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Angie T.C. Souza

Sabrina B.L. Araujo

Walter A. Boeger

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Review

The Evolutionary Dynamics of Infectious Diseases on an Unstable Planet: Insights from Modeling the Stockholm Paradigm

Angie T.C. Souza,[1,2] Sabrina B.L. Araujo,[1,2,3] and Walter A. Boeger[1,2]

1 Biological Interactions, Universidade Federal do Paraná, Curitiba, PR 81531-980, Brazil
2 Programa de Pós-graduação em Ecologia e Conservação, Universidade Federal do Paraná, Curitiba, PR 81531-980, Brazil
3 Departamento de Física, Universidade Federal do Paraná, Curitiba, PR 81531-980, Brazil

Corresponding author – Angie T.C. Souza, Biological Interactions, Universidade Federal do Paraná, Curitiba, PR 81531-980, Brazil, email angietcsouza@gmail.com

ORCID:
Angie T. C. Souza https://orcid.org/0000-0003-0592-8070

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 fundaments to understand the dynamics of diseases and design proactive measures to avoid the emergence and reemergence of infectious diseases. In this review, 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 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

Introduction

Among the most worrisome consequences of the changes we are presently subjected to on Earth is the alarming increase in the 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 viewpoint 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 insects; predator and prey) that follow their own rules (Nylin et al., 2018). Since the beginning, life has been linked in a single, vast, 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" (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 host 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 reflects a process of *ecological fitting* (EF) (Janzen, 1985; Brooks and McLennan, 2002; Agosta, 2006; Agosta and Klemens, 2008) (see Box 1). More than a characteristic of antagonistic associations, EF is widely common for 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.

Box 1

Definitions of some conceptual elements of the Stockholm paradigm

Here are some definitions related to the interaction between the nature of the conditions and the nature of the organism in a host-parasite context.

Fitness space (FS)

Fitness space (FS) can be considered the intersection of the nature of the organism (i.e., capacity) and the nature of the conditions (i.e., for pathogens, resources provided by potential host species). FS represents all sets of conditions (including host characteristics) in which a given parasite or pathogen can survive and reproduce, with a realized fitness different than null.

Ecological fitting (EF)

Ecological fitting (EF) (Janzen, 1985) is the ecological change (colonization of new hosts) that can occur by the parasite or pathogen exploring portions of the FS, without the need of immediately emerged evolutionary novelties (e.g., mutations). In the context of EIDs, EF is the process by which pathogens use preexisting capacities (that evolved in another context) when colonizing new hosts and that allows persistence of the association.

Realized fitness space (RFS)

Realized fitness space (RFS) is the part of the FS currently in use. For pathogens, the RFS comprises the host species parasitized in a given time and space.

Sloppy fitness space (SFS)

The FS is said to be "sloppy" because of the difference between the FS and the RFS. Sloppy fitness space (SFS) refers to pathogens or parasites that can potentially utilize more hosts than they do at a given time and in a certain space.

Pathogens, as with any other species, *explore* their environments and available resources, thus reaching, colonizing, and then *exploiting* new hosts through *ecological fitting* (Janzen, 1985; Brooks and McLennan, 2002; Agosta and Klemens, 2008), often causing emergences of new infectious diseases. *Opportunity* and *compatibility* between actors (actors being the host and the parasite or pathogen)

determine, to a great extent, the level of *exploration* and *exploitation* (Araujo et al., 2015; Braga et al., 2018; Brooks et al., 2019).

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

The current crisis generated by the SARS-Cov-2 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 allowed us to react inefficiently when a threat of this magnitude presents 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 Stockholm paradigm (SP).

The SP (Brooks et al., 2014, 2019; Hoberg and Brooks, 2015) is a theoretical framework that accommodates the Darwinian theory of evolution into the evolution of associations, such as those involving hosts and pathogens. It is basically composed of three previously proposed elements, as follows: *ecological fitting* (Janzen, 1985), *oscillation* (Janz and Nylin, 2008), and *taxon pulse* (Erwin, 1985). The SP provides the theoretical fundaments to understand the dynamics of emergences of diseases and design proactive measures to avoid emergence and reemergences of infectious diseases (Brooks et al., 2021; Trivellone et al., 2022). The SP provides the framework for the DAMA protocol (Brooks et al., 2019, 2014; Hoberg and Brooks, 2015), a set of steps that **D**ocument pathogens in nature, **A**ssess their potential for emergence, **M**onitors environments for changes, and based on these previous steps, **A**cts by designing proactive strategies.

The SP also recognizes that the interaction between actors that compose host-pathogen networks is complex (Brooks and Boeger, 2019). While the production, analysis, or reanalysis of new or available empirical data provide opportunities to study complex systems (Patella et al., 2017; Boeger et al., 2022), computer models that simulate biological systems provide important insights for understanding the emerging ecological and evolutionary processes (Dieckmann and Doebeli, 1999; Giacomini, 2007). Models can also provide adequate testing for purely 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 adequately handle the simulation of complex interactions that are expected in biological systems is known as *agent-based models* (ABMs) or *individual-based models* (IBMs) (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, as can their behavioral rules of interaction with other individuals and with the environment in which they are inserted. From this set of rules of behavior, limitations, and individual needs, the system dynamics emerge (Giacomini, 2007).

Thus, in this review, 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 these dynamics, and provide suggestions on how to integrate these findings into the DAMA protocol.

Synthesis of the Models Developed under the SP

Since 2015, the time of publication of the first model that simulated theoretical assumptions associated to the SP (Araujo et al., 2015), several manuscripts have been published testing many elements of this theoretical framework (see Table 1). Among other outcomes, subsequent models explored the accumulated evidence that the different

Table 1. Synthesis of models created from the theoretical assumptions associated with SP

Article	**Goals** T	**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 are 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 suboptimal 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 mediated by 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.
Feronato et al. (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 pathogen individuals (with phenotype p_0) are allowed to attempt colonization the host. – Each time step represents a new cycle of asexual reproduction and of 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.

(*continued*)

Table 1. Synthesis of models created from the theoretical assumptions associated with SP (*continued*)

Article	Goals T	Methods	Main results
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 revealed that stochastic host-switching events can change the evolutionary trajectory of parasites. – Host-switching is more frequent on a local than regional scale.

elements of the SP represent emerging properties in a complex system that is directly associated with the ability of biological systems (e.g., molecules, species, communities) to realize ecological fitting (Janzen, 1985; Agosta, 2006).

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 (z_i); (2) the resources impose selection pressure on parasite individuals around an optimum phenotype (z_h); 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 1)—surviving organisms reproduce according to their frequency within the

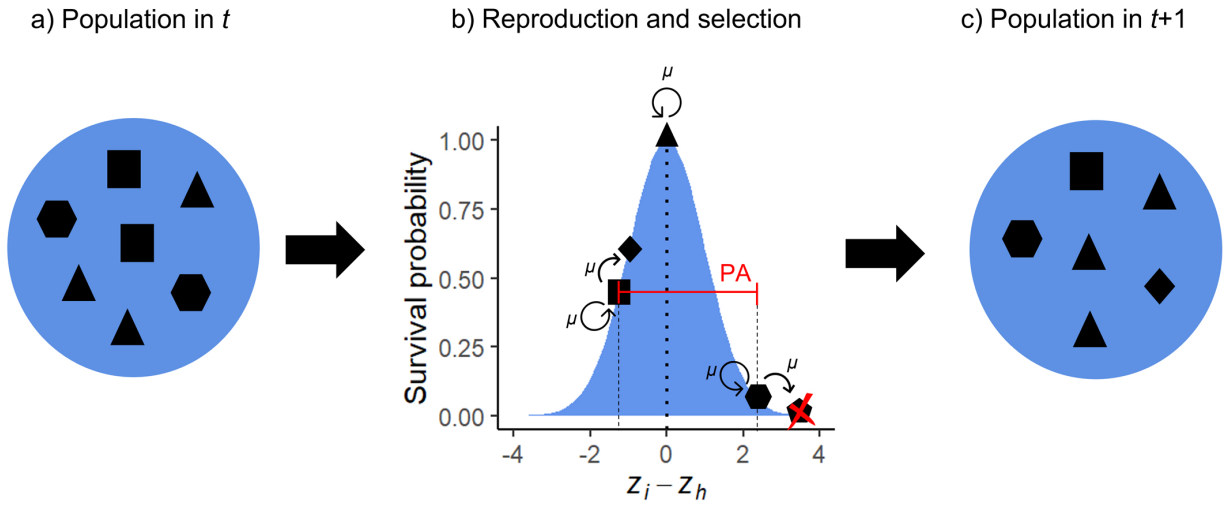

Figure 1. Population dynamics common to individual-based models (IBMs) of Araujo et al. (2015), Braga et al. (2018), and Feronato et al. (2021). **(a)** In time *t*, the parasite population inhabiting a given host (blue circle) is composed of three different phenotypes (triangle, square, and hexagon). **(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. **(c)** Individuals that 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.

parental generation. The Fitness Space (FS; see Box 1) represents the capacity of the pathogen to realize EF and in the models it is assumed to be correlated to the phenotypic amplitude of a population in each generation (PA in Figure 1b). The greater the phenotype amplitude, the wider is the range of possible hosts with which pathogens could interact by ecological fitting.

The first model (Araujo et al., 2015) evaluated the relationship between the historical fluctuations of the FS and the potential for pathogens to colonize hosts representing different sets of resources by ecological fitting. At each time step, a reproductive cycle occurs, and a new host is available to be colonized (see Figure 2). 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 (see Fig. 2) 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 population can survive for long periods under suboptimal condition, and (4) that host colonization can occur by a "stepping-stone" process (subsequent colonization of hosts depicting different nature of resources).

Subsequently, the model by Braga et al. (Braga et al., 2018) extended the previous model (Araujo et al., 2015) by allowing the evolution of the pathogens with more than one host coinhabiting the same community (maximum opportunity) and by monitoring the evolution of all pathogen populations simultaneously. During one generation, a portion of the pathogens can migrate to a randomly chosen host. When the exploration of the new host results in its colonization, the same lineage of pathogens exploits and evolves under a selective regime different from that of the original host. The model describes the pathogen genome and restricts mating to a minimal genotypic similarity. This restriction was used also as a proxy to delimit species. When the gene flow is reduced between populations of pathogens, a speciation event may occur. Exploitation of new hosts increases phenotypic and genotypic variation of the pathogen population, which, with reduction in reproductive exchange, and may result in speciation of the pathogen, generating host range cycles through time (= oscillations).

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. (2022) 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 between hosts at any time. Based on the idea that phylogenetically close hosts represent more similar resources (Gilbert and Webb, 2007; Streicker et al., 2010; Imrie et al., 2021), D'Bastiani et al. (2022) assume that the probability of success in the exchange of pathogens between closely related hosts is high and that this probability decays as the host diversifies and differentiates. The model was able to reproduce the ecological and evolutionary patterns of all nine empirical studies analyzed, suggesting that host-switching is a strong determinant in parasite evolution. The ecological and evolutionary patterns were measured by the dissimilarity of parasite composition per host species (beta diversity—Baselga, 2013, 2010) 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 the latter.

Although the mathematical models presented here allow a better understanding of the resource-pathogen dynamics, the code of all these models does not provide a user-friendly interface, restricting the audience from manipulating the model. Recently, Trivellone and collaborators created an R package, "HostSwitch" (Trivellone et al., 2021), 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 2 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.

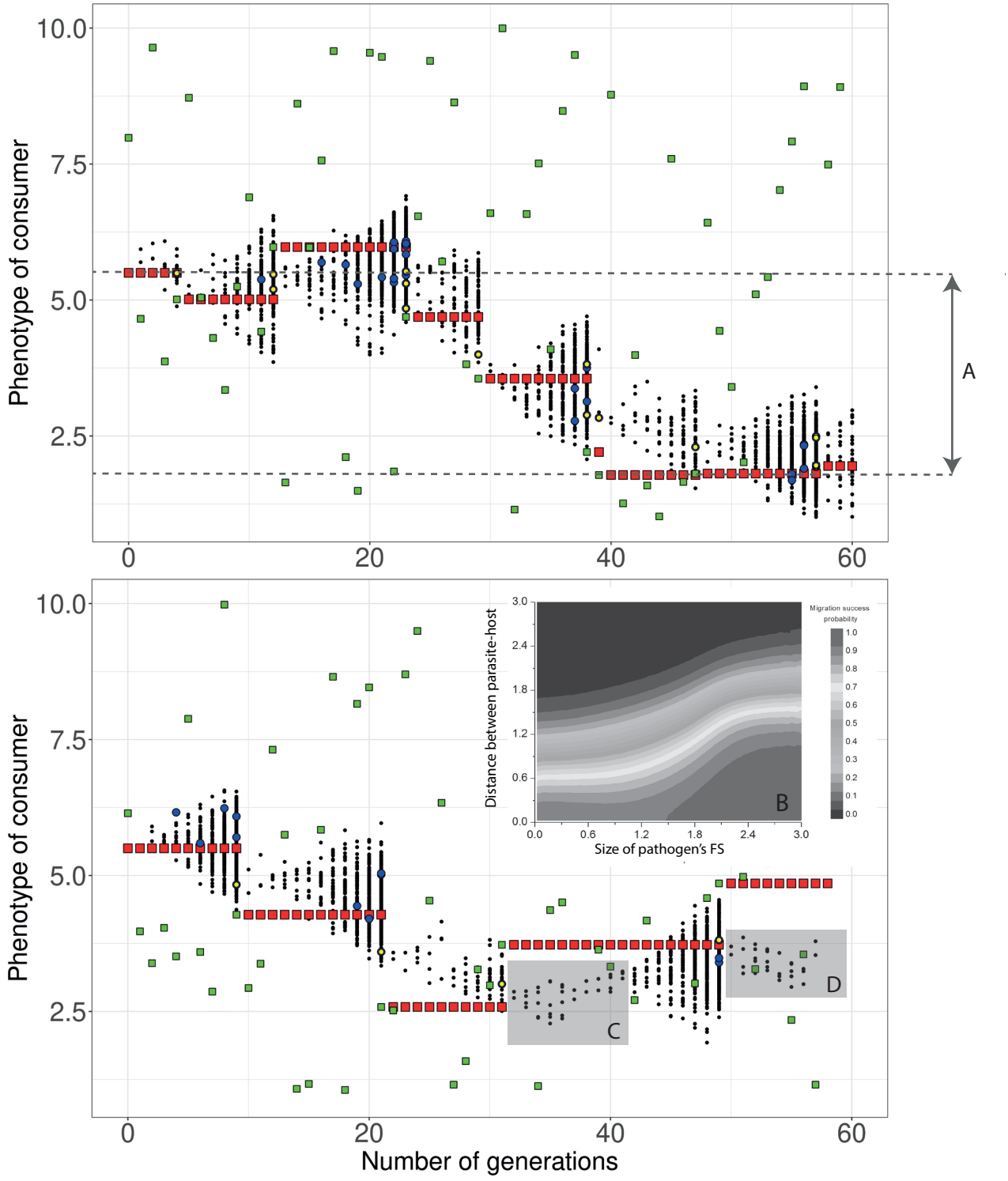

Figure 2. Two independent simulations of temporal evolution of the phenotype of the pathogen population (consumer). These graphs were generated from the "HostSwitch" package (Trivellone et al., 2021) based on the model of Araujo et al. (2015). The green squares represent the optimum phenotype of the pathogen to survive on that specific host resource; red squares are host resources in use at that moment; black dots represent 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 host.

Insights derived from the simulations

Connecting the elements of the SP 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 fractal or multilevel network of interactions and make a complex system. Species involved in such associations are never playing in pairs but in networks of interactions among many other species. That creates a level of complexity in which the behavior of the system cannot be understood nor predicted easily. Published models (Araujo et al., 2015; Braga et al., 2018; D'Bastiani et al., 2022) 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 ecological fitting. Taxon pulse, the highest element of the SP, is the interaction between the increased opportunity associated with environmental disruptions and it, thus, likely also represents an emergent property in this chain of complexity levels—an emergent property resulting from the interaction of communities with potential for oscillation and an unstable environment.

By exploring the available capacity represented by the 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). During the simulation presented in Araujo et al. (2015), part of the pathogen population tries to colonize a new host but only a fraction succeeds. Consequently, the FS of the population in this new host is reduced when compared to the original host. During exploitation of the new host, the accumulation of evolutionary novelties often results in the increase of the FS but with a qualitatively distinct nature due 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 insight that evolution of interactions under ecological fitting may generate oscillations as an emergent property, in the subsequent model (Braga et al., 2018), the opportunity to colonize variable hosts was continuous and maximized 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 pathogen lineages oscillate between generalists and specialists. The result supports that host oscillation is a property of a community of interacting species that change their ecology by ecological fitting, and that oscillation does not require the geographic vector as suggested in Janz and Nylin (2008).

The evidence that the SP is composed of elements defined as fundamental (ecological fitting) and emergent properties (oscillation and taxon pulse) reveals the flexibility of the many levels of complexity of the biological system. This flexibility is far greater than that expected under the prevailing paradigm of evolution (i.e., maximum adaptation/specialization). That includes greater than expected flexibility at several levels, including metabolic (Khersonsky et al., 2006; Carbonell et al., 2011), cellular (Margulis, 1971; Alison et al., 2002), organismal, population (Schradin et al., 2012), and community (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 species on an unstable planet and its biosphere (Brooks and Agosta, 2012; Agosta and Brooks, 2020).

This relatively great flexibility of the actors involved in the complex fractal and the instability of the planet also increases the capacity of pathogens to explore and exploit available hosts. That is the fundamental reason for the ongoing emergent infectious disease crisis on a planet greatly interconnected by human activities and under climate change.

The dynamics of infectious diseases under the SP

Modeling has allowed recognition of ecological and evolutionary patterns of pathogens during processes of exploration 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 infrapopulation). 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 (a pathogen property) 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-switching events performed by D'Bastiani et al. (2022) assumed host phylogeny as a proxy for pathogens' colonization. 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-switching is considered. Moreover, the authors recovered the expected pattern that host-switching 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-switching should be smaller for an entire community composed of 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 range, these tend to stabilize as closely related hosts (i.e., those bearing a similar nature of resources) are colonized and exploited (Brooks et al., 2019).

This scenario 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 during observation of the multihost dynamics in the ongoing SARS-CoV-2 pandemic (Fenollar et al., 2021; Boeger 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 show up 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 unmeasurable intensity of change in the opportunity of encounter—in time and space—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 quality and quantity (Figure 3.1).

Whenever opportunities exist, pathogens are continuously probing the nature of the resource provided by different host species within a community (Figure 3.2). Some explorations (exploratory infections) are successful (Figure 3.3); however, most are likely not, with no or little propagation of the pathogen in the new host (Figure 3.3—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; many of these have been revealed by the simulations generated with IBMs (Araujo et al., 2015; Braga et al., 2018; Feronato et al., 2021).

Both stochastic and deterministic processes are involved in determining the success of each colonization attempt (Araujo et al., 2015; Feronato et al., 2021). One of the more 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 quantity) is still possible (Figure 2). That same simulation also suggested that there is clearly 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 is not achieved, and the pathogen cannot exploit the resource provided by the host (Figure 2B). However, empirical evidence and simulations have recovered a process that makes it possible for pathogens to indirectly colonize hosts bearing relatively distance resources—this is known as the host-range expansion by stepping-stone (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 expect that this type of transmission involves only a single species intermediary in the expansion to new hosts. Given time, especially for microorganisms that have been shown to have fast evolutionary rates, stepping-stone may also facilitate colonization of distant host resources through changes in the nature of the capacity space associated with gradual and sequential influence of the selection imposed by hosts intermediary in the process (Figure 2) (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 expand host range through exploration. Feronato et al. (2021) varied demographic features—reproductive rate, rate of emergence of evolutionary

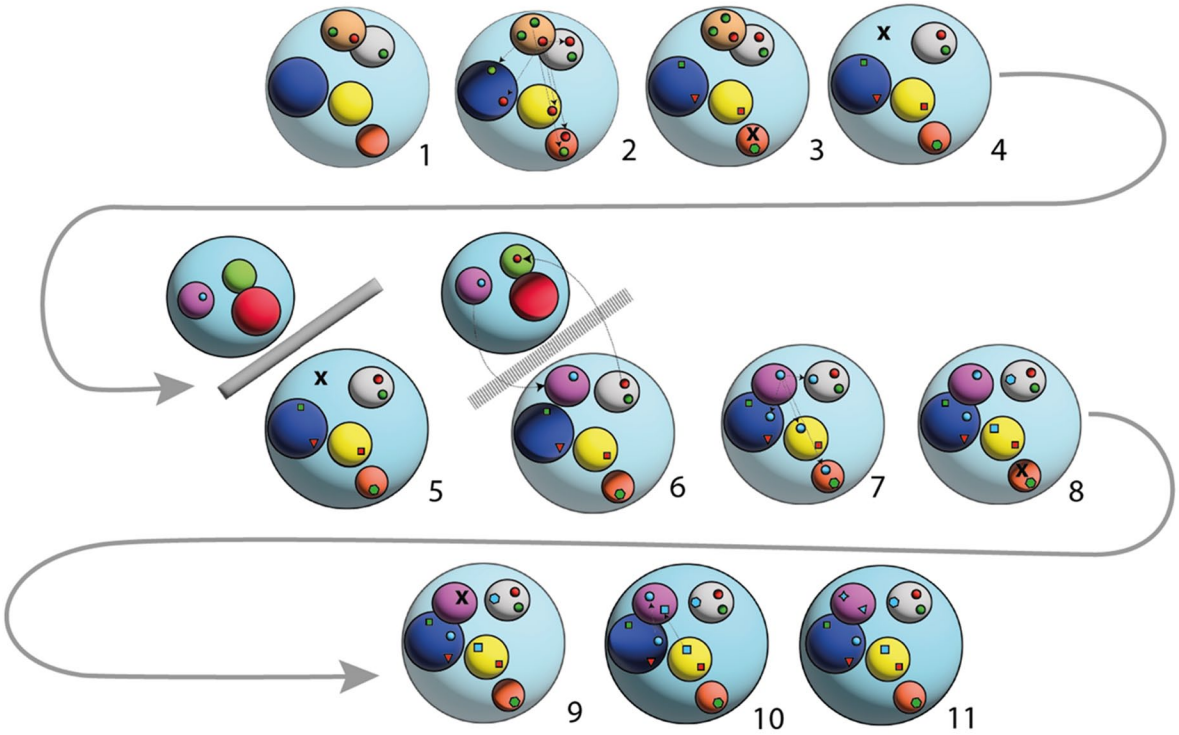

Figure 3. The putative dynamics of diseases under the perspective of the Stockholm paradigm. **1.** In an isolated community, five host species are present, two of which are in association with pathogens (the orange species with two pathogen lines—green and red—and the ash, also parasitized by the green pathogen. **2.** Still in isolation, pathogens exploit the species available when the opportunity presents itself. **3.** Exploration may result in successful or nonsuccessful colonization (failure to establish the red pathogen is 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. **10.** However, retrocolonization 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.

novelties (e.g., mutations), and propagule pressure—for simulated pathogens and concluded that propagule pressure was more important in determining the success of host expansions. 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 viruses 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). 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. Greater lagloads may result in an increase of rate of emergences (e.g., mutation) and in the nature of new evolutionary novelties in the population of pathogens (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). At first glance, from the view of the observer, the pathogen has simply expanded its host repertoire (*sensu* Braga and Janz, 2021) (Figure 3.3—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; see Box 1) within the FS (Figure 4), the accumulation of evolutionary novelties (e.g., mutations in viruses), can generate new variants or even new species (Figure 3.3—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 3.1 to 3.4, pathogens are oscillating between expansion (exploring) and isolation (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 oscillation of the pathogen's capacity—that is, variation in FS—a consequence of demographic processes associated with colonization of new host resources. 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 of these hosts goes extinct (Figure 3.4—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 of one host by persisting in another (Figure 3.4—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 and probing new host species never ceases, but successful colonization of new hosts (and resources) decreases in rate through time as compatible hosts become colonized and are exploited by pathogens. Furthermore, evolution has generated enough differences in the nature of the resource so that many resources and hosts are never reached by or exposed to the pathogens, either directly or by a stepping-stone process (despite maximized opportunity) (see, for instance, Braga et al., 2014). Gaps in the nature of the resource within a biological community likely result from differences in the historical pathway of lineages of hosts and consequent historical constraints of the capacity space 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 3.6); 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).

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 a long time (in terms of generations) on hosts that represent only marginally adequate resources (Figure 2C; Figure 4). 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 2C, D). Under this scenario, pathogen populations may be small due to strong selective forces within this host, and detection by sanitary inspections (sampling) are likely to be hampered because of small sample size and the number of introductions. However, Feronato et al. (2021) has 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 a similar population size to those with greater fitness, likely causing epidemies.

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 EIDs 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 4), 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 represent a distinct but exploitable resource. Since the probability of sampling marginal and low-frequency variants of the pathogen in its original host is comparatively smaller, an inadequate sampling

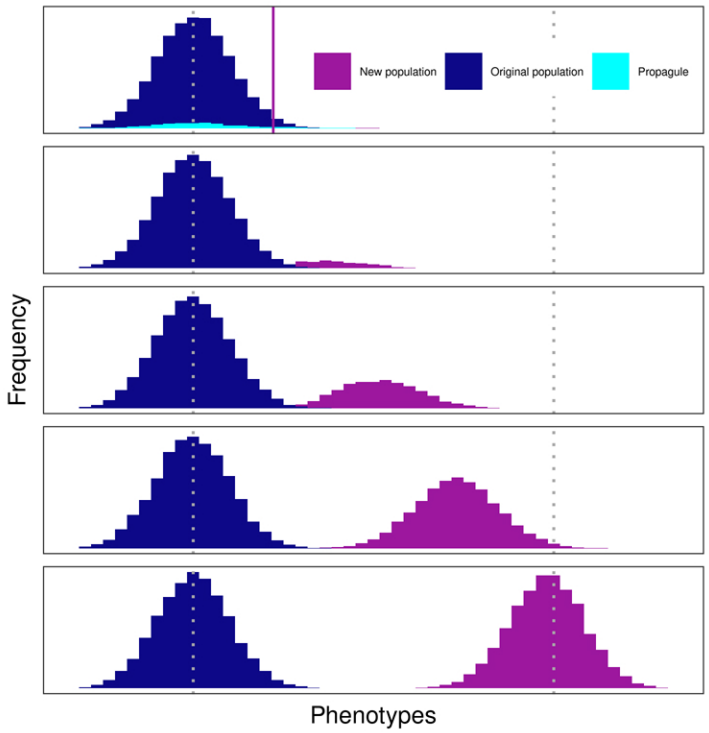

Figure 4. Evolution of the phenotypic profile of a population of pathogens after host switch. A portion (propagule) of the original population of pathogens can migrate to a new host. Only a fraction of these individuals survives the new selective pressure, and the mean phenotype of the survivors is identified by the pink vertical line. Over time, the new population has an increase in the number of individuals and, because of 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.

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 are necessarily associated with the "right mutation" emerging at the "right time" (Kellogg, 1907).

Environmental disruptions can promote changes in the relative permeability of ecological barriers (Figure 3.6), creating interfaces among communities (or systems). 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 and exploitation (Figures 3.6–3.10). 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 became 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 newly emerged Zika virus, dengue, and chikungunya. However, the spatial and temporal behavior of SARS-Cov-2 revealed an unexpected dynamics of host use. While the involvement of other mammal species in the dynamics 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 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; 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 on the origin of new variants (Boeger et al., 2022; Hoberg et al., 2022). The above-proposed dynamics of pathogenic species was replicated in many regions of the planet, involving

most likely a much larger number of species than we presently know (Boeger et al., 2022).

This proposed generalized model for the dynamics of antagonistic associations—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 of whether biodiversity influences amplification or dilution (Clay et al., 2009; Keesing et al., 2010; Ostfeld and Keesing, 2012; Rohr et al., 2020) of pathogens, thus influencing 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 3. 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). Thus, the answer to the dilution/amplification paradox may be eco-evolutionary and needs to be evaluated in this way in the future.

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; 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 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 strongly alerts toward 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 with capacity or opportunity) for pathogens to reach focal host species. This is a counterintuitive conclusion that contrasts 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 the same geographic area or 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 of SARS-CoV-2 (and likely of many others—Boeger et al., 2022) is thought by many to have been the result of exploring and exploiting 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 perceived by us (Manrubia, 2012; Sprouffske et al., 2018). The putative cycle of reduction in variability 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 ecological fitting. **Monitoring the ecological and evolutionary dynamics** of change of pathogens is, thus, fundamental.

Indeed, SARS-Cov-2 revealed how the evolutionary dynamics of the virus influenced the epidemiological characteristics of the disease. Substantial evidence supports that SARS-Cov-2 can expand into other mammal species by ecological fitting in spite of minor differences in the nature of the membrane-bound 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 far greater 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.

In analogy, we are living in a mine field 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 (the second A).

Models help us understand the dynamics of the diseases based on the elements of the Stockholm paradigm. 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.

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