar-Rodríguez, J.; Sniegowski, P.; Wagner, A. 2018. High mutation rates limit evolutionary adaptation in *Escherichia coli.* PLOS Genetics 14: e1007324. https://doi.org/10.1371/journal.pgen.1007324

Steward, R.A.; Epanchin-Niell, R.S.; Boggs, C.L. 2022. Novel host unmasks heritable variation in plant preference within an insect population. Evolution 76: 2634–2648. https://doi.org/10.1111/evo.14608

Streicker, D.G.; Turmelle, A.S.; Vonhof, M.J.; Kuzmin, I.V.; McCracken, G.F.; Rupprecht, C.E. 2010. Host phylogeny constrains cross-species emergence and establishment of rabies virus in bats. Science 329: 676–679. https://doi.org/10.1126/science.1188836

Techer, M.; Roberts, J.; Cartwright, R.; Mikheyev, A. 2021. The first steps toward a global pandemic: reconstructing the demographic history of parasite host switches in its native range. Research Square preprint. https://doi.org/10.21203/rs.3.rs-196900/v1

Trivellone, V.; Araujo, S.B.L.; Panassiti B. 2021. HostSwitch: Simulate the Extent of Host Switching by Consumers. 12 pp. https://cran.rproject.org/web/packages/HostSwitch/HostSwitch.pdf

Trivellone, V.; Araujo, S.B.L.; Panassiti, B. 2023. HostSwitch: an R package to simulate the extent of host-switching by a consumer. The R Journal 14: 179–194. https://doi.org/10.32614/RJ-2023-005

Trivellone, V.; Hoberg, E.P.; Boeger, W.A.; Brooks, D.R. 2022. Food security and emerging infectious disease: risk assessment and risk management. Royal Society Open Science 9: 211687. https://doi.org/10.1098/rsos.211687

Wei, C.; Shan, K.-J.; Wang, W.; Zhang, S.; Huan, Q.; Qian, W. 2021. Evidence for a mouse origin of the SARS-CoV-2 Omicron variant. Journal of Genetics and Genomics. https://doi.org/10.1016/j.jgg.2021.12.003

WHO [World Health Organization]. 2022. WHO Coronavirus (COVID-19) Dashboard [WWW document]. Accessed January 19, 2022. https://covid19.who.int

Wilkinson, D.M. 2004. The parable of Green Mountain: Ascension Island, ecosystem construction and ecological fitting. Journal of Biogeography 31: 1–4. https://doi.org/10.1046/j.0305-0270.2003.01010.x

Yamaguchi, R.; Iwasa, Y. 2017. Parapatric speciation in three islands: dynamics of geographical configuration of allele sharing. Royal Society Open Science 4: 160819. https://doi.org/10.1098/rsos.160819

3. CAPÍTULO 2

Chapter 2

Where did it come from? Elusive variants and new emergences

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3.1 Abstract

The establishment of associations between hosts and parasites requires opportunity and compatibility - a “perfect fit” or new genetic adaptations is not essential. The phylogenetic conservatism of host and parasite species traits can facilitate parasites to incorporate closely related host species into their repertoire. Hypothetically, phenotypically diverse larger propagule sizes are more likely to contain parasite individuals capable of surviving in new hosts. Based on these premises, our goals were to evaluate if the phenotypic variability of propagules favors the acquisition of more distant hosts, and if the establishment of new and rare associations (with very distant hosts) is based on individuals with less-fit phenotypes in the original population. Additionally, we track the phenotypic evolution of the parasite population following colonization in order to understand the effect of the distance between hosts (donor and recipient) on parasite diversification. We simulate the dynamics of host repertoire expansion by parasites through an Individual-Based Model (IBM) in which some individuals - the propagule - inhabiting a donor host can switch to a new host. We contrasted scenarios with and without phenotypic variability of propagules and recorded the phenotypes of individuals following successful colonization. Larger propagule sizes and propagules with phenotypic variability were the ones with the greatest success in establishing in new hosts, and in colonizing more distant hosts. Additionally, the elusive variants (low frequency phenotypes in the donor parasite population) were responsible for the more distant host colonization's. Phenotypic variability generated after colonization of a new host was directly associated with the distance between the hosts used, increasing the differentiation between variants that inhabit distant hosts. This situation highlights the risk of emerging diseases, especially when the access of parasites to new hosts has been

facilitated through human actions that, daily, displace several species, making geographic distant potential hosts available for colonizing.

Keywords: Stockholm Paradigm, evolution, symbiosis, host switching.

3.2 Introduction

The world is experiencing what is being called by some an Emergent Infectious Diseases Crisis (Garrett 1994; Brooks 2011; Brooks et al. 2021). Unexpectedly, the emergence or re-emergence of diseases in humans, animals (Baskin 2006), and plants (Brooks et al. 2021) is accelerating (Rosenthal et al. 2015; O'Dowd 2007). This crisis is most certainly a consequence of the current scenario of the planet, catalyzed by changes imposed by our civilizations (Broglio and Solé 2004). Climate change, increase in human population size, globalization, and biological invasions, among other factors, increase the frequency of encounters between parasites and previously naïve hosts (Altizer et al. 2013; Brooks and Boeger 2019a; Wilson 1995; Conn 2014). For instance, intentionally and unintentionally, daily human activities carry several species beyond their regions of natural distribution (Wilson 1995). In a few hours, travelers can reach the opposite side of the ocean, potentially carrying with them new and previously eradicated pathogens. The recent SARS-Cov2 pandemic is a good example of this situation. However, while the focus of health organizations has been the emergence of infectious diseases in humans, all species we depend on are also at risk in these times of change (Brooks et al. 2021; Trivellone et al. 2022). It is estimated that more than 22% of the production of the main food crops (wheat, rice, maize, potatoes, and soybeans) is lost annually due to pathogens and pests (Savary et al. 2019). In a world with 8 billion people, and with an expectation of rapid and proximate growth (UN-DESA 2022), ensuring food security must be a priority (Brooks et al. 2021). In this context, understanding how these associations are regulated is extremely important for our safety (Brooks et al. 2014a; Brooks and Boeger 2019b).

The Stockholm Paradigm (Brooks et al. 2014a) presents a framework of theories explaining the evolution of host-parasite associations. According to this paradigm, the origin of new interactions occurs through ecological fitting (Agosta,

Janz, and Brooks 2010; Janzen 1985). Ecological fitting is a process of changing ecology (e.g., emergence of new associations) through pre-existing capacities, often associated with exaptation, phenotypic flexibility, phylogenetic conservatism, and correlated trait evolution (Agosta and Klemens 2008a). Therefore, given the opportunity (See Araujo et al. 2015), parasites can incorporate new host species into their repertoire by colonizing hosts that provide resources and conditions similar to those offered by a donor host (Agosta and Klemens 2008b). Considering the conserved nature of the evolutionary process allow us to infer that acquiring new hosts closely related phylogenetically to those already utilized is more likely to succeed when compared to acquiring more distantly related hosts (Charleston and Robertson 2002; De Vienne, Giraud, and Shykoff 2007; D'Bastiani et al. 2023b).

Additionally, phenotypic variability in a parasite population provides a range of capacities to explore and exploit different hosts. The frequencies of phenotypes and genotypes of parasites in a specific host are not uniform nor always expressed. Some phenotypes and genotypes generally occur in higher frequencies than others simply because they are positively selected under the present selection regimen - while many others likely go unnoticed by researchers due to their low frequency or no expression. The Stockholm Paradigm hypothesizes that these elusive phenotypes have a significant role in colonizing phylogenetically distant hosts. A possible actual example is SARS-COV-2 - although its origin is uncertain, due to its unsampled record in other non-human mammals, it is believed that the recent human pandemics originated from bats (Andersen et al. 2020). In fact, the recorded history of SARS-COV-2 also reveals many other instances of colonization and recolonization of distantly related hosts which may be associated to the origin of variants (Boeger et al. 2022).

Recently, a theoretical model for evaluating the probability of parasites colonizing new host species was proposed (Feronato, Araujo, and Boeger 2021). The authors evaluated the success in colonization of new hosts by pathogens for different scenarios of replication rate, mutation rate, and propagule size. While replication and mutation rates are self-explanatory, propagule size - number of individuals released per introduction event - is not commonly used in describing elements involved in the dynamics of infectious diseases in general. However, it is an important concept that has been widely explored in the field of Biology of

Invasions (see, for instance, Holle and Simberloff 2005; Simberloff 2009; Cassey et al. 2018). Among other results of Feronato and colleagues (2021), the larger propagule size and the synergy between these parameters greatly favors new host colonization.

Thus, in the present study, we take one step ahead of the model presented by Feronato et al. (2021) and approach the effect of propagule variability on new host colonization. We built an individual-based model in which parasite individuals are explicitly modeled and characterized by phenotypes that can evolve over generations. At a given time, a fraction of the population - the propagule - attempts to switch to a new host, which imposes a different selection pressure. We track the temporal phenotype evolution of the individuals responsible for founding the new population and investigate the role of elusive variants (i.e., low-frequency phenotypes). We present our results, highlighting how host colonization can favor new parasite variants and how elusive variants can be responsible for new colonization of less-compatible host species.

3.3 Methods

We simulate the dynamics of host repertoire expansion (acquisition of new hosts) by parasites through an Individual-Based Model (IBM) in which some individuals, the propagule, inhabiting a host can switch to a new host. Our model was inspired by that proposed by Feronato, Araujo, and Boeger (2021) but, additionally to the previous model, here we contrasted scenarios with and without propagule's phenotypic variability. We also recorded the phenotypic composition of both the propagules and the founding population and tracked the evolution of the phenotypes in the new population throughout time.

3.3.1 Parasite and host descriptions

An explicitly modeled genotype (or any inheritable trait) characterizes each parasite individual. The genotype consists of a sequence of "0" and "1" of size L (hereafter genome), and its sum corresponds to the phenotype (p_i) of the individual i (Nuismer and Thompson 2006; Braga, Araujo, et al. 2018; Feronato,

Araujo, and Boeger 2021). Unlike parasites, host individuals do not evolve and are characterized by a carrying capacity (*K*) and by a constant value that represents a host peak fitness that imposes an optimal phenotype value (P_h) on parasite The phenotype of the parasite (p_i) will be subject to selection imposed by the host (P_h) and, therefore, it is what determines the compatibility between them (See details in *Selection*).

3.3.2 Dynamics

Initially, *K* clonal parasite individuals inhabit a unique host, H_1 (Fig. 1). The genome is randomly defined, ensuring that its sum (the phenotype) is equal to the optimal phenotype imposed by the host (P_{h1}). Each time step (*t*) is composed of a cycle of parasite *Replication* and *Selection* (detailed below). In time t_{int}, a sample of *S* individuals (the propagule) is randomly selected in H_1 and released in a new host, H_2. Upon arriving at the new host, the parasites are first subjected to a new selective pressure (imposed by P_{h2}; detailed in *Selection*) and the surviving individuals go through the cycles of *Replication* and *Selection.* Parental generation is replaced by the offspring, which means that there is no overlap of generations.

3.3.3 Replication

For simplicity, the parasites reproduction is asexual, and each offspring individual corresponds to one copy of the parental genome potentially modified by an evolutionary novelty rate per locus (μ) - that is, each gene locus of each offspring individual has a probability μ of mutating from “0” to “1”, or vice-versa. The number of offspring generated in each generation corresponds to the number of parasites present in the host multiplied by a constant *b*, with an upper limit of *K* individuals per host. All individuals have an equal probability of generating offspring. Therefore, *b,* hereafter replication rate, can be understood as the average number of descendants per individual in absence of competition (imposed by the carrying capacity). The number of individuals present at t+1 can be smaller than the number of individuals generated in *t* due to selective pressure.

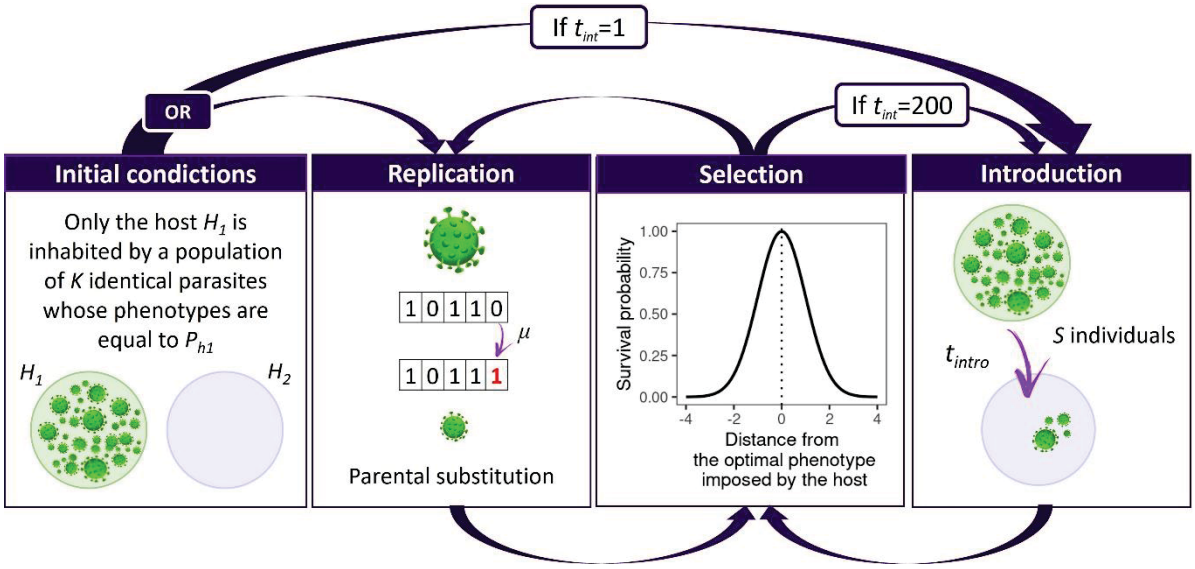

Figure 1. Model dynamics flowchart. Initially, the host H_1 is inhabited by a clonal population of parasites. Each iteration is composed of a cycle of *Replication* and *Selection.* The offspring inherit the parental genotype, but each locus can mutate with probability μ. A survival probability models the selection imposed by the inhabited host; it decreases as the parasite phenotype diverges from the optimum imposed by the host. At the time t_{int}, S parasite individuals from H_1 switch to H_2, where they are subjected to a new selective pressure. We evaluate two scenarios: clonal propagule (t_{int} =1), and variable propagule (t_{int} =200, time enough to promote phenotypic variability in H_1).

3.3.4 Selection

All parasite individuals are subject to selection imposed by the host they are interacting with. This selection is modeled by a normal distribution where the probability of an individual *i* surviving in the host decreases as the distance (*d*) between its phenotype (p_i), and the optimum imposed by its host (P_h) increases:

$$\boldsymbol{P_{surv} = exp[\frac{-d_i^2}{2}]}, \quad (1)$$

where *d* is measured in units of the standard deviation $\boldsymbol{\sigma}$ of the normal distribution:

$$d_i = \frac{p_i - P_h}{\sigma}. \quad (2)$$

It means that individuals whose phenotype is equal to the optimum imposed by the host (d = 0) has maximum survival probability. As the value of d increases, the probability of survival decreases. Surviving individuals continue the dynamics through a new cycle of *Replication* and *Selection.*

3.3.5 Simulations and data analysis

For all analyses, the genome size was kept constant at L = 1000 loci, the mutation rate at $\mu = 10^{-3}$, the carrying capacity at K = 200 individuals per host, the deviation rate imposed by the survival probability (Eq. 1) at σ = 10, and the optimal phenotype imposed by the host H_1 at P_{h1} = 500 (Table 1).

In order to understand the effect of the phenotypic variability of the propagule on the host repertoire expansion, we compared scenarios in which the host switch occurred at the first-time step (t_{int} = 1), when all individuals are clonal, with scenarios in which it occurs later (t_{int} = 200), and individuals had accumulated variation (see the variability accumulation in Fig S1).

Table 1: Parameters present in the model, a short description and their values used in simulations.

Parameter	Description	Investigated values
S	Propagule size	1, 10 and 100 individuals
b	Replication rate	15 descendants per parental individual (average).
K	Carrying capacity	200 individuals
L	Genome size	1000 loci
μ	Mutation rate	10^{-3}
σ	Deviation rate for survival probability	10
P_{h1}	Optimum phenotype imposed by the donor host	500
P_{h2}	Optimum phenotype imposed by the colonized host	$500 \leq P_{h2} \leq 540$ ($0 \leq D \leq 4$)
t_{int}	Time to migration	1 and 200

In our first assessment, we estimated the *probability of establishment* in the new host as a function of the phenotypic distance between hosts. For that, we fixed the optimum phenotype of the donor host at P_{h1}=500 and varied P_{h2} between *500* and *540* every 1, which corresponds to a distance between hosts, $D = \frac{(P_{h2} - P_{h1})}{\sigma}$, from 0 to 4, measured in units of standard deviation σ . The D value can be understood as a continuum of differentiation between any host traits that influence parasite compatibility. This parameter is commonly interpreted as the "phylogenetic distance effect" (Longdon et al. 2014; Engelstädter and Fortuna 2019). Although the distribution of characteristics across phylogenies is not linear,

phylogenies are the best proxy for the distribution of biological characteristics we have access to.

We define the *probability of establishment* as the percentage of simulations with individuals present in H_2 for 50 generations after the introduction of the propagule. We also investigated the effects of three propagule sizes, S = 1, 10 and 100 individuals. The results consist of an average of 1000 replicates for each combination of parameters. We measured the *farther distance the parasite can colonize* as distance D for which the probability of establishment reaches at least 5%. The *host repertoire expansion* due to propagule variability will be presented as a percentage ($D_{tint=200}/D_{tint=1}$*100).

We also tracked the colonization process and phenotype evolution after host switching. We recorded the phenotype of each individual present in the propagule, if it survived the selective pressure imposed soon after its arrival, the *number of phenotypes* (number of unique phenotypes), and the *phenotypic amplitude* ($max(p_i) - min(p_i)$) in both hosts after 1000 generations. If the number of phenotypes equals the phenotypic amplitude, we conclude that the phenotypes of parasite individuals have a continuous distribution. Otherwise, the discontinuity can indicate the emergence of new phenotype lineages. These results were only considered when the success of establishment in H_2 occurred in at least 5% of replicates. For this approach, we restricted t_{int} = 200, S = 100, and investigated the dynamics for different distance between hosts, D = {0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0}. For $D \geq 3.5$, the success of establishment was smaller than 5%. The remaining parameter values (b, K, L, μ, and σ) are the same ones used in the previous approach (listed in Table 1). For these results consider 200 replications for each parameter combination.

We considered as a "*rare event*" when the success of establishment occurred less than 5% of the repetitions. To evaluate if the rare events are related to individuals with low frequent phenotypes in the original population, we ran new simulations until 100 establishment successes were achieved. We recorded the phenotype of each individual present in the propagule, if it survived the selective pressure imposed soon after its arrival, and the phenotype evolution up to 1000 generations. Here we fixed the distance between host to D = 3.5 (P_{h2} = 535), t_{int} = 200, S = 100, and the other parameters are the same applied previously (Table 1).

3.4 Results

3.4.1 Propagule size and variability

The values of propagule size and its phenotypic variability may increase the success of establishment of a parasite population in a new host (Figure 2). The increase in the propagule size from 1 to 10 individuals was more relevant to the host repertoire expansion than the increase from 10 to 100 individuals in scenarios with phenotypic variability; while the first increased the reached distance in 22.72% (from D = 2.2 to D = 2.7) the later increased in 11.11% (from D = 2.7 to D = 3.0) (Table 2). In scenarios without phenotypic variability, this effect was smaller (9.09% and 8.33%, respectively). The host repertoire expansion due to propagule variability was 12.5% (S = 10, from D = 2.4 to D = 2.7) and 15,38% (S = 100, from D = 2.6 to D = 3.0) (Table 2).

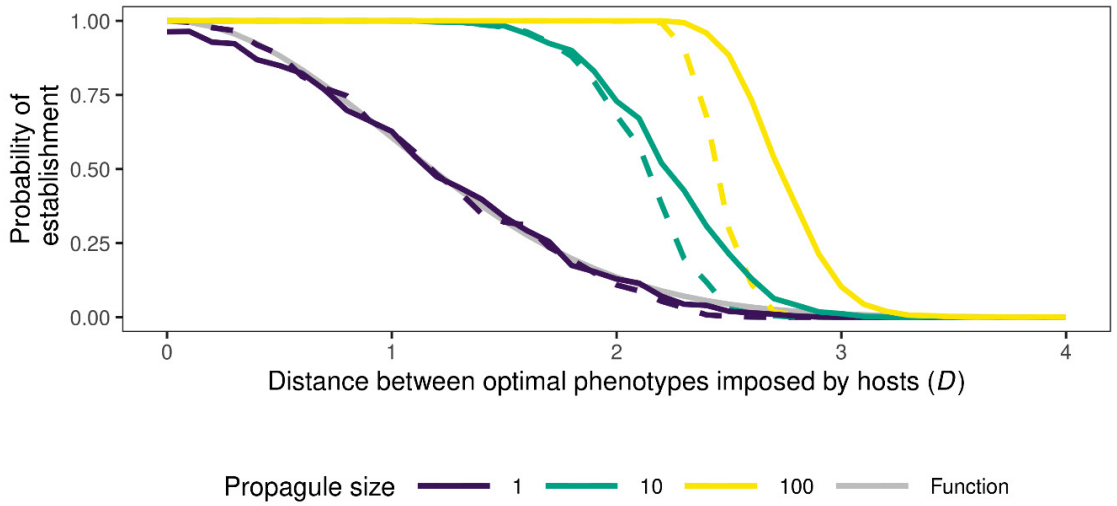

Figure 2: Probability of establishment as a function of the distance between hosts (measured in units of σ). Dashed line: scenario without propagule variability. Continuous line: scenario with propagule variability. Gray line (Function): probability of a single parasite surviving after introduction into the new host (Eq. 1). The graph shows that both propagule variability and size can increase the probability of establishment. The other parameters used in these simulations are listed in Table 1.

Table 2: Farther distance between hosts (*D*) reached by parasite for different propagule sizes, and time to migration (t_{int}).

Propagule size	t_{int} = 1	t_{int} = 200
1	2.2	2.2
10	2.4	2.7
100	2.6	3.0

Since the propagules are randomly sampled, their phenotype distribution is not equivalent to the original population in a single sampling event. The phenotype distribution showed in Figure 3 results of accumulated data from 200 repetitions and, therefore, is equivalent to 200 sampling events. However, note that the phenotype distribution is, on average, equivalent to the original population (same average and standard deviation). Nonetheless, individuals whose phenotypes are closer to P_{h2} have a higher chance of surviving, thereby modifying the phenotype distribution for the surviving propagules (Figure 3).

For successful establishments in a new host, the phenotypic amplitude and the number of different phenotypes at the end of 1000 generations were positively related to the distance between hosts (Fig. 4). The phenotypes encompass a continuous range when the distance between hosts is up to D = 1.5: the number of different phenotypes equals the phenotypic amplitude for $D \leq 1.5$ (compare Fig. 4.A to Fig. 4.B). However, when the colonization occurs between more distant hosts ($D > 1.5$), the phenotype amplitude is greater than the number of different phenotypes, meaning that the phenotype continuity is broken and phenotypically different lineages emerge. We do not present the results for D > 3 because the frequency of successful establishment was smaller than 5% (rare events).

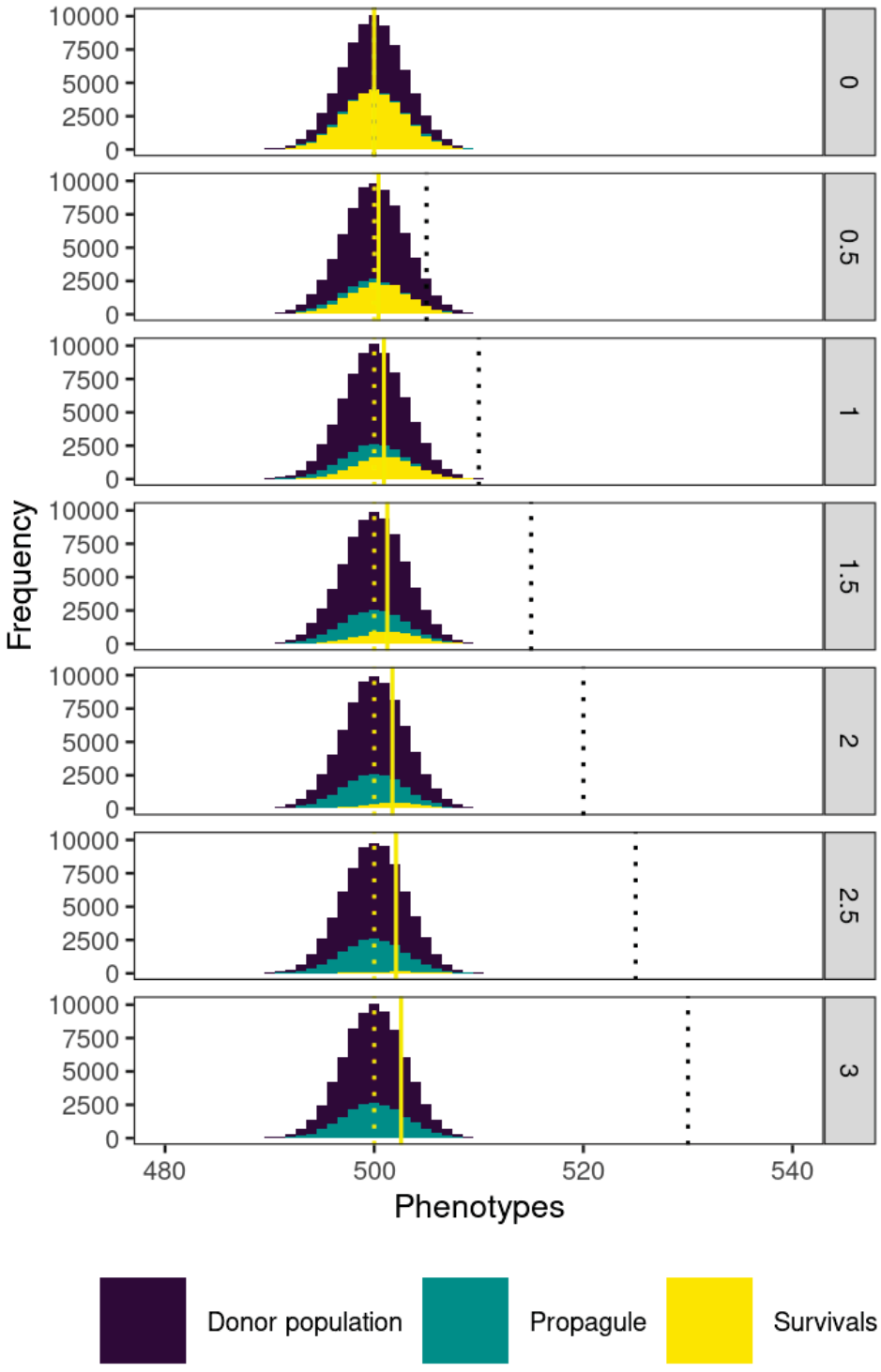

Figure 3: Phenotype distribution of donor population, propagule (with phenotypic variability) and survivals (indicated by the legend). The dotted yellow and black lines indicate the optimum phenotype imposed by the original and destination hosts, respectively. The continuous yellow line indicates the mean phenotype of the surviving propagules. The values on the right show the distance D between hosts in standard deviation units. Each graph accumulates data of 200 repetitions, and uses $t_{int} = 200$, $S = 100$. The other parameters are the same used in the previous simulations and are listed in Table 1.

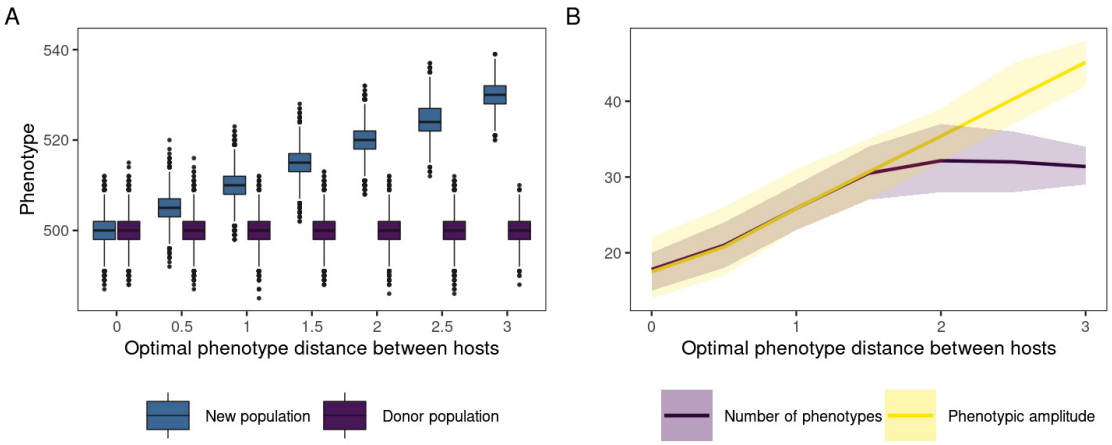

Figure 4: Effect of host colonization on parasite phenotypes as a function of the distance between original and new hosts. (A) Phenotype distribution in original and destination hosts (indicated in the legend). (B) Number of different phenotypes and phenotype amplitude (max(p_i) - min(p_i)) (indicated in the legend), considering all parasites, regardless of the host. Each graph accumulates data of 200 repetitions considering 1000 generations, t_{int} = 200, S = 100. The other parameters are the same used in the previous simulations and are listed in Table 1.

3.4.2 Rare events

When the destination host is far from the original (D = 3.5), most surviving propagules have phenotypes on the tail of the distribution in the population of the donor host (rare phenotypes) (Figure 5). Phenotypes greater than 507 represent 0.77% of the original distribution of propagule phenotypes. However, tail phenotypes represent 71.22% of the individuals that succeed in the colonization event. After the host switching, the population formed from one or a few individuals has phenotypes whose survival probability in the new host is very low ($P_{surv} \leq 0.13$). Over generations, the population size of parasites grows in the newly colonized host and the generated phenotypes approach the optimal value imposed by the host, stabilizing around P_{h2} (Figure 5, bottom).

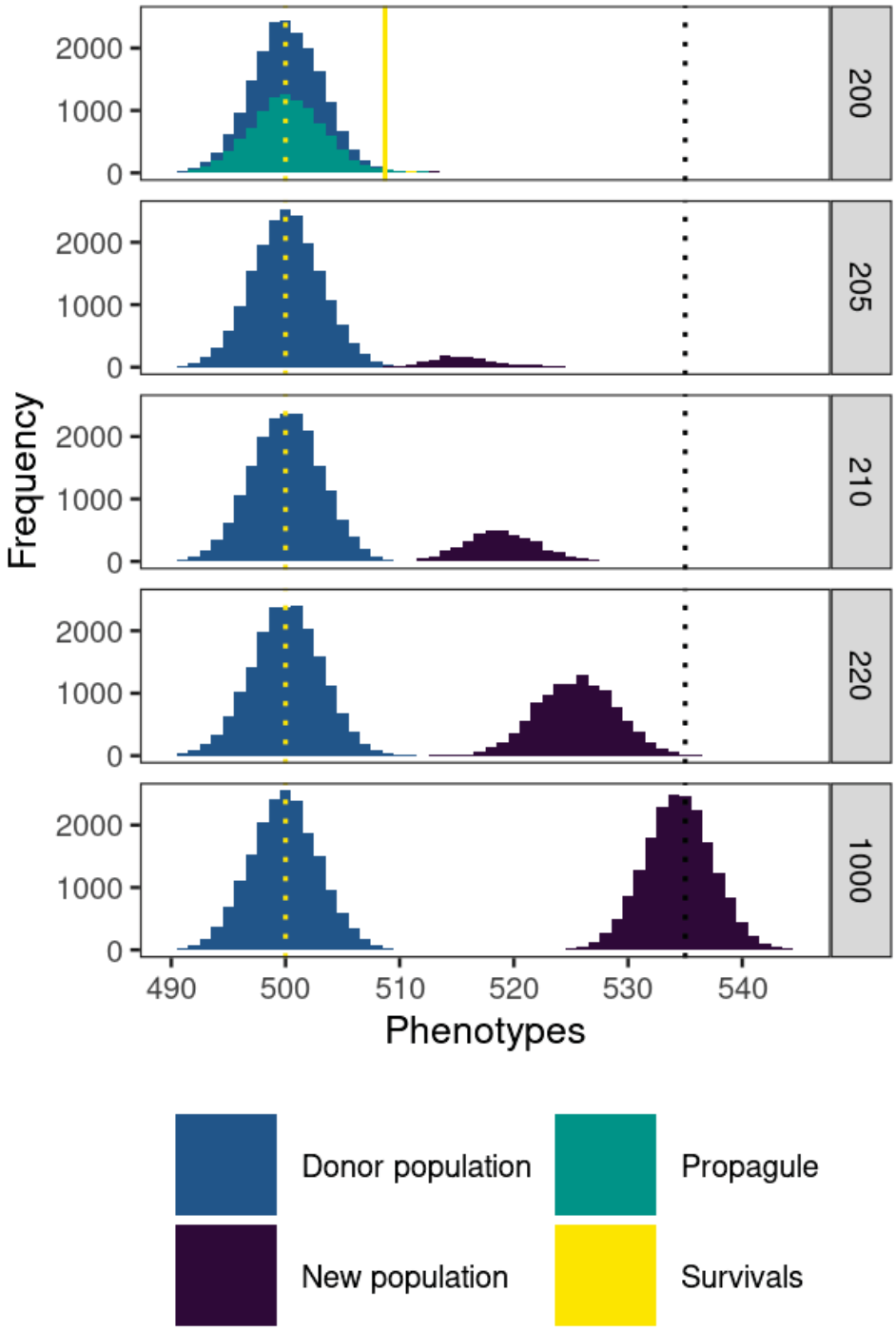

Figure 5: Evolution of colonization by rare phenotypes. The graphs show the phenotype distribution of original population, propagules, surviving propagules and the new parasite population over time (indicated in the right of each graph). The dotted yellow and black lines indicate the optimum phenotype imposed by the donor and new hosts, respectively. The continuous yellow line indicates the mean phenotype of the surviving propagules. Each graph accumulates data of 100 repetitions considering 1000 generations, t_{int} = 200, S = 100. The other parameters are the same used in the previous simulations and can be found in Table 1.

3.5 Discussion

In this study, we investigated the effect of parasite phenotypic variability on the success of establishment in new hosts and parasite evolution using an Individual Based Model. We observed that: (i) propagule phenotypic variability increases the success of colonization of new hosts, (ii) the colonization of distant hosts favors phenotypic divergence between parasite populations, and (iii) the elusive variants (low frequency phenotypes in the donor parasite population) are responsible for more distant host colonization.

When parasites colonize a new host, stochastic and deterministic processes usually reduce the original size of the propagule and respective diversity (Forsman 2014; Zwart and Elena 2015; McCrone and Lauring 2018). It is expected that the number of surviving individuals/variants decreases as the difference between selective regimes imposed by hosts (here represented by distance *D*) increases. Feronato, Araujo, and Boeger (2021) demonstrated that larger propagules have a higher probability of colonizing more distant hosts by providing greater resilience against unfavorable demographic circumstances. Our results suggest that these findings are even more pronounced in simulations incorporating phenotypic variability in the propagule (Fig. 2). In addition to promoting greater resistance to stochasticity, larger propagules contain greater phenotypic variability (See Fig. S2 in supplementary material), which provide a larger set of inheritable information (i.e., capacity) to cope with diverse selective pressures imposed by potential hosts. Although the longer jump between hosts occurs from the synergistic effect of these parameters, our results suggest that any increase in capacity is relevant to promote a greater probability of establishing a new association. However, the propagule size has no influence on the phenotypic amplitude and the number of phenotypes observed at the end of the simulations (See Fig. 4 and Fig. S3 in supplementary material).

Our results also evidenced that, low-frequency phenotypes - the elusive variants - play a significant role in colonizing more distant hosts (Fig. 5). Although the low frequency of some variants may be associated with a poor fit to the current host, their traits may provide a better ability to exploit a new host (Brooks, Hoberg, and Boeger 2019). If the new host represent a set of resources and limitations more favorable to their capacities, these variants can occur at a higher frequency

than in their donor population. In fact, if any compatibility exists, and there are no superior competitors, these variants can quickly colonize and establish populations in the new host, even in the absence of mutational rate to promote a better fit between them and the new host (Feronato, Araujo, and Boeger 2021). When this elusive variant emerges in the new host, it can be mistakenly interpreted like a new mutation that allowed a known variant in the donor host to access the new host. Elusive variants can also play a transient role in the colonization of new hosts. Figure 5 exemplifies the evolution of the parasite phenotypes in the new distant host (D = 3.5). Note that as the population accommodates around the new optimum phenotype imposed by the host, the variants that made up the founding population become extinct over time (by competition). Although this is not a deterministic outcome, it suggests that these elusive variants, those responsible for longer jumps, can be responsible only for the new host colonization, not for the maintenance of the new population.

Subsequent generations of parasites following the colonization of the new host accumulate positively selected mutations driving the new populations toward the optimum phenotype imposed by the host (the peak fitness of the new hosts). As a result, we observed an increase in the phenotypic variability (measured by phenotype amplitude and number of phenotypes) of the parasites as the host distance increased (Fig. 4). Although in our simulations the accommodation of the population around the optimum imposed by the host is always achieved, this is not expected in real life. Unlike real life, our model assumes constant selective pressure throughout the simulation, which means that there is no variability within the host population, nor is there any host evolution. Furthermore, factors such as host defenses (especially in complex organisms), ecological interactions, arrival of new propagules, among other stochastic factors (the lack of adaptative mutations emergence, mainly) can act against this result. Despite these statements, our results are in line with the various evidence of greater sharing of parasites between closely related hosts, and that suggests that host/resource variability can generate a rapid increase in the diversification of their parasites/consumers (Charleston and Robertson 2002; Gilbert and Webb 2007; Streicker et al. 2010; Gómez, Verdú, and Perfectti 2010; Faria et al. 2013; Longdon et al. 2014; Braga, Araujo, et al. 2018; Braga, Guimarães, et al. 2018; Huang, Farrell, and Stephens 2021).

Unfortunately, the above outcomes and conclusions do not align with current public health policies, wherein its assumed that parasites and hosts coevolve towards maximum specialization of the parasite in its host, resulting in the loss of the capacity to utilize other hosts (Molnár, Knickel, and Marizzi 2022; Molnár et al. 2022). In this concept, for the colonization of a new host to occur, the right mutation (i.e., one that generates the right capacity) would occur when the opportunity to colonize a new host arises. Under this scenario, colonization of new host species by parasites should be rare, contradicting the observed frequency of emergence of new associations, including symbionts and pathogens (World Health Organization 2007; De Vienne et al. 2013; Nylin et al. 2018).

Public health measures based on this idea place us in a passive situation in face of emerging diseases, as it is impossible to prepare for something this rare and unpredictable as the occurrence of the right mutation at the right time (Brooks, Hoberg, and Boeger 2019; Molnár, Knickel, and Marizzi 2022; Molnár et al. 2022). Consequently, our only option is to react to the crisis, likely in a delayed way compared to the spread of the disease. Fortunately, the current paradigm, The Stockholm Paradigm (SP), places us in an advantageous position regarding the emergence of diseases, enabling proactive actions for prevention (Molnár, Knickel, and Marizzi 2022). While it is common to think of evolution in terms of changes in characteristics over time, evolution also involves the conservation of traits, and it is what allows us to predict the risk of host-switch without having to wait for an outbreak. The SP recognizes that although it is expected that parasites living with a particular host for long periods tend to accommodate to them, this does not mean a perfect association, in which all individuals in the parasite population are perfectly matched with their host, nor that their capacities not expressed in the current host are lost. Therefore, given the opportunity, the capacity will be expressed. It means that parasites may retain the ability to use ancestral hosts, or those representing conditions and resources similar to those already utilized. If it is true, and it seems to be, we can deduce that host-switching events are neither rare nor totally unpredictable. Our ability to anticipate the emergence of new associations depends on the understanding of the elements that influence opportunity and compatibility. Opportunity is mostly about ecology, about changes in behavior and the movements of species induced by climate changes, human travel and transportation, or natural movements. The capacity

of parasites to colonize new hosts is greatly dependent on the defenses of the hosts – both sets of factors result in compatibility. The combinations of capacity of parasites and defenses of hosts are greatly variable among putative associations in the diverse and complex biosphere, and we ought to use proxies to infer compatibility. Phylogenetic distance among host species has been suggested as the most adequate proxy (Brooks et al. 2014b; Antia et al. 2003; Hoberg et al. 2023) as strongly supported by empirical (Walsh et al. 2023; Damas et al. 2020) and simulations studies (D'Bastiani et al. 2023a).

Finally, it is important to recognize that we only evaluate host-parasite pairs and that there is no reason to believe that parsites are exposed to only one potential new host under real-world conditions. Thus, once colonization of new hosts occurs several times, the values for variability and number of lineages in a parasite population would be much higher. This can be even more extreme if we consider the possibility of "stepping-stone" colonization (Braga, Razzolini, and Boeger 2015; Araujo et al. 2015). This is only one example of the model limitation. When we work with models, simplifications of reality are necessary and, in no way, does this invalidate the learning generated by this tool. The objective of creating models is to generate insights into situations that could hardly be studied in vivo, and, thus, direct us to points of attention regarding the object/mechanism of study.

3.6 Conclusions

Here, we demonstrated the colonization of new hosts based on pre-existing capacities of the parasite. Our results showed that phenotypic variability increases the success of parasite establishment in new host species; that elusive variants can be responsible for the success of establishment in hosts quite different from those previously used; and that colonization of new hosts plays an important role in parasite diversification. We believe that this study will contribute to the understanding of parasite evolution and the mechanism of new host-parasite associations.

3.7 References

Agosta, S.J., Janz, N., Brooks, D.R., 2010. How specialists can be generalists: Resolving the and “parasite paradox” and implications for emerging infectious disease. Zoologia 27, 151–162. https://doi.org/10.1590/S1984-46702010000200001

Agosta, S.J., Klemens, J.A., 2008a. Ecological fitting by phenotypically flexible genotypes: implications for species associations, community assembly and evolution. Ecol. Lett. 11, 1123–1134. https://doi.org/10.1111/j.1461-0248.2008.01237.x

Agosta, S.J., Klemens, J.A., 2008b. Ecological fitting by phenotypically flexible genotypes: Implications for species associations, community assembly and evolution. Ecol. Lett. 11, 1123–1134. https://doi.org/10.1111/j.1461-0248.2008.01237.x

Altizer, S., Ostfeld, R.S., Johnson, P.T., Kutz, S., Harvell, C.D., 2013. Climate change and infectious diseases: from evidence to a predictive framework. science 341, 514–519.

Andersen, K.G., Rambaut, A., Lipkin, W.I., Holmes, E.C., Garry, R.F., 2020. The proximal origin of SARS-CoV-2. Nat. Med. 26, 450–452. https://doi.org/10.1038/s41591-020-0820-9

Antia, R., Regoes, R.R., Koella, J.C., Bergstrom, C.T., 2003. The role of evolution in the emergence of infectious diseases. Nature 426, 658–661.

Araujo, S.B.L., Braga, M.P., Brooks, D.R., Agosta, S.J., Hoberg, E.P., Von Hartenthal, F.W., Boeger, W.A., 2015. Undestanding host-switching by ecological fitting. PLoS ONE 10, 1–17. https://doi.org/10.1371/journal.pone.0139225

Baskin, Y., 2006. Sea Sickness: The Upsurge in Marine Diseases. BioScience 56, 464. https://doi.org/10.1641/0006-3568(2006)56[464:SSTUIM]2.0.CO;2

Boeger, W.A., Brooks, D.R., Trivellone, V., Agosta, S.J., Hoberg, E.P., 2022. Ecological super-spreaders drive host–range oscillations: Omicron and risk space for emerging infectious disease. Transbound. Emerg. Dis. https://doi.org/10.1111/tbed.14557

Braga, M.P., Araujo, S.B.L., Agosta, S., Brooks, D., Hoberg, E., Nylin, S., Janz, N., Boeger, W.A., 2018a. Host use dynamics in a heterogeneous fitness landscape generates oscillations in host range and diversification. Evolution 72, 1773–1783. https://doi.org/10.1111/evo.13557

Braga, M.P., Guimarães, P.R., Wheat, C.W., Nylin, S., Janz, N., 2018b. Unifying host-associated diversification processes using butterfly–plant networks. Nat. Commun. 9, 1–10. https://doi.org/10.1038/s41467-018-07677-x

Braga, M.P., Razzolini, E., Boeger, W.A., 2015. Drivers of parasite sharing among Neotropical freshwater fishes. J. Anim. Ecol. 84, 487–497. https://doi.org/10.1111/1365-2656.12298

Broglio, E., Solé, R.V., 2004. CLIMATE CHANGE AND THE BIODIVERSITY CRISIS AS PROMOTERS FOR EMERGENT Climate change and the biodiversity crisis as promoters for emergent diseases.

Brooks, D.R., 2011. The emerging infectious diseases crisis and pathogen pollution. Balance Nat. Hum. Impact 215–230. https://doi.org/10.1017/CBO9781139095075.022

Brooks, D.R., Boeger, W.A., 2019a. Climate change and emerging infectious diseases: Evolutionary complexity in action. Curr. Opin. Syst. Biol. 13, 75–81.

Brooks, D.R., Boeger, W.A., 2019b. Climate change and emerging infectious diseases: Evolutionary complexity in action. Curr. Opin. Syst. Biol. 13, 75–81. https://doi.org/10.1016/j.coisb.2018.11.001

Brooks, D.R., Hoberg, E.P., Boeger, W.A., 2019. The Stockholm Paradigm: Climate Change and Emerging Disease. University of Chicago Press.

Brooks, D.R., Hoberg, E.P., Boeger, W.A., Gardner, S.L., Galbreath, K.E., Herczeg, D., Mejía-Madrid, H.H., Rácz, S.E., Dursahinhan, A.T., 2014a. Finding them before they find Us: Informatics, parasites, and environments in accelerating climate change. Comp. Parasitol. 81, 155–164. https://doi.org/10.1654/4724b.1

Brooks, D.R., Hoberg, E.P., Boeger, W.A., Gardner, S.L., Galbreath, K.E., Herczeg, D., Mejía-Madrid, H.H., Rácz, S.E., Dursahinhan, A.T., 2014b. Finding them before they find us: informatics, parasites, and environments in accelerating climate change. Comp. Parasitol. 81, 155–164.

Brooks, D.R., Hoberg, E.P., Boeger, W.A., Trivellone, V., 2021. Emerging infectious disease: An underappreciated area of strategic concern for food security. Transbound. Emerg. Dis. tbed.14009. https://doi.org/10.1111/tbed.14009

Cassey, P., Delean, S., Lockwood, J.L., Sadowski, J.S., Blackburn, T.M., 2018. Dissecting the null model for biological invasions: A meta-analysis of the propagule pressure effect. PLoS Biol. 16, 1–16. https://doi.org/10.1371/journal.pbio.2005987

Charleston, M.A., Robertson, D.L., 2002. Preferential host switching by primate lentiviruses can account for phylogenetic similarity with the primate phylogeny. Syst. Biol. 51, 528–535. https://doi.org/10.1080/10635150290069940

Conn, D.B., 2014. Aquatic invasive species and emerging infectious disease threats: A One Health perspective. Aquat. Invasions 9, 383–390. https://doi.org/10.3391/ai.2014.9.3.12

Damas, J., Hughes, G.M., Keough, K.C., Painter, C.A., Persky, N.S., Corbo, M., Hiller, M., Koepfli, K.-P., Pfenning, A.R., Zhao, H., Genereux, D.P., Swofford, R., Pollard, K.S., Ryder, O.A., Nweeia, M.T., Lindblad-Toh, K., Teeling, E.C., Karlsson, E.K., Lewin, H.A., 2020. Broad Host Range of SARS-CoV-2 Predicted by Comparative and Structural Analysis of ACE2 in Vertebrates. bioRxiv. https://doi.org/10.1101/2020.04.16.045302

D’Bastiani, E., Princepe, D., Marquitti, F.M.D., Boeger, W.A., Campião, K.M., Araujo, S.B.L., 2023a. Effect of Host-Switching on the Ecological and Evolutionary Patterns of Parasites. Syst. Biol. 72, 912–924. https://doi.org/10.1093/sysbio/syad022

D’Bastiani, E., Princepe, D., Marquitti, F.M.D., Boeger, W.A., Campião, K.M., Araujo, S.B.L., 2023b. Effect of Host-Switching on the Ecological and Evolutionary Patterns of Parasites. Syst. Biol. 72, 912–924. https://doi.org/10.1093/sysbio/syad022

De Vienne, D.M., Giraud, T., Shykoff, J.A., 2007. When can host shifts produce congruent host and parasite phylogenies? A simulation approach. J. Evol. Biol. 20, 1428–1438. https://doi.org/10.1111/j.1420-9101.2007.01340.x

De Vienne, D.M., Refrégier, G., López-Villavicencio, M., Tellier, A., Hood, M.E., Giraud, T., 2013. Cospeciation vs host-shift speciation: Methods for testing, evidence from natural associations and relation to coevolution. New Phytol. 198, 347–385. https://doi.org/10.1111/nph.12150

Engelstädter, J., Fortuna, N.Z., 2019. The dynamics of preferential host switching: Host phylogeny as a key predictor of parasite distribution*. Evolution 73, 1330–1340. https://doi.org/10.1111/evo.13716

Faria, N.R., Suchard, M.A., Rambaut, A., Streicker, D.G., Lemey, P., 2013. Simultaneously reconstructing viral crossspecies transmission history and identifying the underlying constraints. Philos. Trans. R. Soc. B Biol. Sci. 368. https://doi.org/10.1098/rstb.2012.0196

Feronato, S.G., Araujo, S., Boeger, W.A., 2021. ‘Accidents waiting to happen’—Insights from a simple model on the emergence of infectious agents in new hosts. Transbound. Emerg. Dis. tbed.14146. https://doi.org/10.1111/tbed.14146

Forsman, A., 2014. Effects of genotypic and phenotypic variation on establishment are important for conservation, invasion, and infection biology. Proc. Natl. Acad. Sci. U. S. A. 111, 302–307. https://doi.org/10.1073/pnas.1317745111

Garrett, L., 1994. The coming plague: Newly emerging diseases in a world out of balance. Farrar, Straus and Giroux.

Gilbert, G.S., Webb, C.O., 2007. Phylogenetic signal in plant pathogen – host range 104, 4979–4983. https://doi.org/10.1073/pnas.0607968104

Gómez, J.M., Verdú, M., Perfectti, F., 2010. Ecological interactions are evolutionarily conserved across the entire tree of life. Nature 465, 918–921. https://doi.org/10.1038/nature09113

Hoberg, E.P., Boeger, W.A., Molnár, O., Földvári, G., Gardner, S.L., Juarrero, A., Kharchenko, V., Ortíz, E., Preiser, W., Trivellone, V., others, 2023. The DAMA Protocol: Anticipating to Prevent and Mitigate Emerging Infectious Diseases. Evol. Pathw. Coping Emerg. Infect. Dis. Gardner SL Brooks DR Boeger WA Hoberg EP Eds.

Holle, V., Simberloff, D., 2005. Ecological Resistance to Biological Invasion Overwhelmed by Propagule Pressure Author(s): Betsy. Source Ecol. 86, 3212–3218.

Huang, S., Farrell, M., Stephens, P.R., 2021. Infectious disease macroecology: Parasite diversity and dynamics across the globe. Philos. Trans. R. Soc. B Biol. Sci. 376. https://doi.org/10.1098/rstb.2020.0350

Janzen, D.. H.., 1985. On Ecological Fitting. Oikos 45, 308–310.

Longdon, B., Brockhurst, M.A., Russell, C.A., Welch, J.J., Jiggins, F.M., 2014. The Evolution and Genetics of Virus Host Shifts. PLoS Pathog. 10. https://doi.org/10.1371/journal.ppat.1004395

McCrone, J.T., Lauring, A.S., 2018. Genetic bottlenecks in intraspecies virus transmission. Curr. Opin. Virol. 28, 20–25. https://doi.org/10.1016/j.coviro.2017.10.008

Molnár, O., Hoberg, E., Trivellone, V., Földvári, G., R., D., 2022a. The 3P Framework: A Comprehensive Approach to Coping with the Emerging Infectious

Disease Crisis. MANTER J. Parasite Biodivers. https://doi.org/10.32873/unl.dc.manter23

Molnár, O., Knickel, M., Marizzi, C., 2022b. Taking Action: Turning Evolutionary Theory into Preventive Policies. MANTER J. Parasite Biodivers. https://doi.org/10.32873/unl.dc.manter28

Nuismer, S.L., Thompson, J.N., 2006. Coevolutionary Alternation in Antagonistic Interactions. Evolution 60, 2207. https://doi.org/10.1554/06-111.1

Nylin, S., Agosta, S., Bensch, S., Boeger, W.A., Braga, M.P., Brooks, D.R., Forister, M.L., Hambäck, P.A., Hoberg, E.P., Nyman, T., Schäpers, A., Stigall, A.L., Wheat, C.W., Österling, M., Janz, N., 2018. Embracing Colonizations: A New Paradigm for Species Association Dynamics. Trends Ecol. Evol. 33, 4–14. https://doi.org/10.1016/j.tree.2017.10.005

O'Dowd, A., 2007. Infectious diseases are spreading more rapidly than ever before, WHO warns. BMJ 335, 418. https://doi.org/10.1136/bmj.39318.516968.DB

Rosenthal, S.R., Ostfeld, R.S., McGarvey, S.T., Lurie, M.N., Smith, K.F., 2015. Redefining disease emergence to improve prioritization and macro-ecological analyses. One Health 1, 17–23. https://doi.org/10.1016/j.onehlt.2015.08.001

Savary, S., Willocquet, L., Pethybridge, S.J., Esker, P., McRoberts, N., Nelson, A., 2019. The global burden of pathogens and pests on major food crops. Nat. Ecol. Evol. 3, 430–439. https://doi.org/10.1038/s41559-018-0793-y

Simberloff, D., 2009. The role of propagule pressure in biological invasions. Annu. Rev. Ecol. Evol. Syst. 40, 81–102. https://doi.org/10.1146/annurev.ecolsys.110308.120304

Streicker, D.G.; Turmelle, A.S.; Vonhof, M.J.; Kuzmin, I.V.; McCracken, G.F.; Rupprecht, C.E. 2010. Host phylogeny constrains cross-species emergence and establishment of rabies virus in bats. Science 329: 676–679. https://doi.org/10.1126/science.1188836

Trivellone, V., Hoberg, E.P., Boeger, W.A., Brooks, D.R., 2022. Food security and emerging infectious disease: Risk assessment and risk management. R. Soc. Open Sci. 9. https://doi.org/10.1098/rsos.211687

UN-DESA, 2022. World population prospects 2022: summary of results. United Nations, New York.

Walsh, S.K., Imrie, R.M., Matuszewska, M., Paterson, G.K., Weinert, L.A., Hadfield, J.D., Buckling, A., Longdon, B., 2023. The host phylogeny determines viral infectivity and replication across Staphylococcus host species. PLOS Pathog. 19, e1011433. https://doi.org/10.1371/journal.ppat.1011433

Wilson, M.E., 1995. Travel and the emergence of infectious diseases. Emerg. Infect. Dis. 1, 39.

World Health Organization, 2007. The world health report 2007 : a safer future : global public health security in the 21st century. 1.World.

Zwart, M.P., Elena, S.F., 2015. Matters of Size: Genetic Bottlenecks in Virus Infection and Their Potential Impact on Evolution. Annu. Rev. Virol. 2, 161–179. https://doi.org/10.1146/annurev-virology-100114-055135

3.8 Supplementary

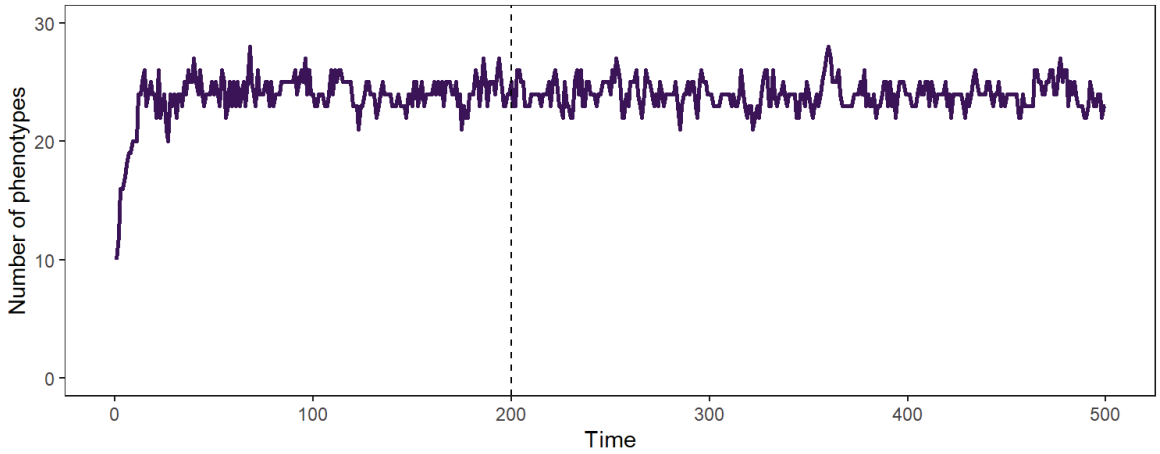

Figure S1: Number of phenotypes over time. The dashed line indicates the moment of host-switching (t_{int} = 200) in scenarios with phenotypic variability.

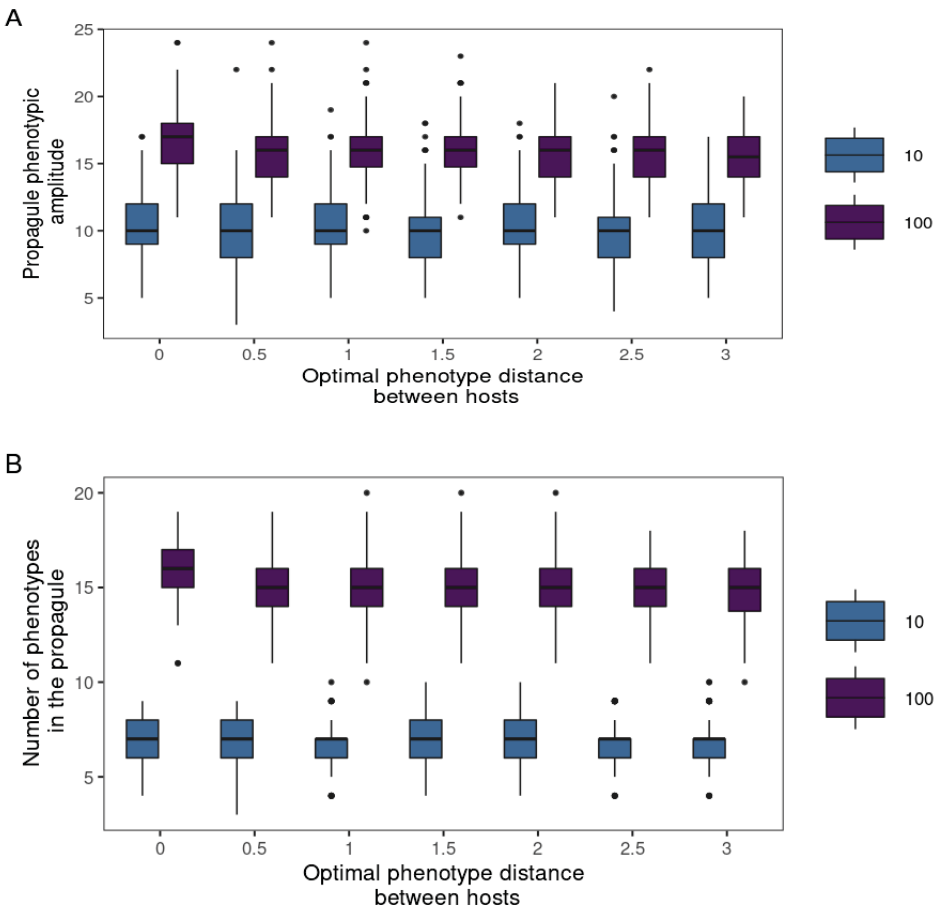

Figure S2: Propagule phenotypic amplitude and number of phenotypes in the propagule.

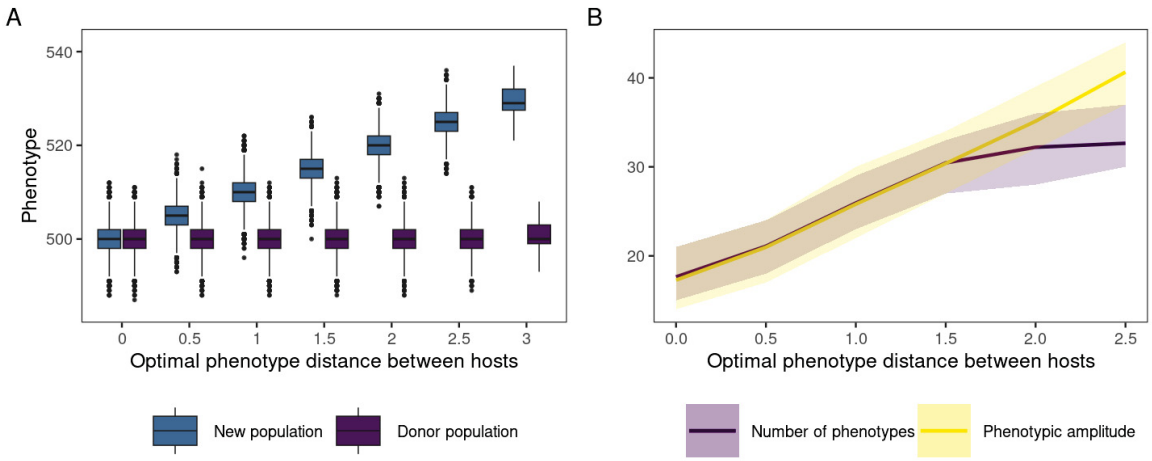

Figure S3: Effect of host colonization on parasite phenotypes as a function of the distance between original and new hosts. (A) Phenotype distribution in original and destination hosts (indicated in the legend). (B) Number of different phenotypes and phenotype amplitude (max(p_i) - min(p_i)) (indicated in the legend), considering all parasites, regardless of the host. Each graph accumulates data of 200 repetitions considering 1000 generations, t_{int} = 200, ***S* = 10**. The other parameters are the same used in the previous simulations and are listed in Table 1.

4. CAPÍTULO 3

Chapter 3

Does the use of new hosts leave signatures in the parasite evolution?

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4.1 Abstract

The current scenario of globalization provides greater chances of encounter between parasites and potential hosts. Considering that colonizations of new hosts are not rare, understanding the ecological and evolutionary aspects of these associations is essential to preventing the emergence of infectious diseases. Here, we link a microevolutionary process, the colonization of a new host, to macroevolutionary patterns displayed by parasites, investigating whether these events can leave signatures on parasite evolution. We developed an individual-based model (IBM) in which some parasite individuals living in a donor host have the opportunity to colonize a new host, and we tracked the evolution of both parasites' populations. We recorded the number of mutations, genetic lineages, extinctions, diversification events, and characterized the phylogenetic patterns in tree balance and acceleration of diversification. We found temporary signatures in all metrics assessed. The signatures are lost as the colonization event recedes further into the past, highlighting the challenge of inferring the microevolutionary event of host switching based on macroevolutionary patterns only.

Keywords: Host colonization, host-switching, macroevolutionary patterns, pathogen, phylogeny.

4.2 Introduction

Understanding what generates and maintains biodiversity is one of the biggest questions in biology (Sutherland et al., 2013). The growing knowledge about how the composition of communities responds to environmental conditions

and the biotic interactions, their effects on the functioning of ecosystems, and, more recently, the consequences generated by Anthropocene climate changes, has highlighted the importance of maintaining biodiversity (Destoumieux-Garzón et al., 2018; Edwards and Abivardi, 1998; Oliver et al., 2015). When we talk about parasites we have an additional layer: their relationship with their hosts. The Stockholm Paradigm (Brooks et al., 2019, 2014) provides a robust theoretical framework to explain the evolution of interactions between parasites and hosts, providing valuable information to understand and cope with the emergence of infectious diseases, and their relationship with climate change. The Stockholm Paradigm suggests flexibility in the use of hosts by parasites, with the host switching being the most common mechanism for parasites diversification. This information has been supported by several studies that evaluated such interactions in different biological groups and by the improvement of methodologies for reconstructing phylogenies (Charleston and Robertson, 2002; De Vienne et al., 2013; Doña et al., 2017; Giraud et al., 2010; Longdon et al., 2014). Such flexibility is explained by the concept of ‘ecological fitting’ (Janzen, 1985) which, applied to parasitism, implies the possibility of switching to a new host (ecological change) once the pre-existing capacity to use the resources it provides, as well as to cope with the defenses that it imposes, exists (Agosta and Klemens, 2008; Araujo et al., 2015).

Theoretical models have already explored how the similarity between hosts/resources increases the chance of successful new colonization (Araujo et al. 2015; Feronato, Araujo, and Boeger 2021; Chapter 2). They show that new colonizations may not be restricted to close related hosts (which offers similar resources), although the colonization probability decreases as the resources differ. Colonization of a sufficient distant host may be rare since it imposes a more different selection pressure on the parasites (Chapter 2). However, once it succeeds, this new selection pressure can drive consumers' evolution in forming new phenotypic variants (Chapter 2). In fact, studies suggest that the greater the divergence in the selective pressure imposed by the hosts used, the more pronounced the differentiation between the populations of parasites that inhabit them (Braga et al., 2018; Freitas et al., 2022; Nyman, 2010). Some of these theoretical studies have explored the colonization process on an eco-adaptative scale (Araujo et al. 2015; Braga et al. 2018; Feronato, Araujo, and Boeger 2021;

Freitas, Araujo, and Campos 2022, Chapter 2), however, even those who consider speciation events (Braga et al. 2018; Freitas, Araujo, and Campos 2022) have not explored the parasites' evolution patterns (such as speciation and extinction rates). Therefore, we still do not completely understand the macroevolutionary consequences that emerged from the microevolutionary dynamics of new colonizations.

A recent example is the case of the Ômicron variant of the SARS-CoV-2 virus. The mutations present in the Spike protein are qualitatively and quantitatively different from those observed in other variants in circulation (Nextrain phylogeny, 2022 in Hadfield et al. 2018; Boeger et al. 2022). Such discrepancies suggest that independent differentiation of this lineage has been occurring since the beginning of the COVID-19 pandemic. One of the hypotheses proposed by the scientific community to explain the origin of Ômicron is that it evolved in a non-human animal species (contaminated from infected humans at the beginning of the pandemic) and subsequently re-colonized us (Kupferschmidt, 2021; Sun et al., 2022). Boeger and colleagues (2022) endorse this idea by suggesting that hosts whose ACE2 receptor structure differs from that found in humans and, therefore, represent a distinct selective regime, would be responsible for the accumulation of variation observed in Ômicron. The scenario presented is an example of how individual-level processes, such as the colonization of a new host by some individuals, can alter the patterns at higher scales.

Phylogenetic trees are representations of the evolutionary history of species. Measures such as speciation and extinction rates, topological structure, and branch lengths can reflect the processes that designed them (Blum and François, 2006; Caron and Pie, 2020; Mooers and Heard, 1997; Morlon, 2014). As it is impossible to empirically follow the processes of extinction and speciation for most biological groups, the use of computational models is a good alternative. Phylogenetic trees derived from simulated populations can be used to understand the reasons why such measurements vary over time and, thus, infer how and which ecological processes are responsible for the biodiversity patterns observed on a macroevolutionary scale (Costa et al., 2019; Freitas et al., 2024; Hagen et al., 2021; Marquitti et al., 2020).

Here, we link a microevolutionary process, the colonization of a new host, to macroevolutionary patterns displayed by parasites. We hypothesize that colonization of new hosts leaves a discernible signature in parasite evolution, and these signatures vary according to how different the selective pressures imposed by the hosts involved. Parasite evolution is described by the temporal variation in the number of mutations, number of genetic lineages, extinctions, diversification events, tree balance (Lemant et al., 2022) and acceleration of diversification (Costa et al., 2019). Our proposed model is an individual-based model (IBM) that follows the same dynamics proposed by Souza et al. (Chapter 2), which will also allow us to discuss how phenotypic lineages can be related to genotypic lineages.

4.3 Methods

To simulate the dynamics of host repertoire expansion by parasites, we used a computational individual-based model proposed by Souza et. al (Chapter 2), in which individuals that inhabit the donor host (H_1) could change to a new host (H_2). At each time step, the parasites replicate and can evolve. For simplicity, parasites are haploid, their genotype is explicitly modeled through a binary genome - a sequence of “0” and “1” of size L and their phenotype (p) corresponds to the sum of its genome. Hosts are characterized by their carrying capacities (K) and by a value that represents the optimal phenotype (Ph_1, Ph_2) imposed on the parasites. These values do not vary over the simulation time, meaning that, unlike parasites, hosts do not evolve. Differently from the original proposal, we added the genetic identification of parasite lineages through time, enabling us to analyze the parasite phylogenetic history.

4.3.1 Dynamic details

Initially, only the H_1 is inhabited by a population of parasites of size K, with identical genotypes and individual phenotypes equal to the optimum determined by the host (P_{h1}). At time t_{int}, a sample of individuals of size S is randomly selected in H_1 and inserted in H_2, free of parasites. At this moment, the selective pressure of H_2 on each individual i is expressed as a probability of survival (P_{surv}) resulting

from the distance (*d*) between the individual's phenotype (p_i) and the optimum imposed by the new host (P_{h2}) in standard deviation units (σ):

$$\boldsymbol{P_{surv} = exp[\frac{-d_i^2}{2}]}, \quad (1),$$

$$\boldsymbol{d_i = \frac{p_i - P_h}{\sigma}}. \quad (2).$$

Surviving individuals can continue in the new host and go through the replication cycle (asexual reproduction).

Replication of parasites occurs in all time steps of the model. The maximum size of the offspring generated at each cycle corresponds to the number of parasites present in the host at time *t* multiplied by a reproduction rate *b*, with an upper limit equal to *K*. All individuals have an equal probability of being drawn to leave offspring and there is no limitation on the number of times the same individual can be drawn. Each new individual corresponds to a copy of the parental genome potentially modified by an evolutionary novelty rate per locus (*μ*) - that is, each gene locus of each descendant individual has probability *μ* of inverting the parental “0” by “1”, and vice versa. Next, the selective pressure, Eq.(1), is imposed on the offspring. Finally, the parental generation is replaced by the offspring and the cycle repeats. (Fig. 1)

4.3.2 Lineage identification

At the end of each replication cycle, all genomes (regardless of the parasitized host) are compared to each other, locus by locus, forming groups that share a minimum genetic similarity (*G*) to be considered the same lineage. When the genetic differences between all pairs of individuals from different groups exceed *G*, the model assumes lineage diversification occurs (Fig. 1). It means that any two individuals from different group lineages have a genetic similarity smaller than *G*. However, it does not guarantee that all individuals from a lineage differ less or equal to *G*.

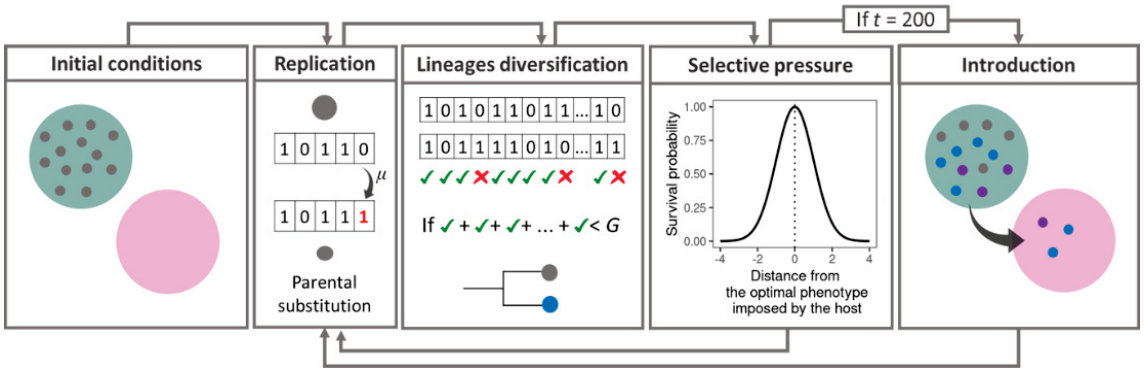

Figure 1: Model dynamics flowchart. Initially, the H_1 host is inhabited by a clonal population of parasites (small grey dots). At t = 200, 100 random individuals from H_1 (the donor host) are transferred to H_2 (possible new host), where they are subjected to new selective pressure. At each iteration, a replication cycle occurs in which the offspring are characterized by the parental genotype subjected to a rate of evolutionary novelty (μ) at each locus and host selective pressure. The parental generation is replaced by survivors. The genotype of all individuals is compared locus by locus among themselves and if the genetic similarity between individuals of the same lineage is less than the minimum genetic similarity (G) the lineages are separated. The cycle of replication and lineage separation continues to occur until the end of the simulation.

4.3.3 Simulations and parameters

To understand the effect of the distance between the hosts used on the phylogeny of the parasites, we performed multiple simulations varying the distance (D) between the optimal phenotype imposed by the hosts used. For this, we set the optimal phenotype of the original host P_{h1} = 500 and vary P_{h2} between 500 and 525 every 5 units (the same as $0 < D < 2.5$, every 0.5). The investigated amplitude was defined due to the low probability of survival/colonization of hosts more than two and a half standard deviations away from the original one (Fig. S1.1). We performed 100 replications with 1000 generations for each host pair. The other parameters used can be seen in Table 1.

For the construction of the phylogenies of the parasites we recorded, every 5 generations, the identity of the individuals present in the two hosts, the identity of the parental lineage, the generation (time step) in which the lineage originated, and the generation in which the lineage became extinct.

For all simulation periods, we also recorded the number of diversification events (as the number of new lineages formed), extinctions (when a lineage

disappears), and the frequency of mutations that occurred in the parasites present in each host (average per individual). The mutations record was made separately for conversions from “0” to “1” and from “1” to “0”, and we considered only mutations present in individuals that survived host-imposed selection.

Table 1: Parameters present in the model, a short description, and their values used in simulations.

Parameter	Description	investigated values
G	Minimum genetic similarity	95% of the loci
S	Propagule size	10 and 100 individuals
b	Replication rate	15 descendants per parental individual (average)
K	Carrying capacity	200 individuals
L	Genome size	1000 *loci*
μ	Mutation rate	10^{-3}
σ	Deviation rate for survival probability	10
P_{h1}	Optimum phenotype imposed by the donor host	500
P_{h2}	Optimum phenotype imposed by the new host	$500 \leq P_{h2} \leq 525$
D	Distance between the optimal phenotype imposed by the hosts	0, 0.5, 1, 1.5, 2 and 2.5
t_{int}	Time to migration	200

4.3.4 Trees’ Analyses

For all trees, we calculated temporally (i.e., each five-time steps) the number of lineages and two tree topology indexes: tree balance (J – Lemant et al. 2022) and acceleration of diversification (α-value – Costa et al. 2019) (Fig. 2A). The tree balance evaluates how much diversification events occur uniformly over the phylogeny branches, regardless of when diversification events occur (that is, in a non-ultrametric phylogeny). This metric ranges from zero to one, where the higher the value of J, the more balanced the phylogeny (and clades

speciate more uniformly) (see Lemant et al., 2022 for more details). The acceleration of diversification (α-value) is a metric without lower or higher boundaries that evaluates the acceleration of speciation events; if it is zero, the speciation events occur more uniformly over time; if it is negative, the speciation events occur more often near the root of the phylogeny (steammy trees); if it is positive, the speciations events are more concentrated in the leaves (tippy trees) (see Costa et al. 2019 for more details). We chose the *J* and *α* metrics because they allow for comparisons between trees regardless of their number of branches. Additionally, *J* is not restricted to bifurcation trees.

We performed these calculations for phylogenies considering the parasites of both hosts simultaneously, and to the donor and the new hosts separately (Fig. 2B). The topology indices were calculated only in the presence of at least three parasitic lineages simultaneously at the evaluated time. In addition, we also evaluated these measures for complete phylogenetic trees (with extinctions) and extant phylogenies (current lineages/without extinctions). To build the extant trees we used the “drop.fossil” function of the ape package in R (Paradis and Schliep, 2019). The results were compared between different host distances (*D*). The simulations made for the host pair at $D = 0$ are the equivalent of a control group for the entire duration of the simulations.

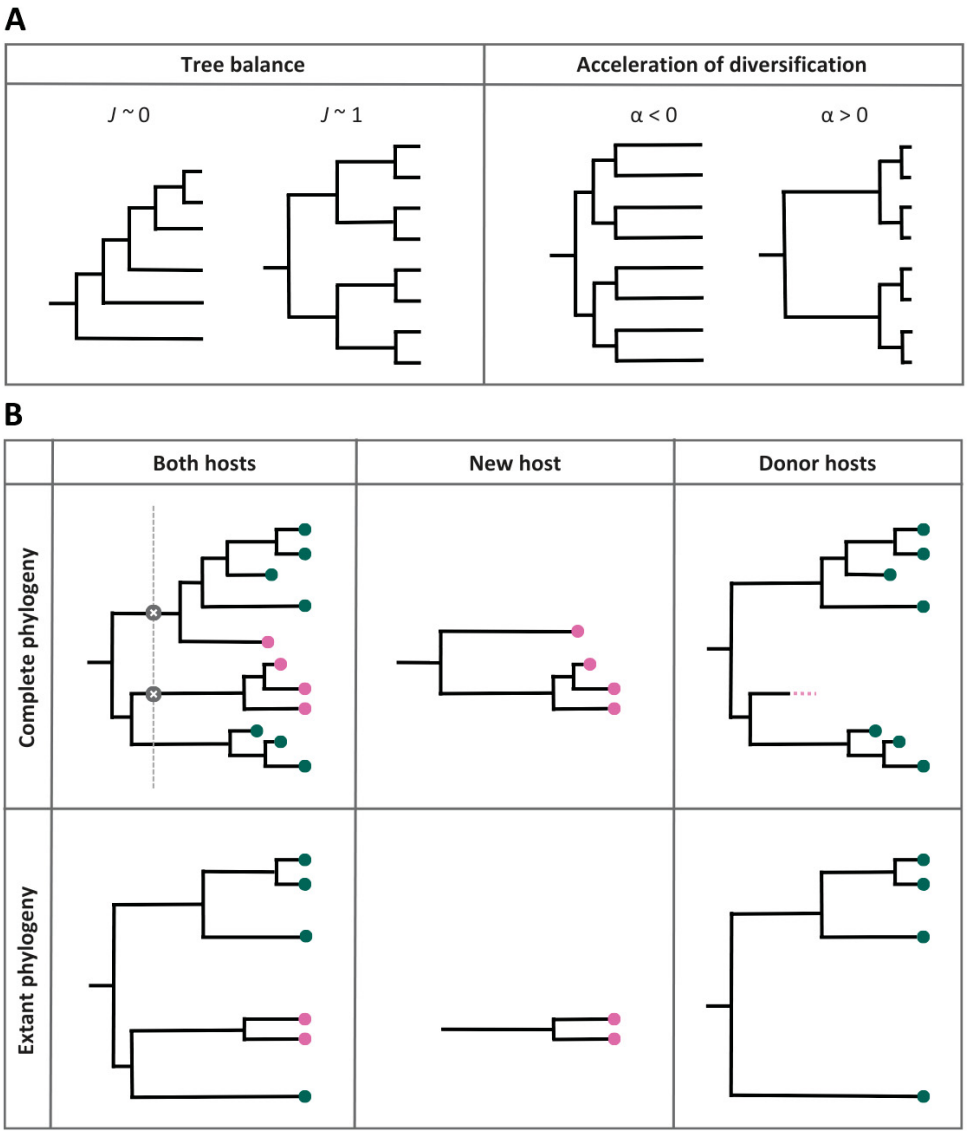

Figure 2: Tree topology indexes representation and kinds of phylogeny assessed. A) The tree balance evaluates how much the speciation events occur uniformly over the phylogeny branches, regardless of when the speciation events occur. This metric ranges from zero to one, where the higher the value of *J*, the more balanced the phylogeny (and clades speciates more uniformly). The acceleration of diversification events (α-value) is a metric without lower or higher boundaries; however, if it is zero, the speciation events occur more uniformly over time; if it is negative, the speciation events occur more often near the root of the phylogeny (steammy trees); if it is positive, the speciations events are more concentrated in the leaves (tippy trees). B) Complete phylogenies show all the evolutionary history of parasites (including extinctions), while extant phylogenies show only the history of living lineages. The complete and extant phylogenies were assessed considering the parasites present in both hosts, as well as in the new and donor hosts separately. The green color represents, in all figures, the donor host (H_1); pink represents the new host (H_2). The dashed line marks the moment of the host switch event, and the “x”s indicate the lineages that colonize the new host.

4.4 Results

The frequencies of mutations from "1" to "0" and from "0" to "1" changed in parasite populations in new hosts just after their colonization (Fig. 3). The greater the distance between the optimum phenotypes imposed by the two hosts (*D*), the higher the frequency of mutations "0" to "1" and lower “1” to “0” (Fig. 3) of parasites in the new hosts. It means that parasites in the new host are fixing more alleles “1” than “0”. It occurs because the optimum phenotype imposed by the new host is greater than the one imposed by the donor host ($P_{h2} > P_{h1}$), imposing a selection towards more alleles “1” (Fig. 4). Stabilization of the frequency of mutations in both directions occurred in all evaluated cases. However, a greater number of generations was required at larger distances between hosts (*D*) (Fig. 3). In the asymptotic regime (after a long time) the mutations of parasites in the new host stabilized in different values from the mutations in the donor host (more evident as *D* increases, Fig 3). To understand it, consider the case where the selection pressure in the new host imposes an optimum phenotype $P_{h2}=525$ (Fig. 4). After a sufficiently long time the genome of size 1000 will have on average 525 loci “1” and 475 loci “0”. So, with more “1”s than “0”s, there is a greater chance of mutations from “0” to “1” than the opposite. In fact, with 525 loci “1”s the average mutation frequency to “0” is 525μ $(=0.525$, when $\mu=10^{-3})$, and the average mutation frequency from “0” to “1” is 475μ $(=0,475)$ (The horizontal lines in Fig. 3 highlight the expected number of mutations for each *D* value). Although the chance of mutating to “0” is greater, the selection pressure imposed by the new host disfavors the individuals with more frequent mutations to “0”, maintaining the numbers of “0”s and “1”s around the optimum phenotype imposed by the new host.

We observed that the averages of the number of extinction and diversification events remain around one at all distances between hosts (*D*) evaluated (Figs. 5 and 6). The number of parasite diversification events peaks in the donor host at the beginning of the simulation. Similarly, when the new host is colonized a peak occurs, however, it is more evident as *D* increases. In both cases, stabilization of the average occurs in less than 100 generations.

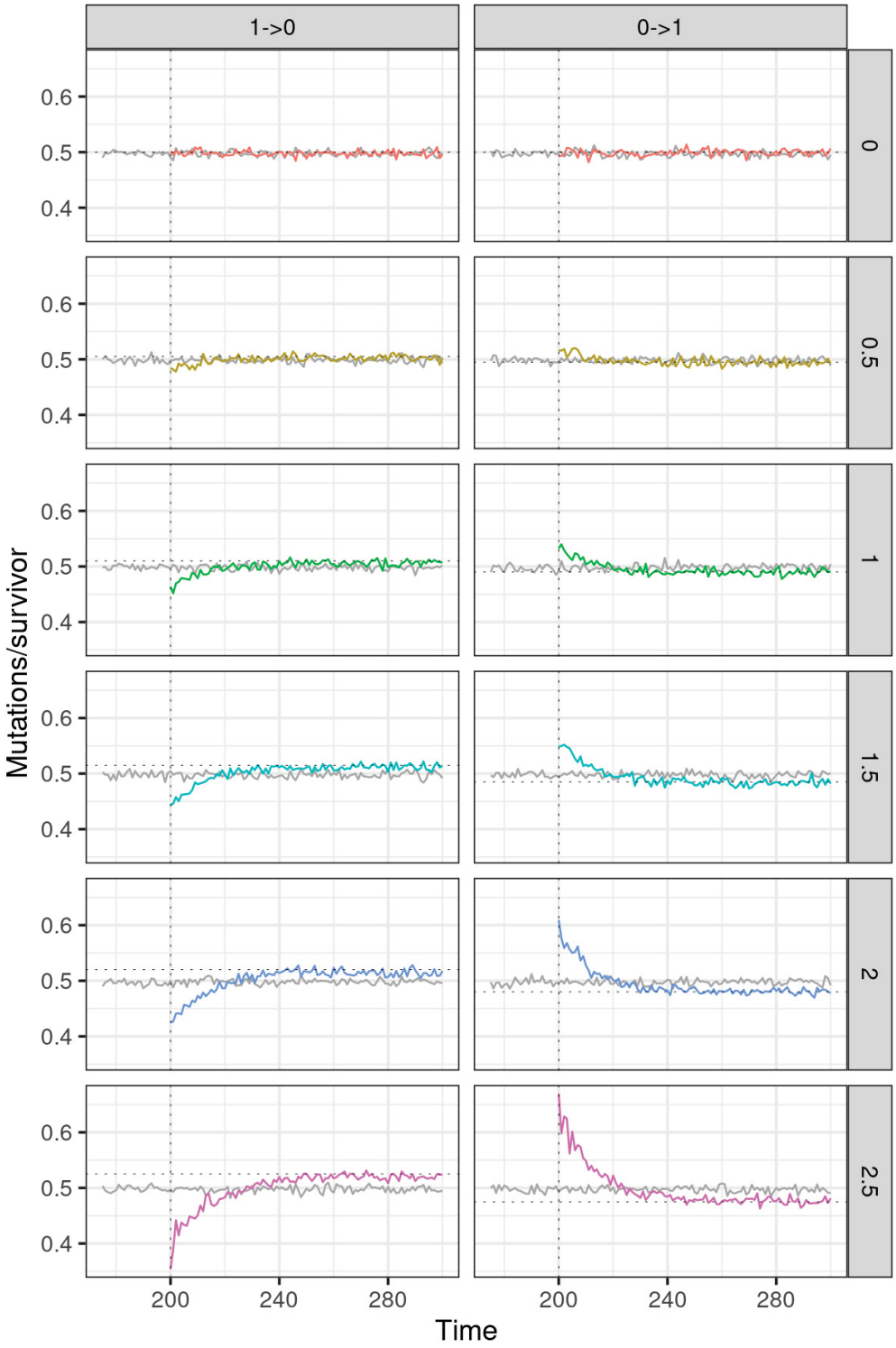

Figure 3: Temporal evolution of the average frequency of mutations exhibited by parasite individuals that have survived selection imposed by the host. The values to the right represent the distances (*D*) between the evaluated hosts. The columns *1–> 0* and *0–> 1* mean the mutations from 1 to 0 and from 0 to 1, respectively. The grey line represents the mutations in parasites that inhabit the donor host. Dashed horizontal lines indicate the frequency of mutations expected by chance in the asymptotic regime (after a long time).

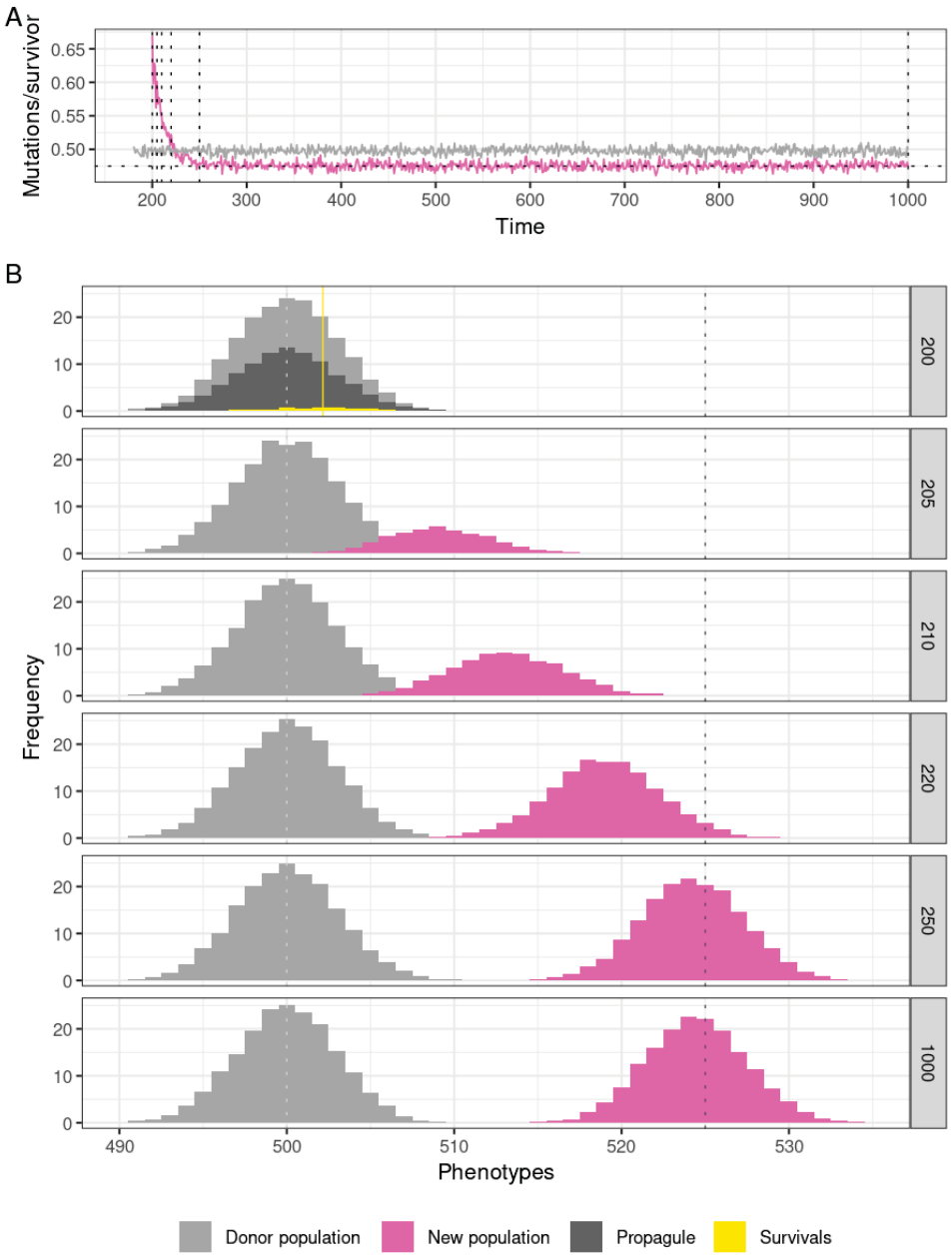

Figure 4: Parasite evolution after host-switching. A) Temporal evolution of the average frequency of mutations (0 to 1) exhibited by individuals that have survived selection imposed by the host. Dashed vertical lines indicate each time shown in B, and the dashed horizontal line indicates the frequency of mutations from "0" to "1" expected by chance. B) The individuals present in the propagule arise in a new host, but only a fraction survive the new selective pressure (t = 200). The new population increases over time, and the phenotypic profile evolves toward the optimum phenotype value (P_{h2}) imposed by the new host. After 50 generations of introduction (t = 250), the new population exhibits a phenotypic profile totally distinct from the original. The yellow line indicates the mean phenotype of survivals, and the dashed lines indicate the optimum phenotype values imposed by each host (P_{h1} = 500 and P_{h2} = 525). The values represent the mean to 90 replicates (number of replicates with successful colonization os the new host) for D = 2.5.

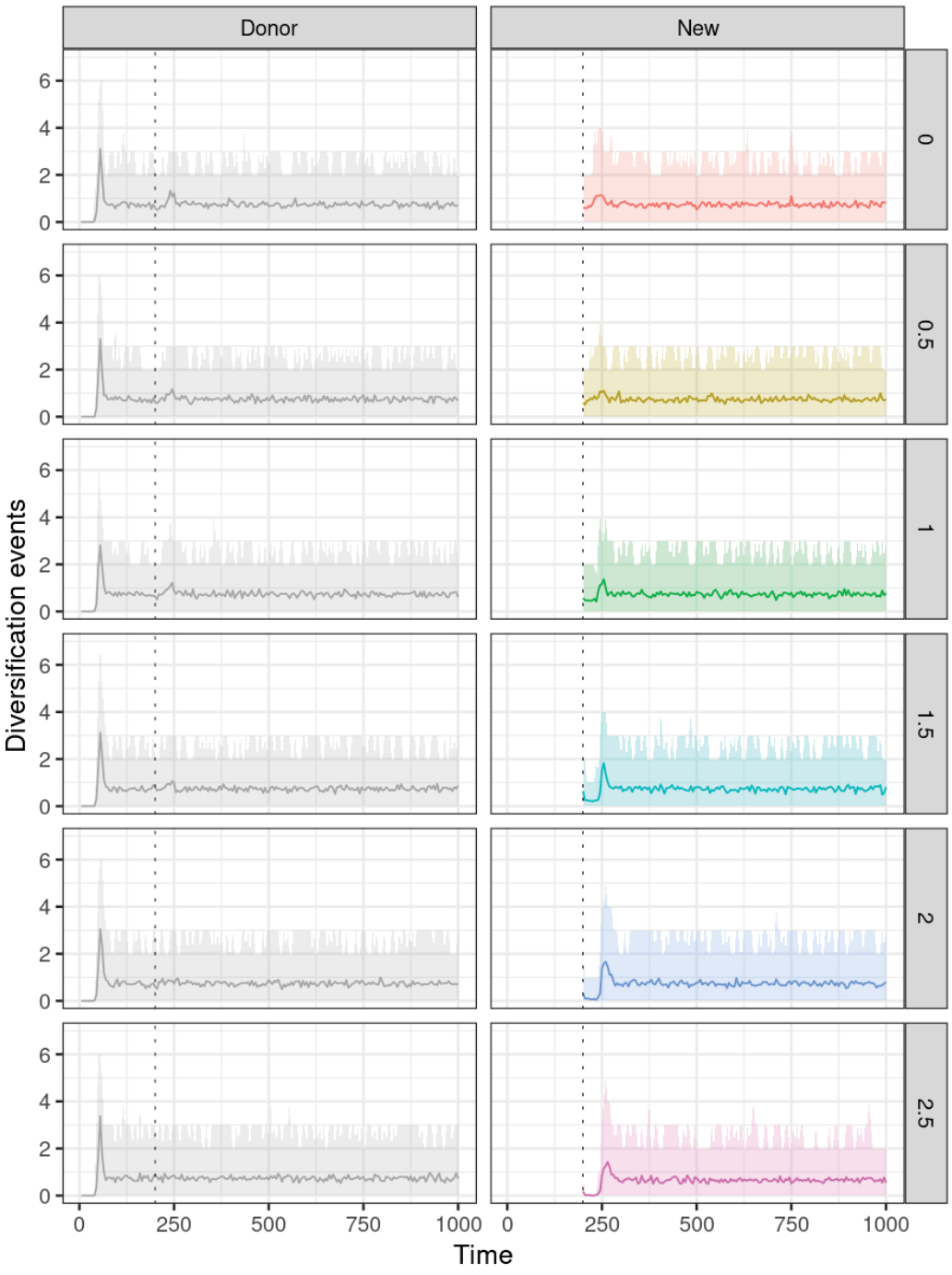

Figure 5: Number of diversification events in each host by distance (*D*). The results represent the average for replicates with successful colonization of a new host (100 replicates to *D* = 0, 0.5, 1, 1.5, and 2; and 90 replicates to *D* = 2.5) and the shadow area a confidence interval of 95%.

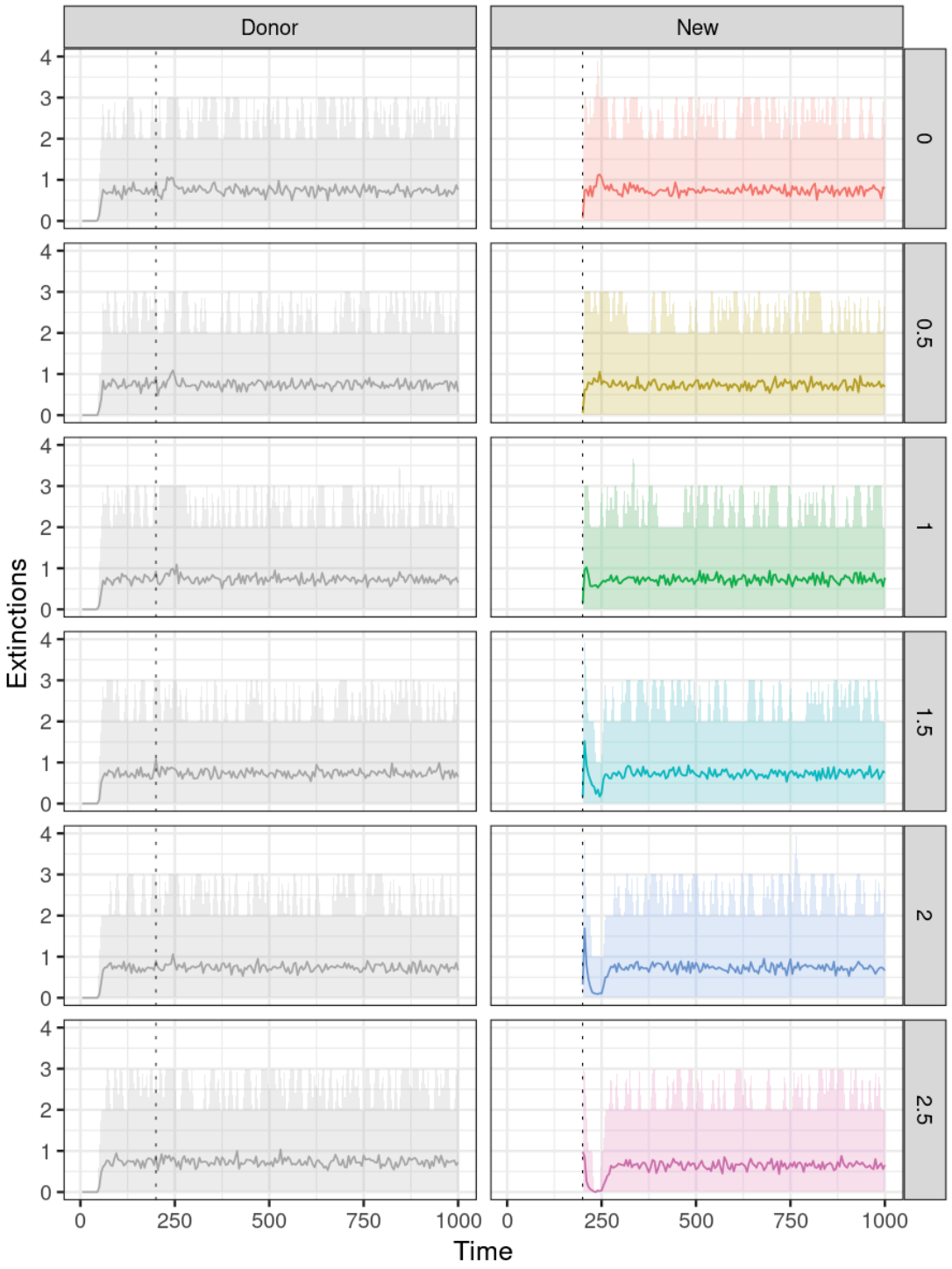

Figure 6: Number of lineage extinctions in each host by distance (*D*). The results represent the average for replicates with successful colonization of a new host (100 replicates to *D* = 0, 0.5, 1, 1.5, and 2; and 90 replicates to *D* = 2.5) and the shadow area a confidence interval of 95%.

The number of lineages in the complete phylogenies (Fig. 7A-C) refers to the accumulation of lineages generated throughout the entire simulation. Although the accumulation of lineages occurs at a similar intensity in both hosts, we observed a slight delay at higher values of *D*, resulting from the smaller number of founding lineages (Fig. 7B and E). Note that the immediate reduction in the number of lineages was more intense as the distance between hosts (*D*) increased, a result of the difference in selective pressure imposed by the donor and the new hosts. In all cases, the stabilization of the average number of lineages occurred around 200 generations after the colonization of the new host. No change in the number of lineages was observed between the donor and the new hosts since the two hosts have the same carrying capacity. Furthermore, the number of simultaneous parasite lineages doubled, on average, with the expansion of the number of hosts used (Fig. 7D), again, probably due to the overall increase in the carrying capacity. After the host switching, the abundances of each parasite lineage are different between parasites in the donor and new host, however, it becomes equivalent as time goes on (Fig. S1.2).

The *J* Index revealed a downward trend in the balance of the complete phylogenies throughout the entire simulated period (Fig. 8A-C). The initial iterations after the colonization of the new host showed a slight difference between the evaluated distances, converging to the same average over time (Fig. 8B). We also observed a sharp decline in the balance of the extant phylogeny constructed from both hosts in the first times following the colonization event, especially for long distances (Fig. 8D). After this decline, the metric increases until stabilizing at values around 0.9 for all evaluated distances, showing a slightly more balanced trend compared to the phylogenies derived from parasites present in each host separately (Fig. 8E and F).

While the complete phylogenies and the extant phylogeny for both hots exhibited a trend of increasing acceleration (Fig. 9A-D), the extant phylogenies for the new and donor hosts separately demonstrated a more stable behavior (Fig. 9D-F). However, all the extant phylogenies showed a higher acceleration compared to complete phylogenies. In both cases, it was possible to observe greater variation in the metric just after the colonization of the new host, especially in phylogenies for parasites present in the new host (Fig. 9D-E).

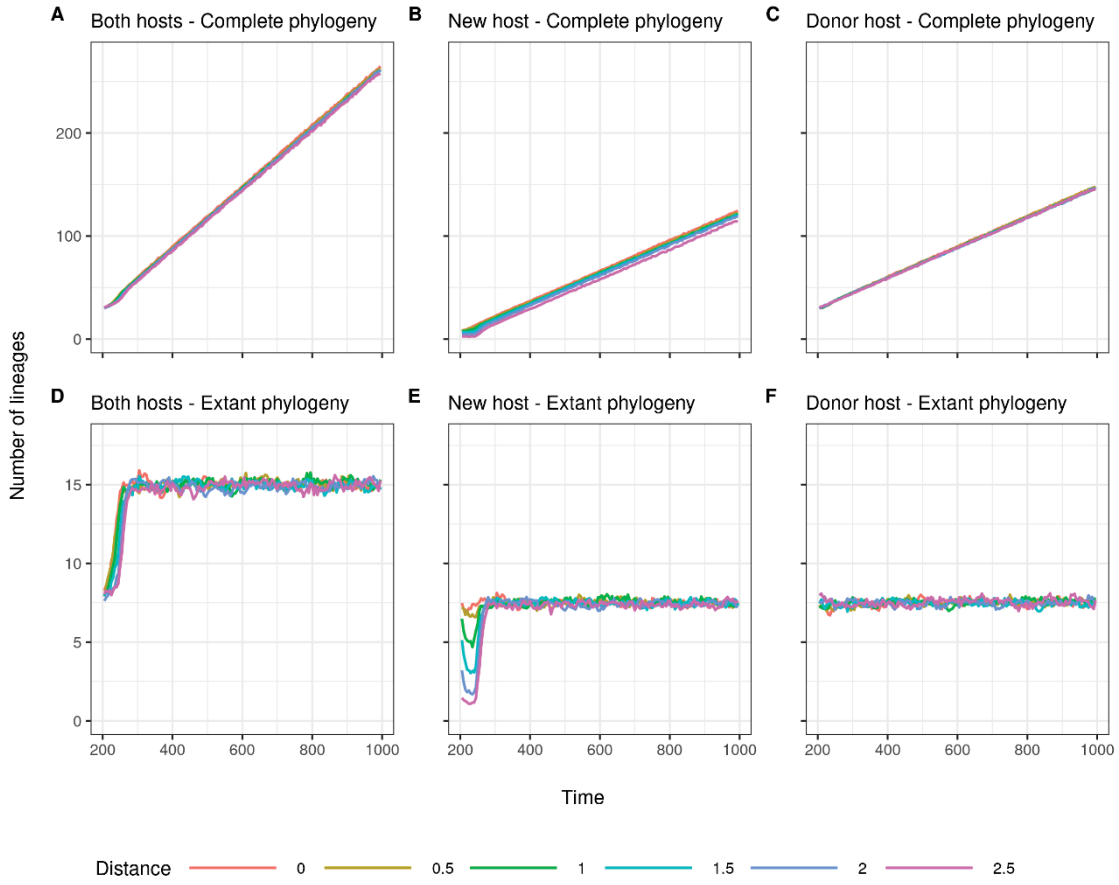

Figure 7: Number of parasite lineages accumulated (complete phylogenies) and number of current lineages (extant phylogenies) over time. The "both hosts" phylogenies include all parasite lineages, regardless of which host they inhabit. The "new" and "donor" are filters of the first phylogeny ("both hosts"), including only the lineages present in each host. The results represent the average for replicates with successful colonization of a new host (100 replicates to D = 0, 0.5, 1, 1.5, and 2; and 90 replicates to D = 2.5).

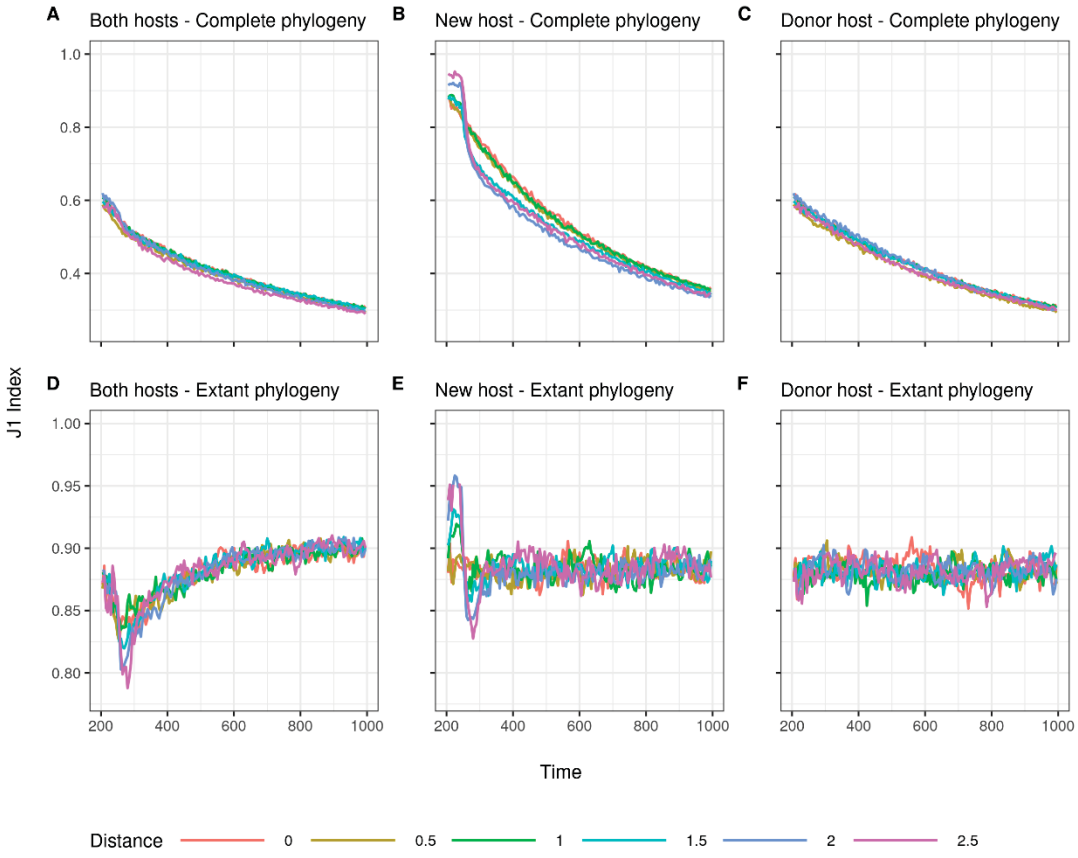

Figure 8: Temporal evolution of phylogenies balance (*J*) for complete phylogenies (with extinctions) and extant phylogenies (current lineages) over time. The "both hosts" phylogenies include all lineages, regardless of which host they inhabit. The "new" and "donor" are filters of the first phylogeny ("both hosts"), including only the lineages present in each host. This metric ranges from zero to one, and the higher the value of *J*, the more balanced the phylogeny (and clades speciates more uniformly). The results represent the average for replicates with successful colonization of a new host (100 replicates to D = 0, 0.5, 1, 1.5, and 2; and 90 replicates to D = 2.5).

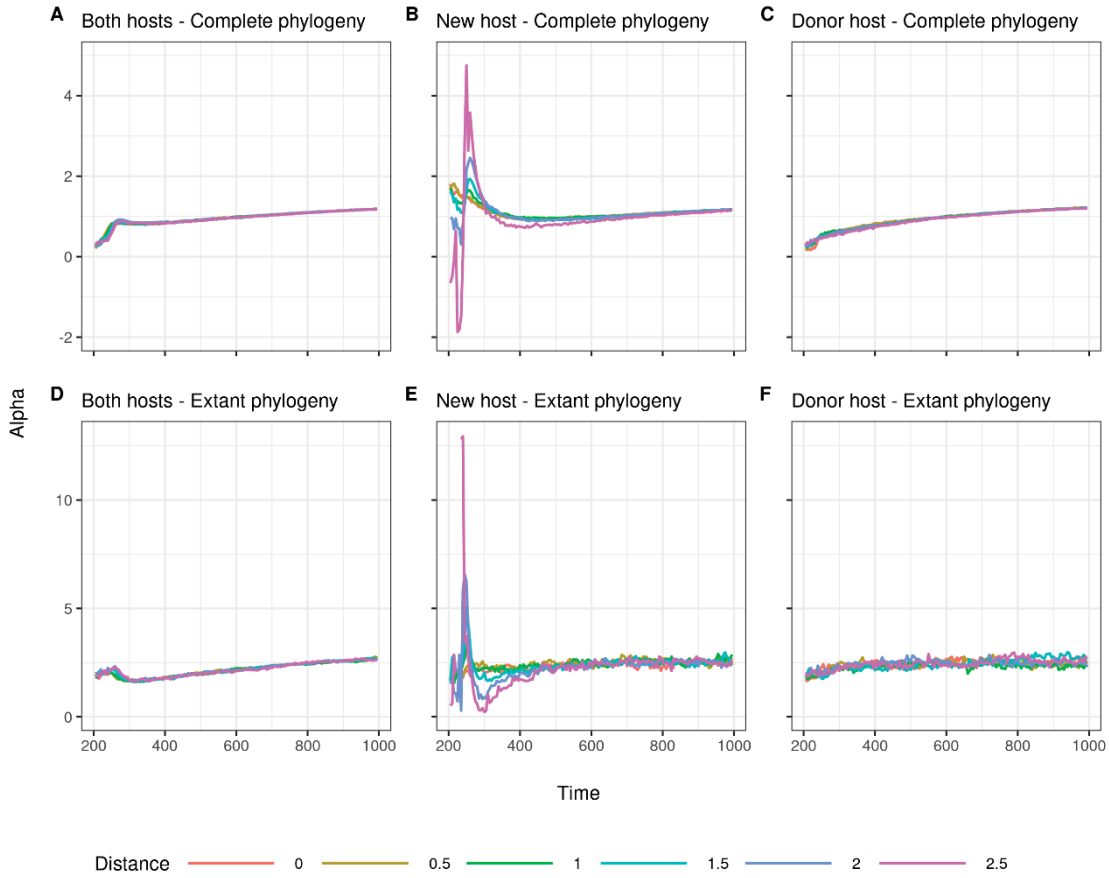

Figure 9: Temporal evolution of acceleration of diversification (α) for complete phylogenies (with extinctions) and extant phylogenies (current lineages) over time. The "both hosts" phylogenies include all lineages, regardless of which host they inhabit. The "new" and "donor" are filters of the first phylogeny ("both hosts"), including only the lineages present in each host. If α is zero, the speciation events occur more uniformly over time; if it is negative, the speciation events occur more often near the root of the phylogeny; if it is positive, the diversification events are more concentrated in the leaves. The results represent the average for replicates with successful colonization of a new host (100 replicates to D = 0, 0.5, 1, 1.5, and 2; and 90 replicates to D = 2.5).

Lastly, our results do not depend on propagule size. In Supplementary 2 it is possible to observe similar evolutionary patterns in simulations made from S = 10. The choice of propagule size used here (S = 100) is simply due to the greater number of successful simulations of establishment in the new host at greater distances (S = 100: 100 replicates to D = 0, 0.5, 1, 1.5, and 2, and 90 replicates to D = 2.5; S = 10: 100 replicates to D = 0, 0.5, and 1; 98 to D = 1.5; 68 to D = 2; and 19 to D = 2.5).

4.5 Discussion

In this paper, we investigate whether the colonization of a new host can leave signatures on parasite evolution. We developed an individual-based model (IBM) in which some parasite individuals living in a donor host have the opportunity to colonize a new host, and we tracked the evolution of both parasites' populations. We recorded the number of mutations, genetic lineages, extinctions, diversification events, and characterized the phylogenetics patterns in tree balance (Lemant et al., 2022) and acceleration of diversification (Costa et al., 2019). We found temporary signatures in all metrics assessed. The distance between the optimal phenotype imposed by the hosts (*D*) affected parasites present in the new host just after host colonization. As time goes on, the signature of the ecological event is lost.

4.5.1 Signatures on mutations

Although our work does not represent a direct parallel to that of Boeger et al. 2022, our results corroborate their position regarding the accumulation of mutations observed in Ômicron resulting from the use of a non-human host. The parallel of our work concerning this is that each $D \neq 0$ can be considered equivalent to a non-human host species; and that as greater the distance, the more intense the changes in phenotypic and genotypic profiles observed in the parasites. The concept of lagload (Smith 1976) explains it. The fundamental idea of lagload is that as the environment changes (in this case, the new selective pressure imposed by the new host), the population tracks it genetically, approaching the genetic profile of the population closer to the optimum imposed by the context in which it is inserted. Note that, in our model, the mutation probability per locus does not change, but the fixation rate of adaptive alleles to the new context. Therefore, the greater the lagload generated by host-switching, the greater the number of adaptive mutations selected at the same time - the "rate of evolution" for Smith (1976). Althought identifying and quantifying mutations in characteristics that are known to be under selection is possible, attributing this result in isolation to a certain distance between hosts used may be impossible. Unlike the simulations, in which we have control over the moment in which the

host exchange occurs and the selective force imposed on parasites, in the real world it is difficult to have this information. Therefore, we cannot determine whether a greater number of fixed mutations is a result of the time since the colonization of the new host or a result of a strong lagload.

Given the relative ease with which parasites switch and adapt to new hosts (Agosta et al., 2010; Araujo et al., 2015; Bashor et al., 2021; Hoberg and Brooks, 2008; Kreuder Johnson et al., 2015; Woolhouse et al., 2005), the current scenario of globalization, which increases the rate of movement of species and, therefore, provides greater chances of encounters between parasites and potential hosts, makes this situation especially worrying. Reinfections by lineages that have evolved in other species can pose as great a risk as infections by lineages with no shared evolutionary history. Potential changes in their epidemiological characteristics, compared to those observed in known lineages - such as increased transmissibility, virulence, pathogenicity and evasion of the immune system - may escape our immediate ability to control their effects, potentialy resulting in the emergence of diseases (Bashor et al., 2021; Woolhouse et al., 2005).

4.5.2 Signatures on phylogenies

There are some expected differences between complete and extant phylogenies that are unrelated to the process being studied. Extant phylogenies tend to be more accelerated and balanced because they miss past diversification events that resulted in extinctions, leaving only the branches that diverged most recently and that may still diverge. In complete phylogenies, the trend to decrease the balance over time is the result of the accumulation of extinction events, as extinct branches are no longer likely to generate new lineages, making it impossible for uniform diversification events between the branches of the phylogeny (Lemant et al., 2022). Our results (Figs. 8 and 9) match this expectation, indicating that our model reproduces expected macroevolutionary patterns.

Variations in α and *J* for different values of *D* occur more clearly in the phylogenies made for the parasites present in the new host shortly after its colonization (about $200 \leq t \leq 300$, note in Figs. 7, 8, and 9, panels B and E),

impacting to a lesser extent the phylogenies for both hosts (Figs. 7, 8 and 9, panels A and D). As time goes on, α and *J* converge, and the signature of host switching distance (*D*) is lost. In terms of events of the formation of new lineages (diversification events, Fig. 5) and extinction (Fig. 6), the differences between *D* are also more evident as *D* increases, however, they last a shorter period (about $200 \leq t \leq 250$), suggesting that after a transient, the dynamics in each host are equivalent. The transient for α and *J* last longer because they use all the past history, and over time the history of moments immediately after the colonization of the new host becomes just a smaller fraction of the whole (Freitas et al., 2024).

We believe that the demographic dynamics shortly after the colonization of the new host is responsible for the differences observed in the diversification of lineages, and consequently in other metrics, concerning the distances evaluated. The history of parasites in the new host begins with 100 or less individuals belonging to different lineages (The higher the *D* value, on average, the lower the number of lineages and surviving individuals - Figures 7E and S1, respectively). This initial difference implies the population size and similarity between individuals from each lineage present in subsequent generations. In a situation in which the founding population is composed of a larger number of individuals divided between different lineages, the distribution of lineages/phenotypes of subsequent generations differs less from the founding population than in a situation in which few individuals colonized the host. In this case, the following generations are composed of a greater number of individuals similar to each other, as each individual of the parental generation will have, on average, more offspring (note that due to the parameters used and the mode of reproduction, the carrying capacity is reached quickly, even when the population is founded from a few individuals). As a consequence, it takes more time until the limit *G* is reached and diversification events start. However, once this occurs, the lineages begin to divide rapidly (Costa et al., 2019), eventually reaching stability. This pattern is similar to that observed at the beginning of the simulations in the donor host, whose parasite history starts from a clonal population of 200 individuals.

4.6 Conclusions

We hypothesize that colonization of new hosts leaves a discernible signature in parasite evolution (i.e., temporal variation in the number of mutations, number of genetic lineages, extinctions, diversification events, tree balance and acceleration of diversification), and these signatures vary according to how different the selective pressures imposed by the hosts involved. Although we found support for all measures tested, in all cases the observed differences are lost over time. Therefore, the simple analysis of phylogeny metrics (done only based on its most recent topology) is not sufficient to identify the signature left by the host-switching. We suggest that temporal analyses of evolutionary patterns are more suitable for identifying the occurrence of microevolutionary processes such as the colonization of new hosts. In addition, the real world likely involves a far greater number of introduction events and potential hosts than considered here, suggesting a direction for future work.

4.7 References

Agosta, S.J., Janz, N., Brooks, D.R., 2010. How specialists can be generalists: Resolving the and “parasite paradox” and implications for emerging infectious disease. Zoologia 27, 151–162. https://doi.org/10.1590/S1984-46702010000200001

Agosta, S.J., Klemens, J.A., 2008. Ecological fitting by phenotypically flexible genotypes: Implications for species associations, community assembly and evolution. Ecol. Lett. 11, 1123–1134. https://doi.org/10.1111/j.1461-0248.2008.01237.x

Araujo, S.B.L., Braga, M.P., Brooks, D.R., Agosta, S.J., Hoberg, E.P., Von Hartenthal, F.W., Boeger, W.A., 2015. Undestanding host-switching by ecological fitting. PLoS ONE 10, 1–17. https://doi.org/10.1371/journal.pone.0139225

Bashor, L., Gagne, R.B., Bosco-Lauth, A.M., Bowen, R.A., Stenglein, M., De

Woude, S.V., 2021. SARS-CoV-2 evolution in animals suggests mechanisms for rapid variant selection. Proc. Natl. Acad. Sci. U. S. A. 118, 1–10. https://doi.org/10.1073/pnas.2105253118

Blum, M.G.B., François, O., 2006. Which Random Processes Describe the Tree of Life? A Large-Scale Study of Phylogenetic Tree Imbalance. Syst. Biol. 55, 685–691. https://doi.org/10.1080/10635150600889625

Boeger, W.A., Brooks, D.R., Trivellone, V., Agosta, S.J., Hoberg, E.P., 2022. Ecological super-spreaders drive host–range oscillations: Omicron and risk space for emerging infectious disease. Transbound. Emerg. Dis. 69, e1280–e1288. https://doi.org/10.1111/tbed.14557

Braga, M.P., Araujo, S.B.L., Agosta, S., Brooks, D., Hoberg, E., Nylin, S., Janz, N., Boeger, W.A., 2018. Host use dynamics in a heterogeneous fitness landscape generates oscillations in host range and diversification. Evolution 72, 1773–1783. https://doi.org/10.1111/evo.13557

Brooks, D.R., Hoberg, E.P., Boeger, W.A., 2019. The Stockholm Paradigm: Climate Change and Emerging Disease. University of Chicago Press.

Brooks, D.R., Hoberg, E.P., Boeger, W.A., Gardner, S.L., Galbreath, K.E., Herczeg, D., Mejía-Madrid, H.H., Rácz, S.E., Dursahinhan, A.T., 2014. Finding them before they find Us: Informatics, parasites, and environments in accelerating climate change. Comp. Parasitol. 81, 155–164. https://doi.org/10.1654/4724b.1

Caron, F.S., Pie, M.R., 2020. The phylogenetic signal of diversification rates. J. Zool. Syst. Evol. Res. 58, 1432–1436. https://doi.org/10.1111/jzs.12379

Charleston, M.A., Robertson, D.L., 2002. Preferential host switching by primate lentiviruses can account for phylogenetic similarity with the primate phylogeny. Syst. Biol. 51, 528–535. https://doi.org/10.1080/10635150290069940

Costa, C.L.N., Lemos-Costa, P., Marquitti, F.M.D., Fernandes, L.D., Ramos, M.F., Schneider, D.M., Martins, A.B., De Aguiar, M.A.M., 2019. Signatures of Microevolutionary Processes in Phylogenetic Patterns. Syst. Biol. 68, 131–144.

https://doi.org/10.1093/sysbio/syy049

De Vienne, D.M., Refrégier, G., López-Villavicencio, M., Tellier, A., Hood, M.E., Giraud, T., 2013. Cospeciation vs host-shift speciation: Methods for testing, evidence from natural associations and relation to coevolution. New Phytol. 198, 347–385. https://doi.org/10.1111/nph.12150

Destoumieux-Garzón, D., Mavingui, P., Boetsch, G., Boissier, J., Darriet, F., Duboz, P., Fritsch, C., Giraudoux, P., Le Roux, F., Morand, S., Paillard, C., Pontier, D., Sueur, C., Voituron, Y., 2018. The One Health Concept: 10 Years Old and a Long Road Ahead. Front. Vet. Sci. 5, 14. https://doi.org/10.3389/fvets.2018.00014

Doña, J., Sweet, A.D., Johnson, K.P., Serrano, D., Mironov, S., Jovani, R., 2017. Cophylogenetic analyses reveal extensive host-shift speciation in a highly specialized and host-specific symbiont system. Mol. Phylogenet. Evol. 115, 190–196. https://doi.org/10.1016/j.ympev.2017.08.005

Edwards, P.J., Abivardi, C., 1998. The value of biodiversity: Where ecology and economy blend. Biol. Conserv. 83, 239–246. https://doi.org/10.1016/S0006-3207(97)00141-9

Feronato, S.G., Araujo, S., Boeger, W.A., 2021. “Accidents waiting to happen” – insights from a simple model on the emergence of infectious agents in new hosts. Transbound. Emerg. Dis. 1–12. https://doi.org/10.1111/tbed.14146

Freitas, O., Araujo, S.B.L., Campos, P.R.A., 2022. Speciation in a metapopulation model upon environmental changes. Ecol. Model. 468, 109958. https://doi.org/10.1016/j.ecolmodel.2022.109958

Freitas, O., Campos, P.R.A., Araujo, S.B.L., 2024. Patch biogeography under intermittent barriers: macroevolutionary consequences of microevolutionary processes. J. Evol. Biol. 1–34. https://doi.org/10.1093/jeb/voae035

Giraud, T., Gladieux, P., Gavrilets, S., 2010. Linking the emergence of fungal plant diseases with ecological speciation. Trends Ecol. Evol. 25, 387–395. https://doi.org/10.1016/j.tree.2010.03.006

Hadfield et al., 2018. Nextstrain: real-time tracking of pathogen evolution. Bioinformatics 34, 4121–4123.

Hagen, O., Flück, B., Fopp, F., Cabral, J.S., Hartig, F., Pontarp, M., Rangel, T.F., Pellissier, L., 2021. gen3sis: A general engine for eco-evolutionary simulations of the processes that shape Earth's biodiversity, PLoS Biology. https://doi.org/10.1371/journal.pbio.3001340

Hoberg, E.P., Brooks, D.R., 2008. A macroevolutionary mosaic: Episodic host-switching, geographical colonization and diversification in complex host-parasite systems. J. Biogeogr. 35, 1533–1550. https://doi.org/10.1111/j.1365-2699.2008.01951.x

Janzen, D.. H.., 1985. On Ecological Fitting. Oikos 45, 308–310.

Kreuder Johnson, C., Hitchens, P.L., Smiley Evans, T., Goldstein, T., Thomas, K., Clements, A., Joly, D.O., Wolfe, N.D., Daszak, P., Karesh, W.B., Mazet, J.K., 2015. Spillover and pandemic properties of zoonotic viruses with high host plasticity. Sci. Rep. 5, 1–8. https://doi.org/10.1038/srep14830

Kupferschmidt, Ka., 2021. Where did 'weird' Omicron come from? https://doi.org/10.1126/science.acx9754

Lemant, J., Le Sueur, C., Manojlović, V., Noble, R., 2022. Robust, Universal Tree Balance Indices. Syst. Biol. 71, 1210–1224. https://doi.org/10.1093/sysbio/syac027

Longdon, B., Brockhurst, M.A., Russell, C.A., Welch, J.J., Jiggins, F.M., 2014. The Evolution and Genetics of Virus Host Shifts. PLoS Pathog. 10. https://doi.org/10.1371/journal.ppat.1004395

Marquitti, F.M.D., Fernandes, L.D., de Aguiar, M.A.M., 2020. Allopatry increases the balance of phylogenetic trees during radiation under neutral speciation. Ecography 1–12. https://doi.org/10.1111/ecog.04937

Mooers, A.O., Heard, S.B., 1997. Inferring Evolutionary Process from Phylogenetic Tree Shape. Q. Rev. Biol. 72, 31–54.

https://doi.org/10.1086/419657

Morlon, H., 2014. Phylogenetic approaches for studying diversification. Ecol. Lett. 17, 508–525. https://doi.org/10.1111/ele.12251

Nyman, T., 2010. To speciate, or not to speciate? Resource heterogeneity, the subjectivity of similarity, and the macroevolutionary consequences of niche-width shifts in plant-feeding insects. Biol. Rev. 85, 393–411. https://doi.org/10.1111/j.1469-185X.2009.00109.x

Oliver, T.H., Heard, M.S., Isaac, N.J.B., Roy, D.B., Procter, D., Eigenbrod, F., Freckleton, R., Hector, A., Orme, C.D.L., Petchey, O.L., Proença, V., Raffaelli, D., Suttle, K.B., Mace, G.M., Martín-López, B., Woodcock, B.A., Bullock, J.M., 2015. Biodiversity and Resilience of Ecosystem Functions. Trends Ecol. Evol. 30, 673–684. https://doi.org/10.1016/j.tree.2015.08.009

Paradis, E., Schliep, K., 2019. ape 5.0: an environment for modern phylogenetics and evolutionary analyses in R. Bioinformatics 35, 526–528. https://doi.org/10.1093/bioinformatics/bty633

Sun, Y., Lin, W., Dong, W., Xu, J., 2022. Origin and evolutionary analysis of the SARS-CoV-2 Omicron variant. J. Biosaf. Biosecurity 4, 33–37. https://doi.org/10.1016/j.jobb.2021.12.001

Sutherland, W.J., Freckleton, R.P., Godfray, H.C.J., Beissinger, S.R., Benton, T., Cameron, D.D., Carmel, Y., Coomes, D.A., Coulson, T., Emmerson, M.C., Hails, R.S., Hays, G.C., Hodgson, D.J., Hutchings, M.J., Johnson, D., Jones, J.P.G., Keeling, M.J., Kokko, H., Kunin, W.E., Lambin, X., Lewis, O.T., Malhi, Y., Mieszkowska, N., Milner-Gulland, E.J., Norris, K., Phillimore, A.B., Purves, D.W., Reid, J.M., Reuman, D.C., Thompson, K., Travis, J.M.J., Turnbull, L.A., Wardle, D.A., Wiegand, T., 2013. Identification of 100 fundamental ecological questions. J. Ecol. 101, 58–67. https://doi.org/10.1111/1365-2745.12025

Woolhouse, M.E.J., Haydon, D.T., Antia, R., 2005. Emerging pathogens: the epidemiology and evolution of species jumps. Trends Ecol. Evol. 20, 238–244. https://doi.org/10.1016/j.tree.2005.02.009

4.8 Supplementary 1

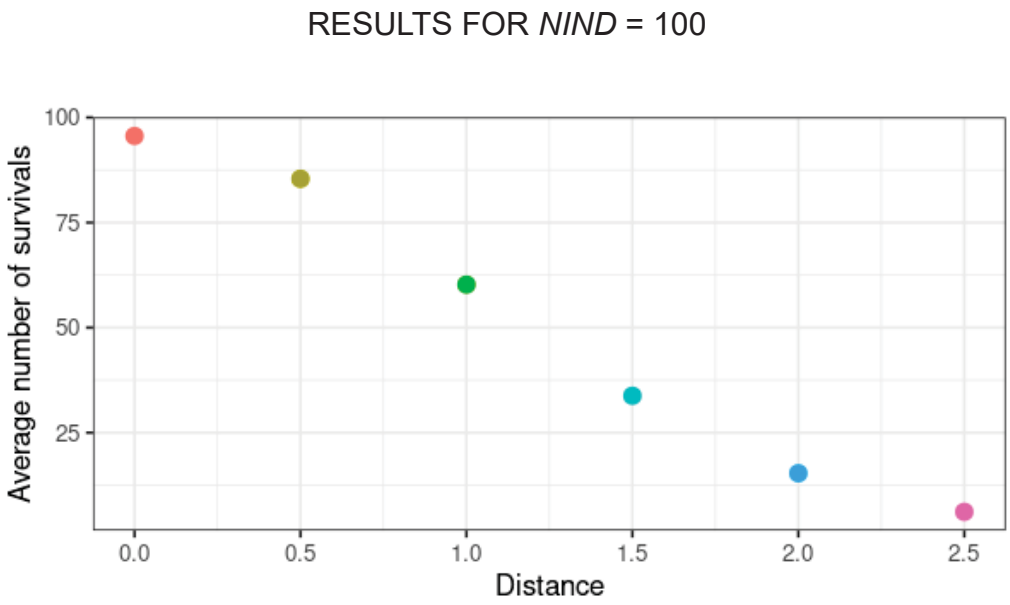

Figure S1.1: Average number of survivals just after a new host colonization. The values represent the average for replicates with successful colonization of a new host (100 replicates to D = 0, 0.5, 1, 1.5, and 2; and 90 replicates to D = 2.5).

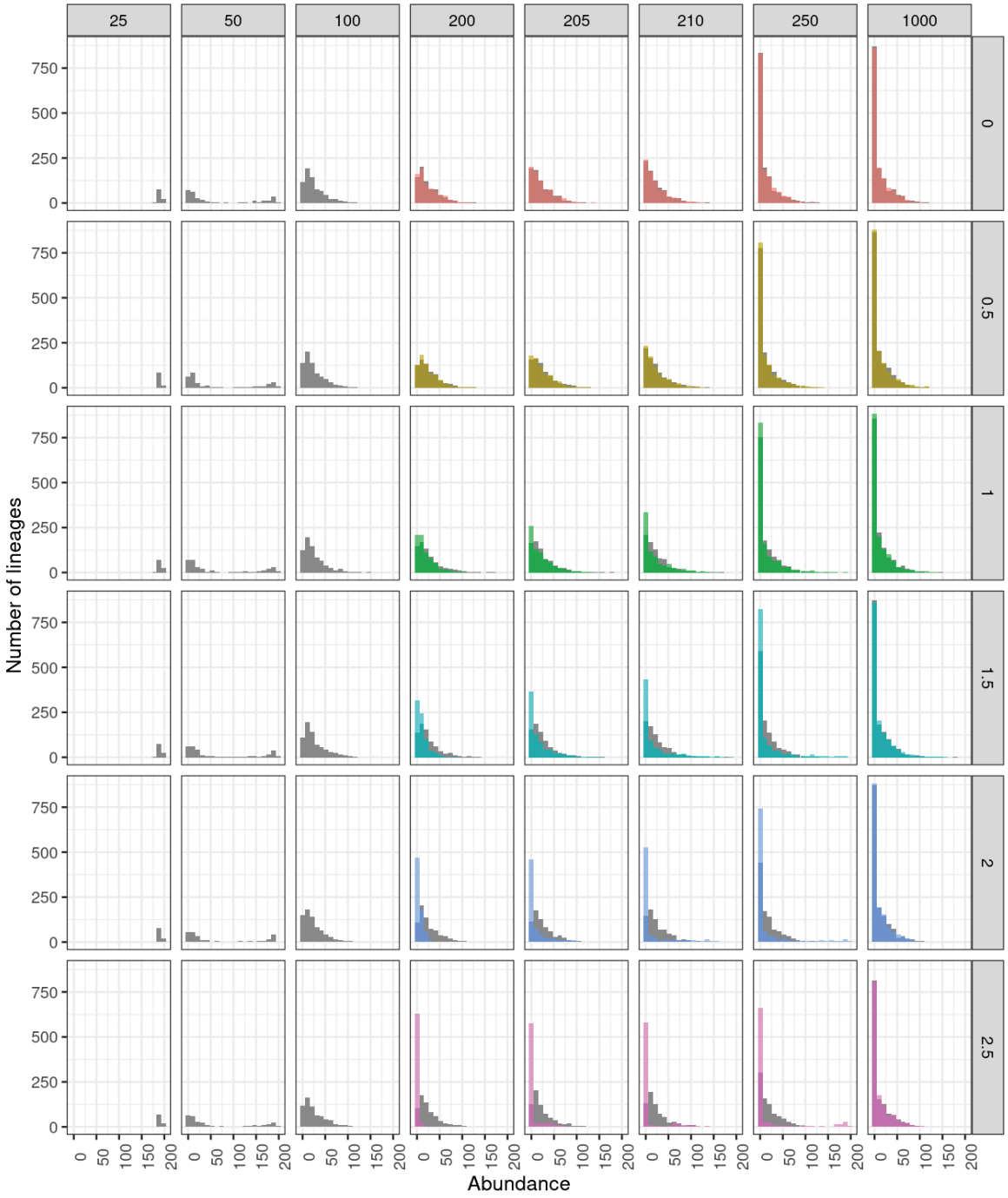

Figure S1.2: Temporal distribution of number of lineages by abundance. The results represent the accumulated results for 100 replicates to D = 0, 0.5, 1, 1.5, and 2, and 90 replicates to D = 2.5 (number of replicates with successful colonization of a new host).

4.9 Supplementary 2

RESULTS FOR *NIND* = 10

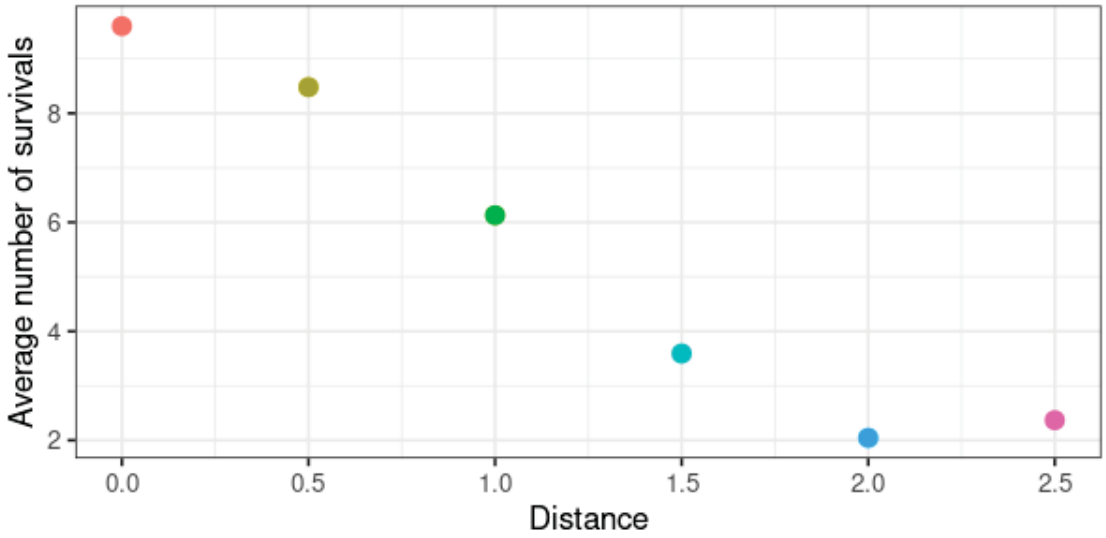

Figure S2.1: Number of survivals just after a new host colonization. The values represent the average for replicates with successful colonization of a new host (100 replicates to *D* = 0, 0.5, and 1; 98 to *D* = 1.5; 68 to *D* = 2; and 19 to *D* = 2.5).

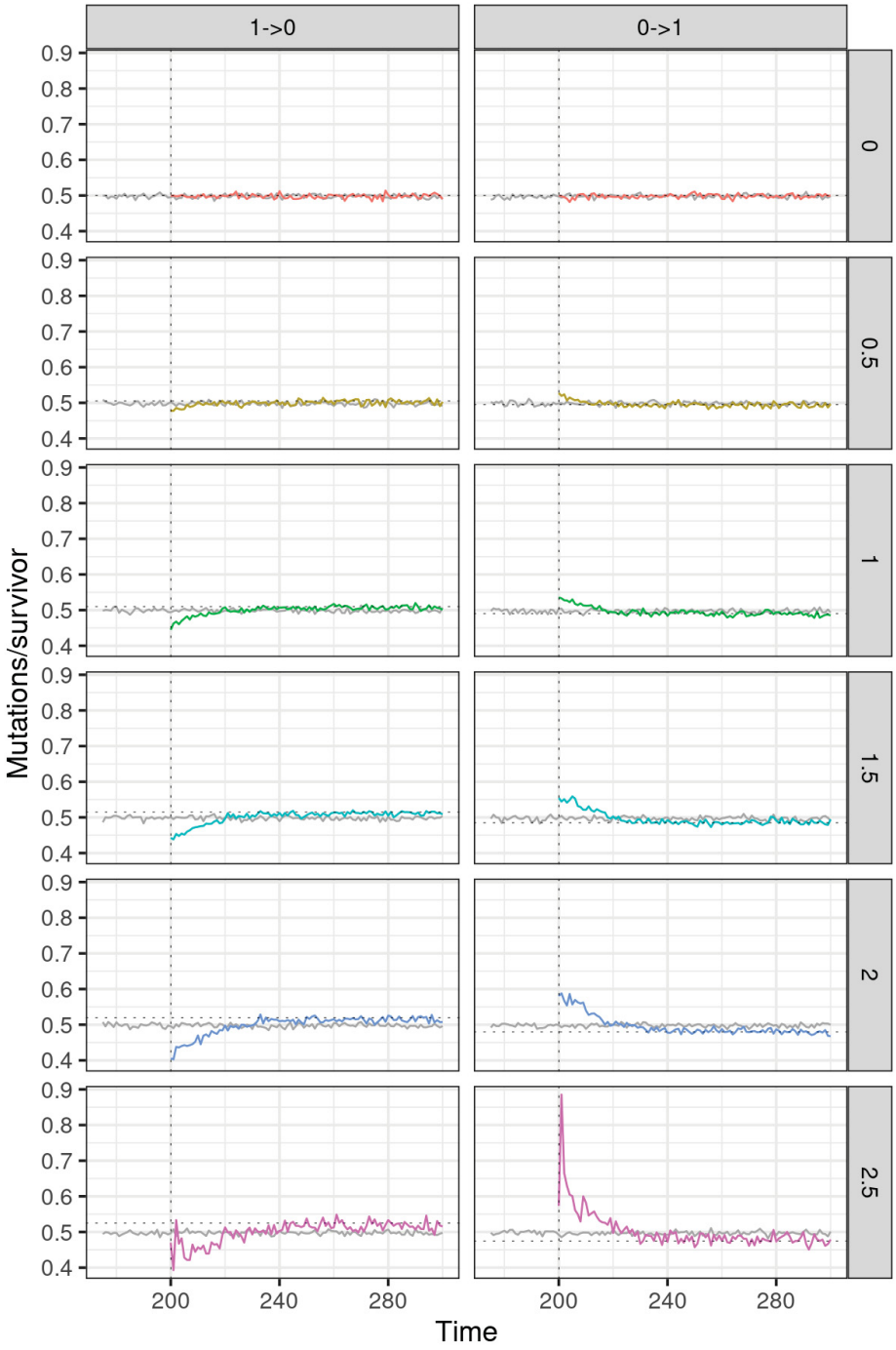

Figure S2.2: Temporal evolution of the average frequency of mutations exhibited by parasite individuals that have survived selection imposed by the host. The values to the right represent the distances (*D*) between the evaluated hosts. The columns *1–> 0* and *0–> 1* mean the mutations from 1 to 0 and from 0 to 1, respectively. The grey line represents the mutations in parasites that inhabit the donor host. Dashed horizontal lines indicate the frequency of mutations expected by chance in the asymptotic regime (after a long time). The values represent the average for replicates with successful colonization of a new host (100 replicates to *D* = 0, 0.5, and 1; 98 to *D* = 1.5; 68 to *D* = 2; and 19 to *D* = 2.5).

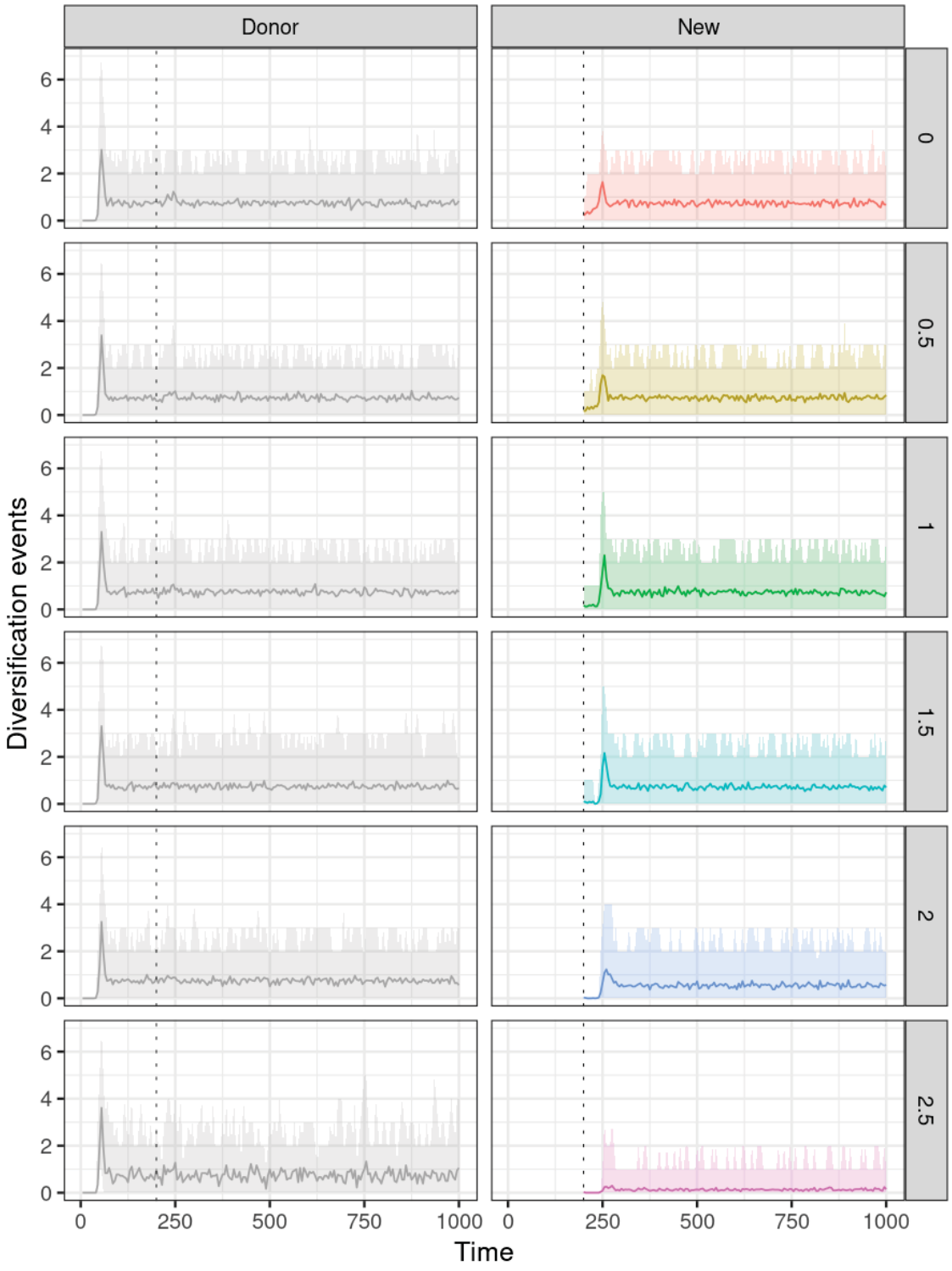

Figure S2.3: Number of diversification events in each host by distance (*D*). The results represent the average for replicates with successful colonization of a new host (100 replicates to *D* = 0, 0.5, and 1; 98 to *D* = 1.5; 68 to *D* = 2; and 19 to *D* = 2.5) and the shadow area a confidence interval of 95%.

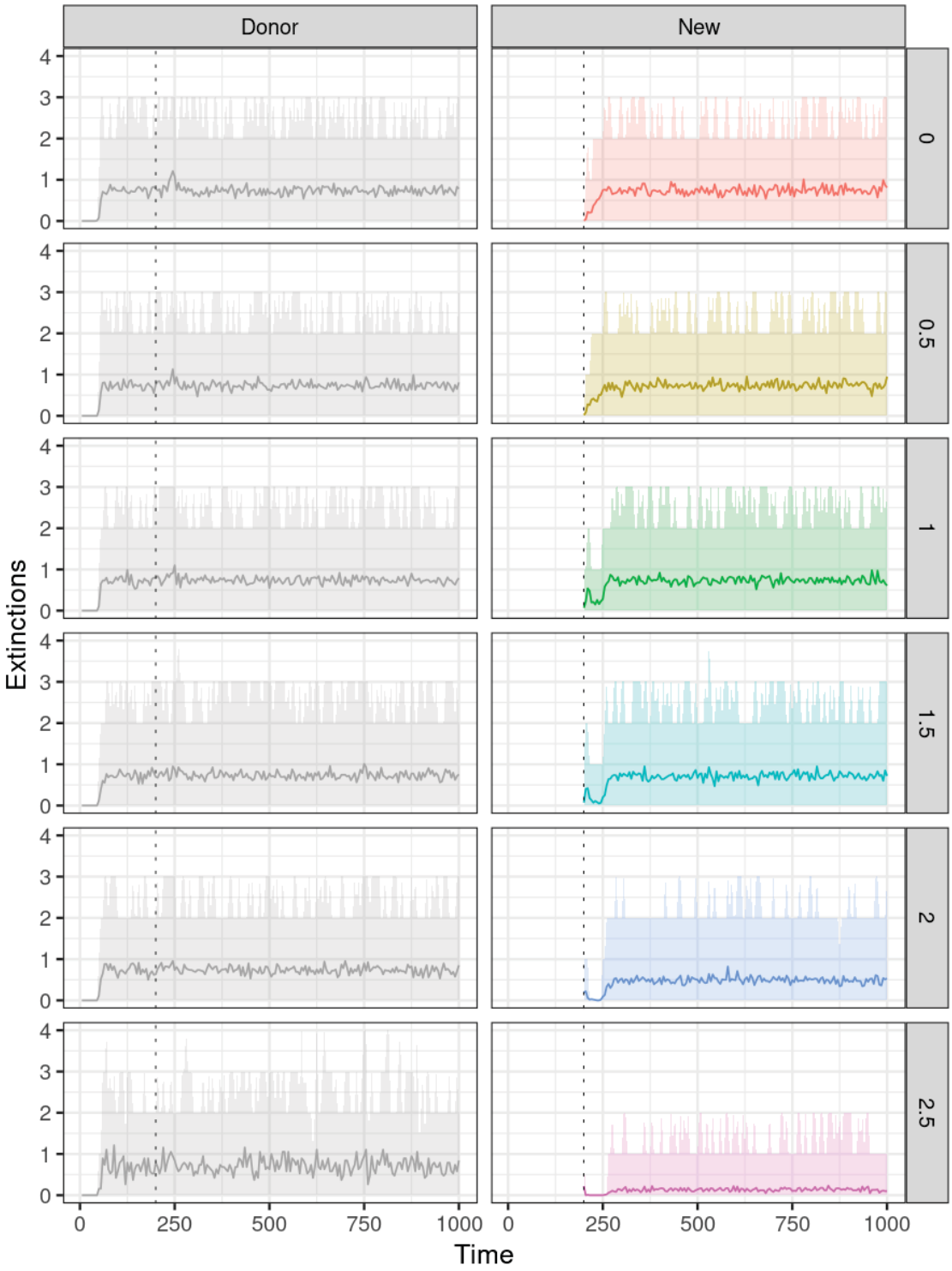

Figure S2.4: Number of extinction events in each host by distance (*D*). The results represent the average for replicates with successful colonization of a new host (100 replicates to *D* = 0, 0.5, and 1; 98 to *D* = 1.5; 68 to *D* = 2; and 19 to *D* = 2.5) and the shadow area a confidence interval of 95%.

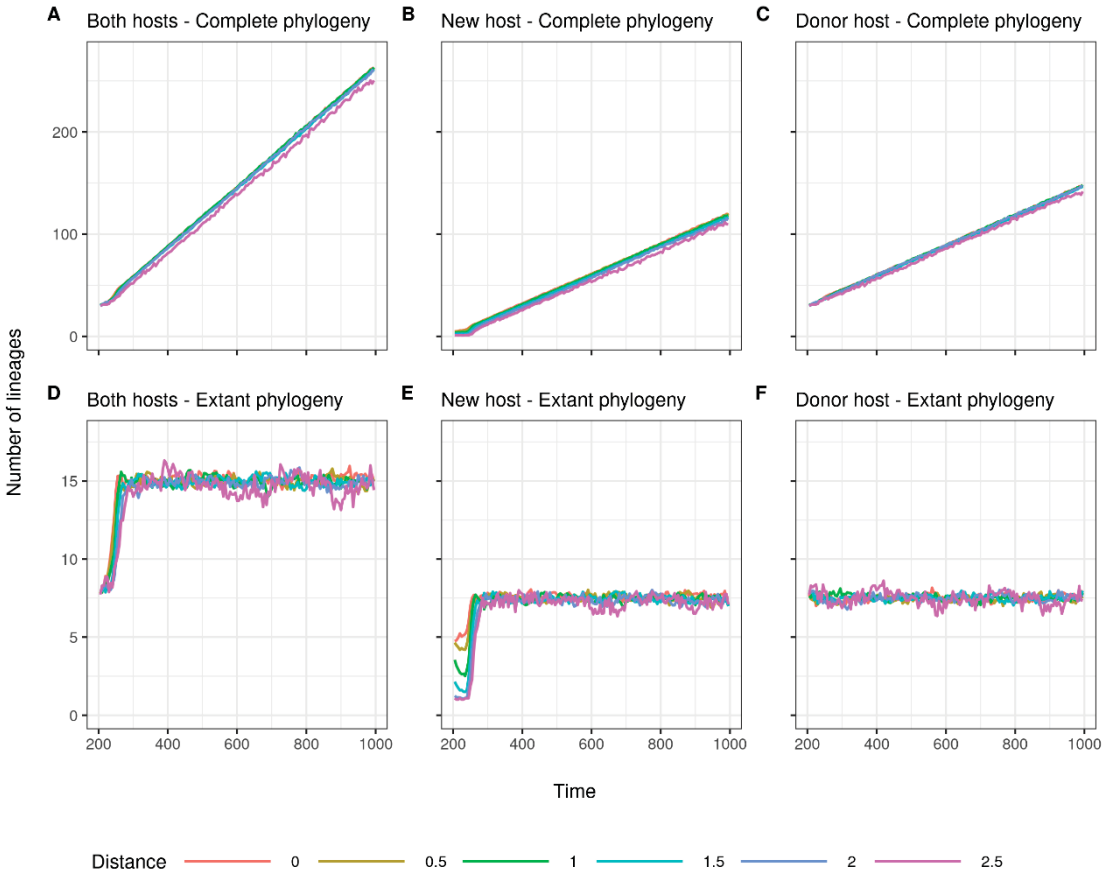

Figure S2.5: Number of parasite lineages accumulated (complete phylogenies) and number of current lineages (extant phylogenies) over time. The "both hosts" phylogenies include all parasite lineages, regardless of which host they inhabit. The "new" and "donor" are filters of the first phylogeny ("both hosts"), including only the lineages present in each host. The results represent the average for replicates with successful colonization of a new host (100 replicates to D = 0, 0.5, and 1; 98 to D = 1.5; 68 to D = 2; and 19 to D = 2.5).

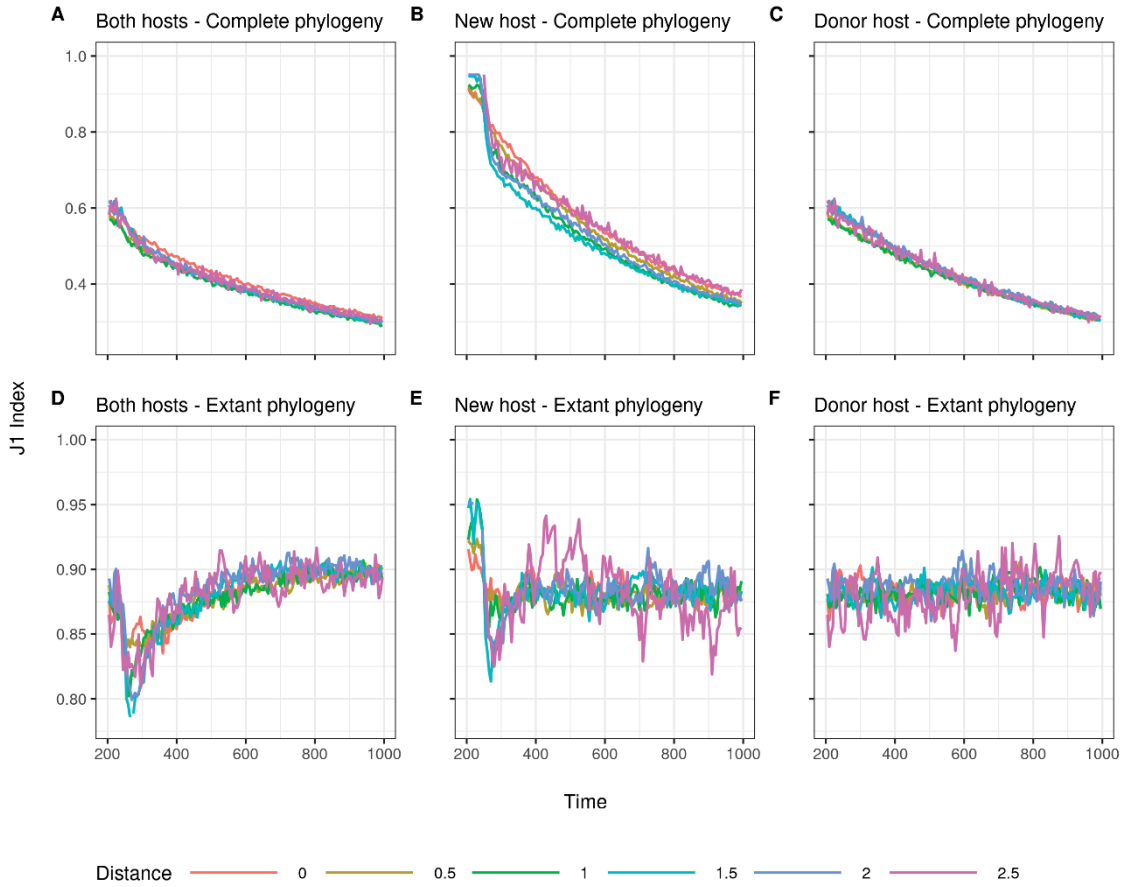

Figure S2.6: Temporal evolution of phylogenies balance (*J*) for complete phylogenies (with extinctions) and extant phylogenies (current lineages) over time. The "both hosts" phylogenies include all lineages, regardless of which host they inhabit. The "new" and "donor" are filters of the first phylogeny ("both hosts"), including only the lineages present in each host. This metric ranges from zero to one, and the higher the value of *J*, the more balanced the phylogeny (and clades speciates more uniformly). The results represent the average for replicates with successful colonization of a new host (100 replicates to $D = 0$, 0.5, and 1; 98 to $D = 1.5$; 68 to $D = 2$; and 19 to $D = 2.5$).

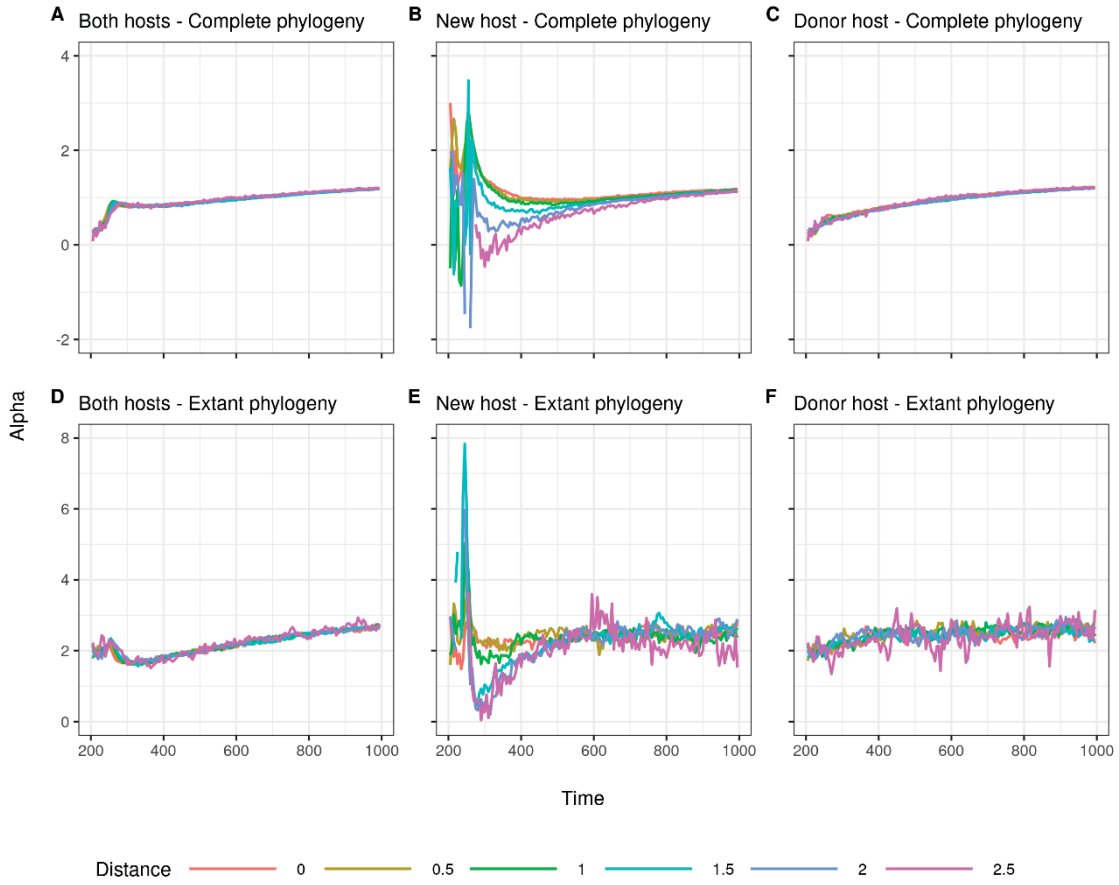

Figure S2.7: Temporal evolution of acceleration of diversification (α) for complete phylogenies (with extinctions) and extant phylogenies (current lineages) over time. The “both hosts” phylogenies include all lineages, regardless of which host they inhabit. The “new” and “donor” are filters of the first phylogeny (“both hosts”), including only the lineages present in each host. If α is zero, the speciation events occur more uniformly over time; if it is negative, the speciation events occur more often near the root of the phylogeny; if it is positive, the diversification events are more concentrated in the leaves. The results represent the average for replicates with successful colonization of a new host (100 replicates to D = 0, 0.5, and 1; 98 to D = 1.5; 68 to D = 2; and 19 to D = 2.5).

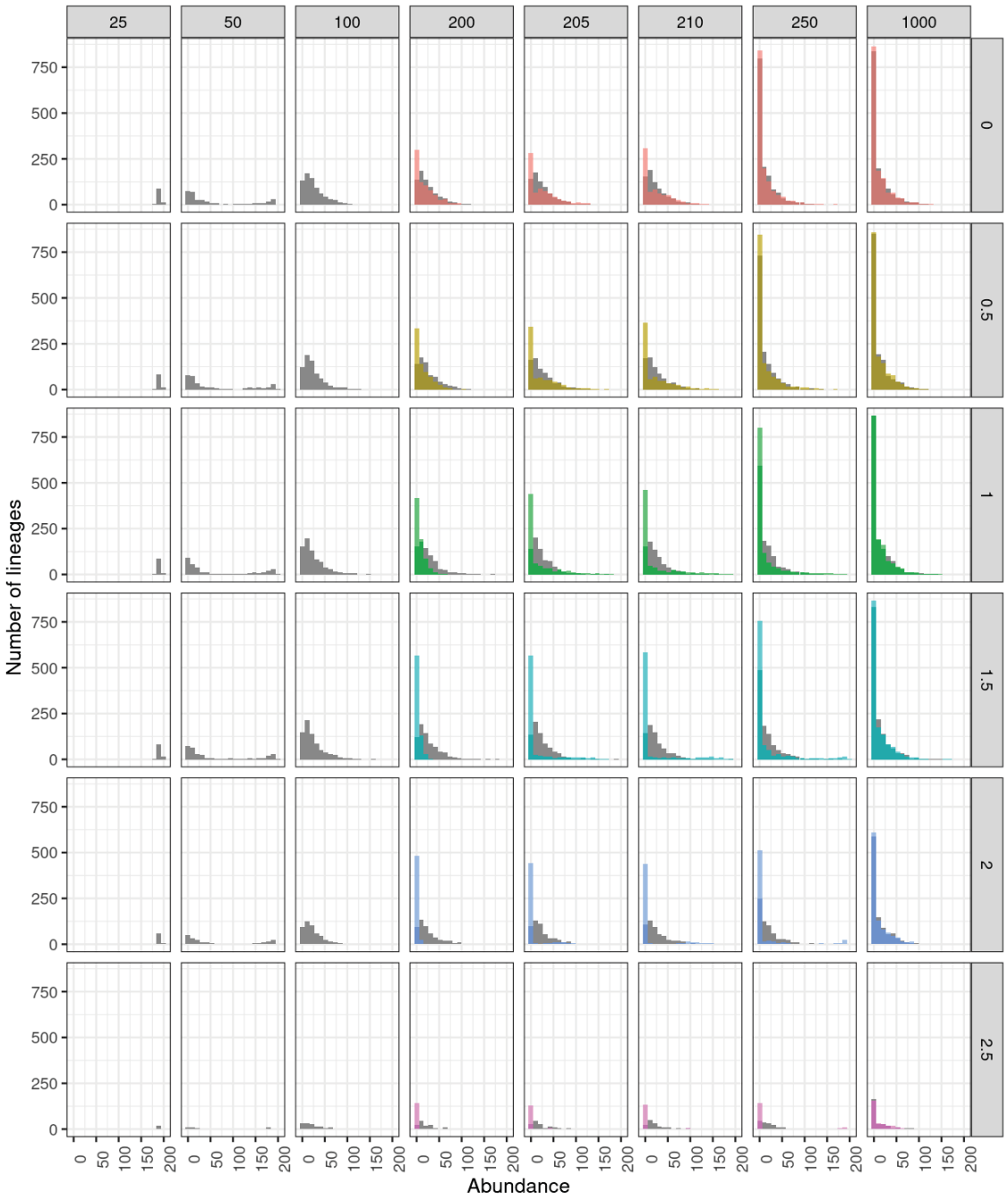

Figure S2.8: Temporal distribution of number of lineages by abundance. The results represent the accumulated values for 100 replicates to D = 0, 0.5, and 1; 98 to D = 1.5; 68 to D = 2, and 19 to D = 2.5 (number of replicates with successful colonization of a new host).

5.1 CONCLUSÕES GERAIS

O reconhecimento de que os parasitas não se restringem aos seus hospedeiros originais destaca a importância de compreender a dinâmica das interações entre parasitas e hospedeiros, especialmente no cenário atual em que o encontro entre parasitas e hospedeiros potenciais é facilitado diariamente. Neste trabalho, discutimos como os modelos teóricos são ferramentas essenciais para entender a dinâmica das doenças e podem fornecer cenários antecipatórios de eventos de troca de hospedeiro. Exploramos ainda como os parasitas exploram os hospedeiros de acordo com suas capacidades e oportunidades. Nossos resultados mostraram que a variabilidade fenotípica aumenta o sucesso do estabelecimento do parasita em novas espécies de hospedeiros; que variantes invisíveis podem ser responsáveis pelo sucesso do estabelecimento em hospedeiros bastante diferentes daqueles usados anteriormente; e que um processo microevolutivo, como a colonização de um novo hospedeiro, desempenha um papel importante na evolução dos parasitas.

Espero que esta pesquisa sirva como um "*stepping-stone*" para uma compreensão mais abrangente das interações parasita-hospedeiro e suas implicações para a dinâmica e o controle de doenças.

5.2 GENERAL CONCLUSIONS

The recognition that parasites are not restricted to their original hosts highlights the importance of comprehending the dynamics of parasite-host interactions, especially in the current scenario in which the encounter of parasites and potential hosts is facilitated daily. In this work, we discussed how theoretical models are essential tools for understanding the dynamics of diseases and can provide anticipatory scenarios of host-switching events, and that parasites explore, colonize, and exploit hosts according to their capacities and opportunities. Our results showed that phenotypic variability increases the success of parasite establishment in new host species; that elusive variants can be responsible for the success of establishment in hosts quite different from those previously used; and that a microevolutionary process, such the colonization of a new host, plays an important role in parasites' evolution.

I hope that this research will serve as a "stepping-stone" towards a more comprehensive understanding of host-parasite interactions and their implications for disease dynamics and control.

6. REFERENCES

Agosta, S.J. 2006. On ecological fitting, plant-insect associations, herbivore host shifts, and host plant selection. Oikos 114, 556–565.

Agosta, S.J.; Brooks, D.R. 2020. The Major Metaphors of Evolution: Darwinism Then and Now. Evolutionary Biology—New Perspectives on Its Development series, vol. 2. Springer, Cham, Switzerland. https://doi.org/10.1007/978-3-030-52086-1

Agosta, S.J.; Janz, N.; Brooks, D.R. 2010. How specialists can be generalists: resolving the “parasite paradox” and implications for emerging infectious disease. Zoologia (Curitiba) 27: 151–162. https://doi.org/10.1590/S1984-46702010000200001

Agosta, S.J.; Klemens, J.A. 2008. Ecological fitting by phenotypically flexible genotypes: implications for species associations, community assembly and evolution. Ecology Letters 11: 1123–1134. https://doi.org/10.1111/j.1461-0248.2008.01237.x

Ali, A.; Roossinck, M.J. 2010. Genetic bottlenecks during systemic movement of Cucumber mosaic virus vary in different host plants. Virology 404: 279–283. https://doi.org/10.1016/j.virol.2010.05.017

Alison, M.R.; Poulsom, R.; Forbes, S.; Wright, N.A. 2002. An introduction to stem cells. Journal of Pathology 197: 419–423. https://doi.org/10.1002/path.1187

Altizer, S.; Ostfeld, R.S.; Johnson, P.T.J.; Kutz, S.; Harvell, C.D. 2013. Climate change and infectious diseases: from evidence to a predictive framework. Science 341: 514–519. https://doi.org/10.1126/science.1239401

Andersen, K.G., Rambaut, A., Lipkin, W.I., Holmes, E.C., Garry, R.F., 2020. The proximal origin of SARS-CoV-2. Nat. Med. 26, 450–452. https://doi.org/10.1038/s41591-020-0820-9

Antia, R., Regoes, R.R., Koella, J.C., Bergstrom, C.T., 2003. The role of evolution in the emergence of infectious diseases. Nature 426, 658–661.

Araujo, S.B.; Braga, M.P.; Brooks, D.R.; Agosta, S.J.; Hoberg, E.P.; von Hartenthal, F.W.; Boeger, W.A. 2015. Understanding hostswitching by ecological fitting. PLOS ONE 10: e0139225. https://doi.org/10.1371/journal.pone.0139225

Baselga, A. 2010. Partitioning the turnover and nestedness components of beta diversity. Global Ecology and Biogeography 19: 134–143. https://doi.org/10.1111/j.1466-8238.2009.00490.x

Baselga, A. 2013. Separating the two components of abundance based dissimilarity: balanced changes in abundance vs. abundance gradients. Methods in Ecology and Evolution 4:552–557. https://doi.org/10.1111/2041-210X.12029

Bashor, L.; Gagne, R.B.; Bosco-Lauth, A.; Stenglein, M.; VandeWoude, S. 2022. Rapid evolution of SARS-CoV-2 in domestic cats. Virus Evolution: veac092. https://doi.org/10.1093/ve/veac092

Bashor, L.; Gagne, R.B.; Bosco-Lauth, A.M.; Bowen, R.A.; Stenglein, M.; VandeWoude, S. 2021. SARS-CoV-2 evolution in animals suggests mechanisms for rapid variant selection. Proceedings of the National Academy of Sciences 118: e2105253118. https://doi.org/10.1073/pnas.2105253118

Baskin, Y., 2006. Sea Sickness: The Upsurge in Marine Diseases. BioScience 56, 464. https://doi.org/10.1641/0006-3568(2006)56[464:SSTUIM]2.0.CO;2

Blum, M.G.B.; François, O. 2005. On statistical tests of phylogenetic tree imbalance: the Sackin and other indices revisited. Mathematical Biosciences 195, 141–153. https://doi.org/10.1016/j.mbs.2005.03.003

Blum, M.G.B., François, O., 2006. Which Random Processes Describe the Tree of Life? A Large-Scale Study of Phylogenetic Tree Imbalance. Syst. Biol. 55, 685–691. https://doi.org/10.1080/10635150600889625

Boeger, W.A.; Brooks, D.R.; Trivellone, V.; Agosta, S.; Hoberg, E. 2022. Ecological super-spreaders drive host-range oscillations: Omicron and risk-space for emerging infectious disease. Illinois Experts reprint. https://doi.org/10.22541/au.164342794.41467213/v1

Braga, M.P.; Araujo, S.B.L.; Agosta, S.; Brooks, D.; Hoberg, E.; Nylin, S.; et al. 2018. Host use dynamics in a heterogeneous fitness landscape generates oscillations in host range and diversification. Evolution 72: 1773–1783. https://doi.org/10.1111/evo.13557

Braga, M.P.; Araújo, S.B.L.; Boeger, W.A. 2014. Patterns of interaction between Neotropical freshwater fishes and their gill Monogenoidea (Platyhelminthes). Parasitology Research 113: 481–490. https://doi.org/10.1007/s00436-013-3677-8

Braga, M.P., Guimarães, P.R., Wheat, C.W., Nylin, S., Janz, N., 2018b. Unifying host-associated diversification processes using butterfly–plant networks. Nat. Commun. 9, 1–10. https://doi.org/10.1038/s41467-018-07677-x

Braga, M.P.; Janz, N. 2021. Host repertoires and changing insect plant interactions. Ecological Entomology 46: 1241–1253. https://doi.org/10.1111/een.13073

Braga, M.P.; Razzolini, E.; Boeger, W.A. 2015. Drivers of parasite sharing among Neotropical freshwater fishes. Journal of Animal Ecology 84: 487–497. https://doi.org/10.1111/1365-2656.12298

Broglio, E., Solé, R.V., 2004. CLIMATE CHANGE AND THE BIODIVERSITY CRISIS AS PROMOTERS FOR EMERGENT Climate change and the biodiversity crisis as promoters for emergent diseases.

Brooks, D.R.; Agosta, S.J. 2012. Children of time: the extended synthesis and major metaphors of evolution. Zoologia (Curitiba) 29: 497–514. https://doi.org/10.1590/S1984-46702012000600002

Brooks, D.R.; Boeger, W.A. 2019. Climate change and emerging infectious diseases: evolutionary complexity in action. Current Opinion in Systems Biology 13: 75–81.

Brooks, D.R.; Ferrao, A.L. 2005. The historical biogeography of co-evolution: emerging infectious diseases are evolutionary accidents waiting to happen. Journal of Biogeography 32: 1291–1299. https://doi.org/10.1111/j.1365-2699.2005.01315.x

Brooks, D.R.; Hoberg, E.P. 2007. How will global climate change affect parasite-host assemblages? Trends in Parasitology 23:571–574. https://doi.org/10.1016/j.pt.2007.08.016

Brooks, D.R.; Hoberg, E.P. 2013. The emerging infectious diseases crisis and pathogen pollution. In: The Balance of Nature and Human Impact. K. Rohde (ed.). Cambridge University Press, Cambridge, England. 215–230 p. https://doi.org/10.1017/CBO9781139095075.022

Brooks, D.R.; Hoberg, E.P.; Boeger, W.A. 2019. The Stockholm Paradigm: Climate Change and Emerging Disease. University of Chicago Press, Chicago.

Brooks, D.R.; Hoberg, E.P.; Boeger, W.A.; Gardner, S.L.; Galbreath, K.E.; Herczeg, D.; et al. 2014. Finding them before they find us: informatics, parasites, and environments in accelerating climate change. Comparative Parasitology 81: 155–164.

Brooks, D.R., Hoberg, E.P., Boeger, W.A., Trivellone, V., 2021. Emerging infectious disease: An underappreciated area of strategic concern for food security. Transbound. Emerg. Dis. tbed.14009. https://doi.org/10.1111/tbed.14009

Brooks, D.R.; McLennan, D.A. 2002. The Nature of Diversity: An Evolutionary Voyage of Discovery. University of Chicago Press, Chicago.

Calderon, A.; Guzman, C.; Salazar-Bravo, J.; Figueiredo, L.T.; Mattar, S.; Arrieta, G. 2016. Viral zoonoses that fly with bats: a review. MANTER Journal of Parasite Biodiversity 6. https://doi.org/10.13014/K2BG2KWF

Carbonell, P.; Lecointre, G.; Faulon, J.-L. 2011. Origins of specificity and promiscuity in metabolic networks. Journal of Biological Chemistry 286: 43994–44004. https://doi.org/10.1074/jbc.M111.274050

Caron, F.S., Pie, M.R., 2020. The phylogenetic signal of diversification rates. J. Zool. Syst. Evol. Res. 58, 1432–1436. https://doi.org/10.1111/jzs.12379

Cassey, P., Delean, S., Lockwood, J.L., Sadowski, J.S., Blackburn, T.M., 2018. Dissecting the null model for biological invasions: A meta-analysis of the

propagule pressure effect. PLoS Biol. 16, 1–16. https://doi.org/10.1371/journal.pbio.2005987

CDC [Center for Disease Control and Prevention]. 2022. What you should know about COVID-19 and pets. [WWWdocument]. Accessed April 27, 2022. https://www.cdc.gov/healthypets/covid-19/pets.html

Charleston, M.A., Robertson, D.L., 2002. Preferential host switching by primate lentiviruses can account for phylogenetic similarity with the primate phylogeny. Syst. Biol. 51, 528–535. https://doi.org/10.1080/10635150290069940

Christaki, E. 2015. New technologies in predicting, preventing and controlling emerging infectious diseases. Virulence 6:558–565. https://doi.org/10.1080/21505594.2015.1040975

Cipollini, D.; Peterson, D.L. 2018. The potential for host switching via ecological fitting in the emerald ash borer host plant system. Oecologia 187: 507–519. https://doi.org/10.1007/s00442-018-4089-3

Clay, C.A.; Lehmer, E.M.; Jeor, S.; Dearing, M.D. 2009. Sin Nombre virus and rodent species diversity: a test of the dilution and amplification hypotheses. PLOS ONE 4: e6467. https://doi.org/10.1371/journal.pone.0006467

Clayton, D.H., Bush, S.E., Goates, B.M., Johnson, K.P., 2003. Host defense reinforces host–parasite cospeciation. Proc. Natl. Acad. Sci. 100, 15694–15699. https://doi.org/10.1073/pnas.2533751100

Combes, C. 2001. Parasitism: The Ecology and Evolution of Intimate Interactions. University of Chicago Press, Chicago. Conn, D.B. 2014. Aquatic invasive species and emerging infectious disease threats: a One Health perspective. Aquatic Invasions 9: 383–390. https://doi.org/10.3391/ai.2014.9.3.12

Conn, D.B., 2014. Aquatic invasive species and emerging infectious disease threats: A One Health perspective. Aquat. Invasions 9, 383–390. https://doi.org/10.3391/ai.2014.9.3.12

Costa, C.L.N., Lemos-Costa, P., Marquitti, F.M.D., Fernandes, L.D., Ramos, M.F., Schneider, D.M., Martins, A.B., De Aguiar, M.A.M., 2019. Signatures of

Microevolutionary Processes in Phylogenetic Patterns. Syst. Biol. 68, 131–144. https://doi.org/10.1093/sysbio/syy049

Dada, J.O.; Mendes, P. 2011. Multi-scale modelling and simulation in systems biology. Integrative Biology 3: 86–96. https://doi.org/10.1039/c0ib00075b

Damas, J.; Hughes, G.M.; Keough, K.C.; Painter, C.A.; Persky, N.S.; Corbo, M.; et al. 2020. Broad host range of SARS-CoV-2 predicted by comparative and structural analysis of ACE2 in vertebrates. Proceedings of the National Academy of Sciences 117: 22311–22322. https://doi.org/10.1073/pnas.2010146117

Darwin, C. 1872. The Origin of Species. 6th ed. John Murray, London.

D'Bastiani, E.; Princepe, D.; Marquitti, F.M.D.; Boeger, W.A.; Campião, K.M.; Araujo, S.L.B. 2021. Effect of host-switching on the eco-evolutionary patterns of parasites. bioRxiv preprint. https://doi.org/10.1101/2021.11.27.47014

D'Bastiani, E., Princepe, D., Marquitti, F.M.D., Boeger, W.A., Campião, K.M., Araujo, S.B.L., 2023. Effect of Host-Switching on the Ecological and Evolutionary Patterns of Parasites. Syst. Biol. 72, 912–924. https://doi.org/10.1093/sysbio/syad022

de Aguiar, M.A.M.; Baranger, M.; Baptestini, E.M.; Kaufman, L.; Bar-Yam, Y. 2009. Global patterns of speciation and diversity. Nature 460: 384–387. https://doi.org/10.1038/nature08168

De Vienne, D.M., Giraud, T., Shykoff, J.A., 2007. When can host shifts produce congruent host and parasite phylogenies? A simulation approach. J. Evol. Biol. 20, 1428–1438. https://doi.org/10.1111/j.1420-9101.2007.01340.x

de Vienne, D.M.; Hood, M.E.; Giraud, T. 2009. Phylogenetic determinants of potential host shifts in fungal pathogens. Journal of Evolutionary Biology 22: 2532–2541. https://doi.org/10.1111/j.1420-9101.2009.01878.x

De Vienne, D.M., Refrégier, G., López-Villavicencio, M., Tellier, A., Hood, M.E., Giraud, T., 2013. Cospeciation vs host-shift speciation: Methods for testing, evidence from natural associations and relation to coevolution. New Phytol. 198, 347–385. https://doi.org/10.1111/nph.12150

Destoumieux-Garzón, D., Mavingui, P., Boetsch, G., Boissier, J., Darriet, F., Duboz, P., Fritsch, C., Giraudoux, P., Le Roux, F., Morand, S., Paillard, C., Pontier, D., Sueur, C., Voituron, Y., 2018. The One Health Concept: 10 Years Old and a Long Road Ahead. Front. Vet. Sci. 5, 14. https://doi.org/10.3389/fvets.2018.00014

Dieckmann, U.; Doebeli, M. 1999. On the origin of species by sympatric speciation. Nature 400: 354–357. https://doi.org/10.1038/22521

Doña, J., Sweet, A.D., Johnson, K.P., Serrano, D., Mironov, S., Jovani, R., 2017. Cophylogenetic analyses reveal extensive host-shift speciation in a highly specialized and host-specific symbiont system. Mol. Phylogenet. Evol. 115, 190–196. https://doi.org/10.1016/j.ympev.2017.08.005

Edwards, P.J., Abivardi, C., 1998. The value of biodiversity: Where ecology and economy blend. Biol. Conserv. 83, 239–246. https://doi.org/10.1016/S0006-3207(97)00141-9

Engelstädter, J., Fortuna, N.Z., 2019. The dynamics of preferential host switching: Host phylogeny as a key predictor of parasite distribution*. Evolution 73, 1330–1340. https://doi.org/10.1111/evo.13716

Faria, N.R., Suchard, M.A., Rambaut, A., Streicker, D.G., Lemey, P., 2013. Simultaneously reconstructing viral cross-species transmission history and identifying the underlying constraints. Philos. Trans. R. Soc. B Biol. Sci. 368, 20120196. https://doi.org/10.1098/rstb.2012.0196

Fauci, A.S.; Morens, D.M. 2012. The perpetual challenge of infectious diseases. New England Journal of Medicine 366: 454–461. https://doi.org/10.1056/NEJM1108296

Fenollar, F.; Mediannikov, O.; Maurin, M.; Devaux, C.; Colson, P.; Levasseur, A.; et al. 2021. Mink, SARS-CoV-2, and the humananimal interface. Frontiers in Microbiology 12: 745. https://doi.org/10.3389/fmicb.2021.663815

Feronato, S.G.; Araujo, S.; Boeger, W.A. 2021. ’Accidents waiting to happen’—insights from a simple model on the emergence of infectious agents in new hosts. Transboundary and Emerging Diseases 69: 1727–1738. https://doi.org/10.1111/tbed.14146

Fitzpatrick, B.M.; Fordyce, J.A.; Gavrilets, S. 2009. Pattern,process and geographic modes of speciation. Journal of Evolutionary Biology 22: 2342–2347. https://doi.org/10.1111/j.1420-9101.2009.01833.x

Forsman, A., 2014. Effects of genotypic and phenotypic variation on establishment are important for conservation, invasion, and infection biology. Proc. Natl. Acad. Sci. U. S. A. 111, 302–307. https://doi.org/10.1073/pnas.1317745111

Freitas, O., Araujo, S.B.L., Campos, P.R.A., 2022. Speciation in a metapopulation model upon environmental changes. Ecol. Model. 468, 109958. https://doi.org/10.1016/j.ecolmodel.2022.109958

Freitas, O., Campos, P.R.A., Araujo, S.B.L., 2024. Patch biogeography under intermittent barriers: macroevolutionary consequences of microevolutionary processes. J. Evol. Biol. 1–34. https://doi.org/10.1093/jeb/voae035

Gascuel, F., Ferriere, R., Aguilee, R., Lambert, A., 2015. How Ecology and Landscape Dynamics Shape Phylogenetic Trees. Syst. Biol. 64, 590–607. https://doi.org/10.1093/sysbio/syv014

Garrett, L., 1994. The coming plague: Newly emerging diseases in a world out of balance. Farrar, Straus and Giroux.

Giacomini, H.C. 2007. Sete motivações teóricas para o uso da modelagem baseada no indivíduo em ecologia [Seven theoretical reasons for using individual-based modeling in ecology]. Acta Amazonica 37: 431–445. https://doi.org/10.1590/S0044-59672007000300015

Gilbert, G.S.; Webb, C.O. 2007. Phylogenetic signal in plant pathogen–host range. Proceedings of the National Academy of Sciences 104: 4979–4983. https://doi.org/10.1073/pnas.0607968104

Gioti, A.; Stajich, J.E.; Johannesson, H. 2013. Neurospora and the dead-end hypothesis: genomic consequences of selfing in the model genus. Evolution 67: 3600–3616. https://doi.org/10.1111/evo.12206

Giraud, T., Gladieux, P., Gavrilets, S., 2010. Linking the emergence of fungal plant diseases with ecological speciation. Trends Ecol. Evol. 25, 387–395. https://doi.org/10.1016/j.tree.2010.03.006

Gómez, J.M.; Verdú, M.; Perfectti, F. 2010. Ecological interactions are evolutionarily conserved across the entire tree of life. Nature 465: 918–921. https://doi.org/10.1038/nature09113

Gubler, D.J. 2010. The global threat of emergent/reemergent vector-borne diseases. In: Vector Biology, Ecology and Control. P.W. Atkinson (ed.). Springer Netherlands, Dordrecht. 39–62 p. https://doi.org/10.1007/978-90-481-2458-9_4

Hadfield et al., 2018. Nextstrain: real-time tracking of pathogen evolution. Bioinformatics 34, 4121–4123.

Hagen, O., Flück, B., Fopp, F., Cabral, J.S., Hartig, F., Pontarp, M., Rangel, T.F., Pellissier, L., 2021. gen3sis: A general engine for eco-evolutionary simulations of the processes that shape Earth's biodiversity, PLoS Biology. https://doi.org/10.1371/journal.pbio.3001340

Haldane, J.B.S. 1951. Everything Has a History. Routledge/Taylor & Francis Group, London.

Hoberg, E. 2022. The DAMA protocol, an introduction: finding pathogens before they find us. MANTER Journal of Parasite Biodiversity 21. https://doi.org/10.32873/unl.dc.manter21

Hoberg, E.P. 2010. Invasive processes, mosaics and the structure of helminth parasite faunas. Revue Scientifique et Technique—Office International des Épizooties 29: 255–272. https://doi.org/10.20506/rst.29.2.1972

Hoberg, E.P., Boeger, W.A., Molnár, O., Földvári, G., Gardner, S.L., Juarrero, A., Kharchenko, V., Ortíz, E., Preiser, W., Trivellone, V., others, 2023. The DAMA Protocol: Anticipating to Prevent and Mitigate Emerging Infectious Diseases. Evol. Pathw. Coping Emerg. Infect. Dis. Gardner SL Brooks DR Boeger WA Hoberg EP Eds.

Hoberg, E.P.; Boeger, W.A.; Brooks, D.R.; Trivellone, V.; Agosta, S.J. 2022. Stepping-stones and mediators of pandemic expansion—a context for humans

as ecological superspreaders. MANTER Journal of Parasite Biodiversity 18. https://doi.org/10.32873/unl.dc.manter18

Hoberg, E.P., Brooks, D.R., 2008. A macroevolutionary mosaic: Episodic host-switching, geographical colonization and diversification in complex host-parasite systems. J. Biogeogr. 35, 1533–1550. https://doi.org/10.1111/j.1365-2699.2008.01951.x

Hoberg, E.P.; Brooks, D.R. 2010. Beyond vicariance: integrating taxon pulses, ecological fitting, and oscillation in evolution and historical biogeography. In: The Geography of HostParasite Interactions. S. Morand and B. Krasnov (eds.). Oxford University Press, Oxford, UK. 7–20 p.

Hoberg, E.P.; Brooks, D.R. 2015. Evolution in action: climate change, biodiversity dynamics and emerging infectious disease. Philosophical Transactions of the Royal Society B—Biological Sciences 370: 20130553. https://doi.org/10.1098/rstb.2013.0553

Holle, V., Simberloff, D., 2005. Ecological Resistance to Biological Invasion Overwhelmed by Propagule Pressure Author(s): Betsy. Source Ecol. 86, 3212–3218.

Holmes, E.C. 2009. The Evolution and Emergence of RNA Viruses. Oxford Series in Ecology and Evolution. Oxford University Press, Oxford, UK.

Huang, S., Farrell, M., Stephens, P.R., 2021. Infectious disease macroecology: Parasite diversity and dynamics across the globe. Philos. Trans. R. Soc. B Biol. Sci. 376. https://doi.org/10.1098/rstb.2020.0350

Hui, C.; Richardson, D.M. 2018. How to Invade an ecological network. Trends in Ecology and Evolution 34: 121–131. https://doi.org/10.1016/j.tree.2018.11.003

Hulme, P.E. 2014. Invasive species challenge the global response to emerging diseases. Trends in Parasitology 30: 267–270. https://doi.org/10.1016/j.pt.2014.03.005

Imrie, R.M.; Roberts, K.E.; Longdon, B. 2021. Between virus correlations in the outcome of infection across host species: evidence of virus by host species interactions. Evolution Letters 5: 472–483. https://doi.org/10.1002/evl3.247

Janz, N.; Nylin, S. 2008. The oscillation hypothesis of host-plant range and speciation. In: Specialization, Speciation, and Radiation: The Evolutionary Biology of Herbivorous Insects. K. Tilmon (ed.). University of California Press. 203–215 p. https://doi.org/10.1525/california/9780520251328.001.0001

Janzen, D.H., 1985. On ecological fitting. Oikos 45: 308–310. https://doi.org/10.2307/3565565

Keesing, F.; Belden, L.K.; Daszak, P.; Dobson, A.; Harvell, C.D.; Holt, R.D.; et al. 2010. Impacts of biodiversity on the emergence and transmission of infectious diseases. Nature 468: 647–652.

Kellogg, V. 1907. Darwinism Today. Holt, New York. Khersonsky, O.; Roodveldt, C.; Tawfik, D.S. 2006. Enzyme promiscuity: evolutionary and mechanistic aspects. Current Opinion in Chemical Biology (Analytical Techniques/ Mechanisms special issue) 10: 498–508. https://doi.org/10.1016/j.cbpa.2006.08.011

Kreuder Johnson, C., Hitchens, P.L., Smiley Evans, T., Goldstein, T., Thomas, K., Clements, A., Joly, D.O., Wolfe, N.D., Daszak, P., Karesh, W.B., Mazet, J.K., 2015. Spillover and pandemic properties of zoonotic viruses with high host plasticity. Sci. Rep. 5, 1–8. https://doi.org/10.1038/srep14830

Kuchipudi, S.V.; Surendran-Nair, M.; Ruden, R.M.; Yon, M.; Nissly, R.H.; Vandegrift, K.J.; et al. 2022. Multiple spillovers from humans and onward transmission of SARS-CoV-2 in white-tailed deer. Proceedings of the National Academy of Sciences 119: e2121644119. https://doi.org/10.1073/pnas.2121644119

Kupferschmidt, Ka., 2021. Where did ‘weird’ Omicron come from? https://doi.org/10.1126/science.acx9754

Lemant, J., Le Sueur, C., Manojlović, V., Noble, R., 2022. Robust, Universal Tree Balance Indices. Syst. Biol. 71, 1210–1224. https://doi.org/10.1093/sysbio/syac027

Le Roux, J.J.; Hui, C.; Keet, J.-H.; Ellis, A.G. 2017. Co-introduction vs ecological fitting as pathways to the establishment of effective mutualisms

during biological invasions. New Phytologist 215: 1354–1360. https://doi.org/10.1111/nph.14593

Longdon, B., Brockhurst, M.A., Russell, C.A., Welch, J.J., Jiggins, F.M., 2014. The Evolution and Genetics of Virus Host Shifts. PLoS Pathog. 10. https://doi.org/10.1371/journal.ppat.1004395

Luis, A.D.; Kuenzi, A.J.; Mills, J.N. 2018. Species diversity concurrently dilutes and amplifies transmission in a zoonotic host-pathogen system through competing mechanisms. Proceedings of the National Academy of Sciences 115: 7979–7984. https://doi.org/10.1073/pnas.1807106115

Malcicka, M.; Agosta, S.J.; Harvey, J.A. 2015. Multi-level ecological fitting: indirect life cycles are not a barrier to host switching and invasion. Global Change Biology 21: 3210–3218. https://doi.org/10.1111/gcb.12928

Mallapaty, S. 2022. How sneezing hamsters sparked a COVID outbreak in Hong Kong. Nature (News, February 4, 2022). https://doi.org/10.1038/d41586-022-00322-0

Manrubia, S.C. 2012. Modelling viral evolution and adaptation: challenges and rewards. Current Opinion in Virology 2: 531– 537. https://doi.org/10.1016/j.coviro.2012.06.006

Margulis, L. 1971. Symbiosis and evolution. Scientific American 225: 48–57. https://doi.org/10.1038/scientificamerican0871-48

Marquitti, F.M.D., Fernandes, L.D., de Aguiar, M.A.M., 2020. Allopatry increases the balance of phylogenetic trees during radiation under neutral speciation. Ecography 1–12. https://doi.org/10.1111/ecog.04937

Mayhew, P.J., 2006. Discovering evolutionary ecology: bringing together ecology and evolution. Oxford University Press, Oxford ; New York.

McCrone, J.T., Lauring, A.S., 2018. Genetic bottlenecks in intraspecies virus transmission. Curr. Opin. Virol. 28, 20–25. https://doi.org/10.1016/j.coviro.2017.10.008

Molnár, O., Hoberg, E., Trivellone, V., Földvári, G., R., D., 2022a. The 3P Framework: A Comprehensive Approach to Coping with the Emerging Infectious

Disease Crisis. MANTER J. Parasite Biodivers. https://doi.org/10.32873/unl.dc.manter23

Molnár, O.; Knickel, M.; Marizzi, C. 2022. Taking action: turning evolutionary theory into preventive policies. MANTER Journal of Parasite Diversity 28. https://doi.org/10.32873/unl.dc.manter28

Mooers, A.O., Heard, S.B., 1997. Inferring Evolutionary Process from Phylogenetic Tree Shape. Q. Rev. Biol. 72, 31–54. https://doi.org/10.1086/419657

Morens, D.M.; Folkers, G.K.; Fauci, A.S. 2004. The challenge of emerging and re-emerging infectious diseases. Nature 430:242–249.

Morse, S.S. 2001. Factors in the emergence of infectious diseases. In: Plagues and Politics. A.T. Price-Smith (ed.). Global Issues series. Palgrave Macmillan, London. 8–26 p. https://doi.org/10.1057/9780230524248_2

Morlon, H., 2014. Phylogenetic approaches for studying diversification. Ecol. Lett. 17, 508–525. https://doi.org/10.1111/ele.12251

Moxon, R.; Kussell, E. 2017. The impact of bottlenecks on microbial survival, adaptation, and phenotypic switching in host-pathogen interactions. Evolution 71: 2803–2816. https://doi.org/10.1111/evo.13370

Nuismer, S.L., Thompson, J.N., 2006. Coevolutionary Alternation in Antagonistic Interactions. Evolution 60, 2207. https://doi.org/10.1554/06-111.1

Nylin, S.; Agosta, S.; Bensch, S.; Boeger, W.A.; Braga, M.P.; Brooks, D.R.; et al. 2018. Embracing colonizations: a new paradigm for species association dynamics. Trends in Ecology and Evolution 33: 4–14. https://doi.org/10.1016/j.tree.2017.10.005

Nyman, T., 2010. To speciate, or not to speciate? Resource heterogeneity, the subjectivity of similarity, and the macroevolutionary consequences of niche-width shifts in plant-feeding insects. Biol. Rev. 85, 393–411. https://doi.org/10.1111/j.1469-185X.2009.00109.x

O'Dowd, A., 2007. Infectious diseases are spreading more rapidly than ever before, WHO warns. BMJ 335, 418. https://doi.org/10.1136/bmj.39318.516968.DB

Oliver, T.H., Heard, M.S., Isaac, N.J.B., Roy, D.B., Procter, D., Eigenbrod, F., Freckleton, R., Hector, A., Orme, C.D.L., Petchey, O.L., Proença, V., Raffaelli, D., Suttle, K.B., Mace, G.M., Martín-López, B., Woodcock, B.A., Bullock, J.M., 2015. Biodiversity and Resilience of Ecosystem Functions. Trends Ecol. Evol. 30, 673–684. https://doi.org/10.1016/j.tree.2015.08.009

Ostfeld, R.S.; Keesing, F. 2012. Effects of host diversity on infectious disease. Annual Review of Ecology, Evolution, and Systematics 43: 157–182. https://doi.org/10.1146/annurev-ecolsys-102710-145022

Paradis, E., Schliep, K., 2019. ape 5.0: an environment for modern phylogenetics and evolutionary analyses in R. Bioinformatics 35, 526–528. https://doi.org/10.1093/bioinformatics/bty633

Patella, L.; Brooks, D.R.; Boeger, W.A. 2017. Phylogeny and ecology illuminate the evolution of associations under the Stockholm Paradigm: Aglaiogyrodactylus spp.(Platyhelminthes, Monogenoidea, Gyrodactylidae) and species of Loricariidae (Actinopterygii, Siluriformes). Vie et Milieu 67: 91–102.

Peeler, E.; Thrush, M.; Paisley, L.; Rodgers, C. 2006. An assessment of the risk of spreading the fish parasite Gyrodactylus salaris to uninfected territories in the European Union with the movement of live Atlantic salmon (Salmo salar) from coastal waters. Aquaculture 258, 187–197. https://doi.org/10.1016/j.aquaculture.2005.07.042

Pérez, S.D.; Grummer, J.A.; Fernandes-Santos, R.C.; José, C.T., Medici, E.P., Marcili, A. 2019. Phylogenetics, patterns of genetic variation and population dynamics of Trypanosoma terrestris support both coevolution and ecological hostfitting as processes driving trypanosome evolution. Parasites & Vectors 12: 473. https://doi.org/10.1186/s13071-019-3726-y

Pinder, A.C.; Gozlan, R.E.; Britton, J.R. 2005. Dispersal of the invasive topmouth gudgeon, Pseudorasbora parva, in the UK: a vector for an emergent

infectious disease. Fisheries Management and Ecology 12: 411–414. https://doi.org/10.1111/j.1365-2400.2005.00466.x

Princepe, D.; Czarnobai, S.; Pradella, T.M.; Caetano, R.A.; Marquitti, F.M.D.; de Aguiar, M.A.M.; Araujo, S.B.L. 2022. Diversity patterns and speciation processes in a two-island system with continuous migration. Evolution 76: 2260–2271. https://doi.org/10.1111/evo.14603

Ribeiro Prist, P.; Reverberi Tambosi, L.; Filipe Mucci, L.; Pinter, A.; Pereira de Souza, R.; de Lara Muylaert, R.; Rhodes, J.R., et al. 2022. Roads and forest edges facilitate yellow fever virus dispersion. Journal of Applied Ecology 59: 4–17. https://doi.org/10.1111/1365-2664.14031

Rohr, J.R.; Civitello, D.J.; Halliday, F.W.; Hudson, P.J.; Lafferty, K.D.; Wood, C.L.; Mordecai, E.A. 2019. Towards common ground in the biodiversity-disease debate. Nature Ecology and Evolution 4: 24–33. https://doi.org/10.1038/s41559-019-1060-6

Rosenthal, S.R., Ostfeld, R.S., McGarvey, S.T., Lurie, M.N., Smith, K.F., 2015. Redefining disease emergence to improve prioritization and macro-ecological analyses. One Health 1, 17–23. https://doi.org/10.1016/j.onehlt.2015.08.001

Rychener, L.; In-Albon, S.; Djordjevic, S.P.; Chowdhury, P.R.; Nicholson, P.; Ziech, R.E.; et al. 2017. Clostridium chauvoei, an evolutionary dead-end pathogen. Frontiers in Microbiology 8: 1–13. https://doi.org/10.3389/fmicb.2017.01054

Sacristán, S.; Malpica, J.M.; Fraile, A.; García-Arenal, F. 2003. Estimation of population bottlenecks during systemic movement of Tobacco mosaic virus in tobacco plants. Journal of Virology 77: 9906–9911. https://doi.org/10.1128/jvi.77.18.9906-9911.2003

Savary, S., Willocquet, L., Pethybridge, S.J., Esker, P., McRoberts, N., Nelson, A., 2019. The global burden of pathogens and pests on major food crops. Nat. Ecol. Evol. 3, 430–439. https://doi.org/10.1038/s41559-018-0793-y

Scheiner, S.M.; Mindell, D.P. (eds.). 2019. The Theory of Evolution: Principles, Concepts, and Assumptions. University of Chicago Press, Chicago. https://doi.org/10.7208/chicago/9780226671338.001.0001

Schradin, C.; Lindholm, A.K.; Johannesen, J.; Schoepf, I.; Yuen, C.-H.; König, B.; Pillay, N. 2012. Social flexibility and social evolution in mammals: a case study of the African striped mouse (Rhabdomys pumilio). Molecular Ecology 21: 541–553. https://doi.org/10.1111/j.1365-294X.2011.05256.x

Simberloff, D., 2009. The role of propagule pressure in biological invasions. Annu. Rev. Ecol. Evol. Syst. 40, 81–102. https://doi.org/10.1146/annurev.ecolsys.110308.120304

Smith, J.M. 1976. What determines the rate of evolution? American Naturalist 110: 331–338. https://doi.org/10.1086/283071

Streicker, D.G., Turmelle, A.S., Vonhof, M.J., Kuzmin, I.V., Mccracken, G.F., Rupprecht, C.E., Science, S., Series, N., August, N., Streicker, D.G., Turmelle, A.S., Vonhof, M., Kuzmin, I.V., Mccracken, G.F., Rupprecht, C.E., 2010. Host Phylogeny Constrains Cross-Species Emergence and Establishment of Rabies Virus in Bats. Science 329.5992 (2010): 676-679.

Sprouffske, K.; Aguilar-Rodríguez, J.; Sniegowski, P.; Wagner, A. 2018. High mutation rates limit evolutionary adaptation in Escherichia coli. PLOS Genetics 14: e1007324. https://doi.org/10.1371/journal.pgen.1007324

Steward, R.A.; Epanchin-Niell, R.S.; Boggs, C.L. 2022. Novel host unmasks heritable variation in plant preference within an insect population. Evolution 76: 2634–2648. https://doi.org/10.1111/evo.14608

Streicker, D.G.; Turmelle, A.S.; Vonhof, M.J.; Kuzmin, I.V.; McCracken, G.F.; Rupprecht, C.E. 2010. Host phylogeny constrains cross-species emergence and establishment of rabies virus in bats. Science 329: 676–679. https://doi.org/10.1126/science.1188836

Sun, Y., Lin, W., Dong, W., Xu, J., 2022. Origin and evolutionary analysis of the SARS-CoV-2 Omicron variant. J. Biosaf. Biosecurity 4, 33–37. https://doi.org/10.1016/j.jobb.2021.12.001

Sutherland, W.J., Freckleton, R.P., Godfray, H.C.J., Beissinger, S.R., Benton, T., Cameron, D.D., Carmel, Y., Coomes, D.A., Coulson, T., Emmerson, M.C., Hails, R.S., Hays, G.C., Hodgson, D.J., Hutchings, M.J., Johnson, D., Jones, J.P.G., Keeling, M.J., Kokko, H., Kunin, W.E., Lambin, X., Lewis, O.T., Malhi, Y.,

Mieszkowska, N., Milner-Gulland, E.J., Norris, K., Phillimore, A.B., Purves, D.W., Reid, J.M., Reuman, D.C., Thompson, K., Travis, J.M.J., Turnbull, L.A., Wardle, D.A., Wiegand, T., 2013. Identification of 100 fundamental ecological questions. J. Ecol. 101, 58–67. https://doi.org/10.1111/1365-2745.12025

Techer, M.; Roberts, J.; Cartwright, R.; Mikheyev, A. 2021. The first steps toward a global pandemic: reconstructing the demographic history of parasite host switches in its native range. Research Square preprint. https://doi.org/10.21203/rs.3.rs-196900/v1

Trivellone, V.; Araujo, S.B.L.; Panassiti B. 2021. HostSwitch: Simulate the Extent of Host Switching by Consumers. 12 pp. https://cran.rproject.org/web/packages/HostSwitch/HostSwitch.pdf

Trivellone, V.; Araujo, S.B.L.; Panassiti, B. 2023. HostSwitch: an R package to simulate the extent of host-switching by a consumer. The R Journal 14: 179–194. https://doi.org/10.32614/RJ-2023-005

Trivellone, V.; Hoberg, E.P.; Boeger, W.A.; Brooks, D.R. 2022. Food security and emerging infectious disease: risk assessment and risk management. Royal Society Open Science 9: 211687. https://doi.org/10.1098/rsos.211687

UN-DESA, 2022. World population prospects 2022: summary of results. United Nations, New York.

Walsh, S.K., Imrie, R.M., Matuszewska, M., Paterson, G.K., Weinert, L.A., Hadfield, J.D., Buckling, A., Longdon, B., 2023. The host phylogeny determines viral infectivity and replication across Staphylococcus host species. PLOS Pathog. 19, e1011433. https://doi.org/10.1371/journal.ppat.1011433

Wei, C.; Shan, K.-J.; Wang, W.; Zhang, S.; Huan, Q.; Qian, W. 2021. Evidence for a mouse origin of the SARS-CoV-2 Omicron variant. Journal of Genetics and Genomics. https://doi.org/10.1016/j.jgg.2021.12.003

WHO [World Health Organization]. 2022. WHO Coronavirus (COVID-19) Dashboard [WWW document]. Accessed January 19, 2022. https://covid19.who.int

Wiens, J.J., Donoghue, M.J., 2004. Historical biogeography, ecology and species richness. Trends Ecol. Evol. 19, 639–644. https://doi.org/10.1016/j.tree.2004.09.011

Wilkinson, D.M. 2004. The parable of Green Mountain: Ascension Island, ecosystem construction and ecological fitting. Journal of Biogeography 31: 1–4. https://doi.org/10.1046/j.0305-0270.2003.01010.x

Wilson, M.E., 1995. Travel and the emergence of infectious diseases. Emerg. Infect. Dis. 1, 39.

Woolhouse, M.E.J., Haydon, D.T., Antia, R., 2005. Emerging pathogens: the epidemiology and evolution of species jumps. Trends Ecol. Evol. 20, 238–244. https://doi.org/10.1016/j.tree.2005.02.009

World Health Organization, 2007. The world health report 2007 : a safer future : global public health security in the 21st century. 1.World.

Yamaguchi, R.; Iwasa, Y. 2017. Parapatric speciation in three islands: dynamics of geographical configuration of allele sharing. Royal Society Open Science 4: 160819. https://doi.org/10.1098/rsos.160819

Zwart, M.P., Elena, S.F., 2015. Matters of Size: Genetic Bottlenecks in Virus Infection and Their Potential Impact on Evolution. Annu. Rev. Virol. 2, 161–179. https://doi.org/10.1146/annurev-virology-100114-055135