"Accidents waiting to happen" – insights from a simple model on the emergence of infectious agents in new hosts.

Running Title: A model of emergence of infectious pathogens

Sofia G. Feronato[1], Sabrina Araujo[1,2], Walter A. Boeger[1,3*]

[1] Biological Interactions, Universidade Federal do Paraná, Curitiba, PR 81531-980, Brazil.

[2] Dept de Física, Universidade Federal do Paraná, Curitiba, PR 81531-980, Brazil.

[3] Dept de Zoologia, Universidade Federal do Paraná, Caixa Postal 19020, Curitiba, PR 81531-980, Brazil.

*Corresponding author: Walter A Boeger, wboeger@gmail.com, fone: +554199985055

Summary: This study evaluates through modeling the possible individual and combined effect of three populational parameters of pathogens (reproduction rate; rate of novelty emergence; and propagule size) on the colonization of new host species – putatively the most fundamental process leading to the emergence of new infectious diseases. The results are analyzed under the theoretical framework of the Stockholm Paradigm using IBM simulations to better understand the evolutionary dynamics of the pathogen population and the possible role of Ecological Fitting. The simulations suggest that all three parameters positively influence the success of colonization of new hosts by a novel parasite population but contrary to the prevailing belief, the rate of novelty emergence (e.g. mutations) is the least important factor. Maximization of all parameters result in a synergetic facilitation of the colonization and emulates the expected scenario for pathogenic microorganisms. The simulations also provide theoretical support for the retention of the capacity of fast-evolving lineages to retro-colonize their previous host species/lineage by ecological fitting. **Capacity** is, thus, much larger than we can anticipate. Hence, the results support the empirical observations that **opportunity** of encounter (i.e. the breakdown in mechanisms for ecological isolation) is a fundamental determinant to the emergence of new associations – especially Emergent Infectious Diseases - and the dynamics of host exploration, as observed in SARS-CoV-2. Insights on the dynamics of Emergent Infectious Diseases derived from the simulations and from the Stockholm Paradigm are discussed.

Keywords: Individual-based model, host-switching, emerging infectious diseases, Stockholm Paradigm.

Introduction

Understanding the ecological mechanisms influencing the origin and evolution of host-pathogen associations is fundamental and has become a vigorous area of research in human health, agriculture, and food security, during recent years (Heard and Hauser, 1995; Woolhouse et al., 2005; Brooks et al., 2014). These studies are of special interest, considering the so-called crisis of Emerging Infectious Diseases (EIDs), present and future (Brooks et al., 2019). This crisis is the fulfilment of the prediction that EIDs are "accidents waiting to happen" (Brooks & Ferrao, 2005).

However, such studies are strongly influenced by the researcher's perspective of its accepted theoretical evolutionary framework (see a summary of this under a historical perspective in Nylin et al., 2018; Brooks & Boeger, 2019; Brooks et al., 2019; Agosta & Brooks, 2020), often influenced by the perspective that parasites are ultimate specialists (Agosta et al., 2010). Traditionally, the nature of host-parasite/pathogen associations is regarded as a strong reciprocal selective interaction (Kaltz & Shykoff, 1998). This vision generated a paradox – the Gambler's Ruin (Brooks & McLennan, 2002) or the Parasite Paradox (Agosta et al., 2010). This paradox results from the accumulation of studies on host-parasite evolution in the last 40 years that, even utilizing protocols strongly biased towards co-speciation, still detected a large amount of what has been called to this date as host-switching (Krasnov & Shenbrot, 2002; Hoberg & Brook, 2008; Agosta et al., 2010; De Vienne et al., 2013). Increasing phylogenetic and historical evidence points out that oscillation in host range (=host repertoire according to Braga et al., 2018) is a primary dynamic in pathogen evolution and ecology. The complex structure of host-pathogen associations strongly indicates that the widely held evolutionary paradigm, which has been conceptually dominant for a century, cannot accommodate the present knowledge on the origin and evolution of symbiotic associations (Nylin et al., 2018).

The Stockholm Paradigm (Brooks et al., 2014; Brooks et al., 2019) represents a robust theoretical framework that accommodates the accumulated knowledge on the evolution of associations. The fundamental element of this new perspective on the evolution and ecology of associations is the recognition that the vast majority of ecological changes occur through Ecological Fitting (Janzen, 1985; Brooks et al., 2006). The other two elements of the Paradigm - the Oscillation Hypothesis (Janz & Nylin, 2008) and the Taxon Pulse (Erwin, 1985 Hoberg & Brooks, 2008) - are thought to represent emergent properties of the complex system composed of species that interact – with other species or the environment - under the ability to change by Ecological Fitting (Brooks et al., 2019).

Under the framework of the Stockholm Paradigm, Araujo et al. (2015) developed a mathematical model that evaluated the colonization of new host species by an evolving population of pathogens. The simulations support the postulate that host colonization by Ecological Fitting is ubiquitous. Among other conclusions, Araujo et al. (2015) also suggested that successful colonizations are not limited to a high degree of compatibility of the pathogen population to the new host nor to immediate emergence of novelties. Support for this perspective has been recently revealed by empirical experimentation on the colonization of novel gerbil hosts (Muridae, Rodentia) by fleas (Khokhlova at al., 2020). Araujo et al. (2015) and subsequent modeling (Braga et al., 2018) also indicate that poorly adapted pathogens can survive in a new

host despite being in a sub-optimum condition, whereas they did not explicitly explore populational parameters that might influence the pathogen's colonization success.

In the present study, we expand the model of Araujo et al. (2015) using an individual-based model (IBM) considering elements of the Stockholm Paradigm. We explore the significance and the interaction of selected parameters that are considered important for the success of colonization of new host species and its consequences to the phenotypic profile of the early generations of the newly established population of pathogen. The tested parameters are the reproduction rate, the rate of novelty emergence (analogous to mutation rate), and the propagule size (*sensu* Simberloff, 2009) of the founder-pathogen population, all of which are frequently considered as key population parameters in studies of biological invasion and epidemiology (Braendle & Flatt, 2006; Briski et al., 2012; Dobson, 2004; Gould & Stinchcombe, 2017; Hoberg, 2010; Hurford, Cownden & Day, 2010; Kreuder Johnson et al., 2015; Lockwood, Cassey, & Blackburn, 2005; Mason, 2016; Simberloff, 2009; Woolhouse, 2001; Woolhouse et al., 2005).

The resulting simulations strongly support previous accounts on the process of colonization of new environmental conditions - in this case of new host-pathogens associations under an ecological perspective - and provides new insights into the process of emerging infectious diseases. The overall result of the simulations offers instrumental support to the recognized crisis of emergence of new infectious diseases (Fauci, 2001; Morens et al., 2004; Brooks & Ferrao, 2005; Brooks et al., 2014; Hoberg & Brooks, 2015; Mondragon et al., 2018; Morand & Figuié, 2018).

The model

An individual-based model (IBM) was designed to investigate the influence of some populational parameters on the colonization success of a new host species. During simulations, pathogens with variable propagule sizes, reproduction rates, and rates of emergence of phenotypic novelties were challenged by new host species representing different levels of compatibility (which are related to the selection pressure that the new host represents). The consumer-resource system can be applied to several different types of symbioses and ecological associations; for simplicity, hereafter we will designate these as the host-pathogen interaction. The model (written in Fortran) is available through Github (https://github.com/sofiagalvao2020/SimpleHost_switching).

Pathogen and host descriptions:

Each pathogen *i* is described by a compound phenotype of G binary individual phenotypes. The binary phenotypes can assume the values of either one or zero, which can be understood as the expression of two distinct traits within the same locus or set of loci. The sum of all characters defines the compound phenotype of each individual (=*realized capacity space* of Agosta and Brooks 2020), which can vary between 0 and G (=*fundamental capacity space* as defined in Agosta and Brooks 2020). The compound phenotype is composed by inheritable features, subjected to change over generations, and under selection according to its compatibility to the host. The compound phenotype is labeled as $p_{i,n}$, in which the subscripts identify the pathogen *i* of the generation *n*. For simplicity, as in Araujo et al. (2015), the host is characterized by a

single number (p_h) which represents the optimum value of the compound phenotype imposed on pathogens (fixed throughout the simulation). Here we assume $p_h = G/2$. Besides defining an interaction pressure around this optimum value, the host is also represented by a carrying capacity on the pathogen population of K individuals.

Dynamics

The dynamics starts with a propagule size of N_0 pathogen individuals challenged to colonize the host - there is only one colonization attempt per simulation. In the beginning of the simulation, the sum of all loci is identical for all propagule individuals ($p_{i,n=0}=p_0 \; \forall \; i$) - creating a standard populational compound phenotype p_0 at the start of the colonization attempt. This scenario creates a pathogen population where all individuals carry distinct phenotypes with the same fitness in the new host (i.e. the compound phenotypes is the same, since it represents the sum of all states, but the sequence of character states are qualitatively not necessarily the same). Each iteration step represents a generation n where the pathogen population above described will undergo *Selection* and *Reproduction* (Fig 1), as detailed below.

Selection

The selection is imposed as the survival probability of each pathogen i in a given generation n and it follows a normal distribution:

$$P_{survival} = \exp\left[\frac{-d_{i,n}^2}{2}\right] \quad , \qquad (1)$$

where

$$d_{i,n} = \frac{p_{i,n} - p_h}{\sigma} \qquad (2)$$

is the distance between the pathogen compound phenotype ($p_{i,n}$) and the optimum imposed by the host (p_h) in units of the deviation rate (σ). The deviation rate represents the selection strength imposed by the new host - the larger the deviation rate, the larger is the diversity of phenotypes that are capable of surviving on that specific host (Fig 1). For the propagule population - with all individuals presenting the same compound phenotype p_0 - the initial phenotype distance from the propagule to the host is $d_0=(p_0-p_h)/\sigma$. The model imposes this survival probability (Eq. 1) to every individual, and the survivors ($N_{s,n}$) go to the next model step, *Reproduction*.

Reproduction

At this step, the pathogens that survived the previous step ($N_{s,n}$) produce offspring depending on the reproduction rate (b, the average number of descendants per parental) and the carrying capacity (K). For simplicity, we assume asexual reproduction. The number of descendants for the next generation $n+1$ will be $N_{s,n}*b$ if this value does not exceed K, otherwise, the number of descendants is K. Random individuals of the surviving population are selected to generate one offspring with reposition - the progenitor can be selected more than once. This process is repeated until the total number of descendants is achieved. Each descendant inherits the same chain of characters of its progenitor with a probability μ of incorporating a novelty per locus (i.e.

changing from 0 to 1 or from 1 to 0). After all reproduction events, all individuals of the previous population die, and the descendants constitute the next population that will be subjected to the new *Selection* and *Reproduction* cycle (Fig 1).

The rate of novelty emergence (μ) refers to any kind of novelty introduced into the pool of capacity of the individual, indirectly influencing the pathogen's fitness to the host. These evolutionary novelties can emerge, accumulate, and be maintained throughout generations simulating inheritance mechanisms, comprising the *capacity space* of the pathogen (called *information space* in Brooks & Agosta, 2012, Jablonka et al., 2014, Brooks et al., 2019; see also Agosta & Brooks 2020). We refrain from using "mutation rate" - as opposed to "rate of emergence of evolutionary novelty" - to avoid the strictly genetic meaning of the expression used in the Modern Synthesis (see Brooks & Agosta, 2012; Laland et al., 2015; Agosta & Brooks, 2020).

Simulations and data analyses

For each parameter combination, we ran 700 simulation repetitions for 1,000 generations or until the pathogen population went extinct. We then calculated the proportion of simulations without extinction and defined it as the *probability of successful establishment* (=colonization success). We explored the sensitivity of the probability of successful establishment to each parameter by submitting each parameter value to variable distances of the propagule compound phenotype from the host (d_0), thus revealing their influence on the probability of establishment of the pathogen population in the new host (Table 1). The values of the parameters used in the simulations were not chosen based on empirical values, in association to any specific taxon - they represent theoretical values. The corresponding importance given to the parameter comes from the effect of variance between values, such as in the case for the rate of novelty emergence, for instance. All conclusions drawn from the sensitivity tests pertain to the divergence between the theoretical values alone – we evaluated the variation between these values and its effect on the colonization success, and not whether the value itself exists in nature.

The parameter p_0 varied between the fittest ($p_0 = p_h = G/2$) to the least fit value ($p_0 = G$ *or* $p_0 = 0$). Given that the propagule survival probability (Eq. 1) depends only on d_0, we fixed $\sigma_d^2 = 10$ and, as a consequence, the propagule compound phenotype distance from the host varied according to $0 \leq d_0 \leq G/20$. The investigated values of novelty rate (μ) are 0, 10^{-7}, 10^{-6},10^{-5}, 10^{-4}, 10^{-3}, 10^{-2},$10^{-1}$and 0.5. Higher novelty rate values, such as 10^{-2} and 10^{-1} are considered analogs to the high mutation rates observed in viruses (Drake & Holland, 1999). Furthermore, although biologically unreal, the null and maximum (0.5) values for μ represent the bottom and top limits of our analysis. We also varied the reproduction rate (b), propagule size (N_0,) (sensu Simberloff, 2009), compound phenotype size (G)(=capacity space), and carrying capacity (K) (Table 1). Our simulations were qualitatively invariable for the parameters G and K - only results in varying b, μ, N_0, and d_0 are presented. A more detailed exploration of these parameters is presented in supplementary material (Figs S1, S2).

Results

We simulated the success of establishment of the pathogen population during colonization of a new host and, when pertinent, the evolution of its compound phenotype under the new selective pressure. Parsing the parameters of the model allowed a better understanding of the individual

and combined influence of various rates of novelty emergence (μ), propagule size (N_0), and reproduction rate (b) on the success of establishment of a new association and the evolution of the fitness and size of the population following colonization of a new host resource.

For a single propagule (N_0=1), the increase of d_0 gradually reduces the probability of establishment (Fig. 2a and b) – which was an expected result since the survival probability decays following this distance (black curves in Figs. 2 represent Eq. 1 for the propagule, $d_{i,n} = d_0$). For the pathogen population to colonize the new host, it needs to survive successive selection events - therefore the probability of establishment is lower than the survival probability for a single colonizing individual to persist until the first reproduction (the black curve in Figure 1).

Greater reproduction rates (b) favor the pathogen establishment (Fig. 2a). As b increases, the establishment success approaches the probability of one individual surviving the selective forces of the new host species (in Fig. 2a; compare non-black probability curves approaching the black curve as b increases). For high b rates (e.g. b = 7.5), the probability of establishment of the pathogen population will be the same as that expected for a single individual surviving until the first reproductive event of the simulation - and the probability of survival will depend only on the effect of d_0.

Only high novelty rate values (10^{-2} and 10^{-1}) had a measurable effect on the populational probability of establishment - all other variations of novelty rate had practically the same low effect on the probability (Fig 2b). For novelty rates between 0.0 and 10^{-3}, the probability of success practically did not differ, reaching 0 for $d_0 \approx 1$ (propagule compound phenotype app. one standard deviation distant from the optimum imposed). The effect of the increasing novelty rate between these values is more evident on the population growth; the population reaches the carrying capacity about twice faster when $\mu=10^{-4}$ than when μ=0 (Fig 3). Less than 10% of establishment success was detected in simulations when d_0 = 2, despite the novelty rate (Fig. 2b).

Simulations have shown that a small increase in the propagule size (from 1 to 10) greatly expanded the diversity of compound phenotypes which resulted in a probability of success greater than 90% for pathogens with a $d_0<0.9$ (Fig. 2c). For larger propagule sizes, this success extends up to $d_0 \approx 1.2$. The effect of the propagule-size on the probability of establishment is especially significant for compound phenotypes that are distant from the optimum imposed by the host (Fig. S1). This high-probability effect quickly diminishes, depicting a cliff-like pattern for survival probabilities of phenotypes higher than $d_0 \approx 1.2$, independent of the propagule size.

Finally, the simultaneous application of high values for the selected parameters (b=7.5; μ=0.1; N_0=200) resulted in a synergetic effect on the probability of successful colonization (Fig. 2). Under this scenario, even host lineages representing distant resources (resources that are less compatible with the pathogen requirements/capacity) have a high probability of colonization, far exceeding the probability observed for the populational parameters of the pathogens tested independently (Fig. 2).

As expected, based in every simulated scenario with a non-null μ, the emergence of phenotypic novelties in the generations following colonization allowed the compound phenotypes to evolve towards and stabilize around the optimal fitness value imposed by the host (Fig. 3). The greater the novelty rate (μ), the faster the evolution towards the optimum, also increasing the diversity of compound phenotypes (Fig. 4, $\mu=10^{-2}$). During simulations, population

size rapidly reaches the established carrying capacity. Even though higher values of μ favors population growth, the carrying capacity is achieved much earlier than phenotype stabilization for all scenarios (Fig. 3). Surprisingly, even in the absence of novelties (Fig. 3, $\mu=0$) many simulated pathogen populations persisted and achieved the carrying capacity in the newly colonized host species.

Varying rates of the emergence of evolutionary novelties revealed also an unexpected outcome on the qualitative profile of the populations, following colonization. High rates of emergence resulted in the retention of compound phenotypes (variants) present in the initial and previous populations during populational growth, with correspondingly larger load (something analogous to the concept of genetic load; Wallace 1970) (Fig. 4a). Lower rates of novelty emergence resulted in populations that depict smaller phenotypic variability, with greater loss of pre-existing phenotypes (Fig. 4b). Simulations varying other parameters (N_0 and b) did not influence significantly the outcome described above (Fig. S2).

Discussion

The general result of the simulations suggests that the increase in the rate of emergence of evolutionary novelties, reproduction rate, and propagule size influence positively the success of colonization of new hosts by a novel pathogen population (Fig. 2). However, within the scope of the simulations, the different values of the explored parameters resulted in distinct impacts on this success. One of the most significant impacts was observed for the propagule size; even not responding to the selection of the new host, due to the complete absence of emergence of novelties imposed by the model, an initial population composed of 10 colonizers resulted in a significant increase of the probability to thrive and persist under suboptimal fitness, even in hosts representing relatively small compatibility ($d_0 \approx 1$).

Indeed, propagule pressure (propagule size and number) is extensively known to positively influence the colonization of new host species (Drolet & Locke, 2016; Hatcher et al., 2012; May et al., 2001) - or geographic areas and corresponding communities in the case of invasive species (Sax et al., 2007; Lockwood et al., 2009; Cassey et al., 2018). Large propagule size (the number of individuals colonizing a novel host at one time) is usually linked with the reduction of consequences of demographic (e.g. stochasticity and Allee effects) (Hufbauer et a., 2013) and genetic (founder's effect) (Simberloff, 2009; Roman & Darling, 2007) processes observed in small population size during changes in ecologic and geographic distribution. Since every simulation involving variation in propagule size used a low rate of emergence of evolutionary novelty and the relative fitness of propagules were kept unchanged (same d_0 despite qualitative differences in the combination of loci), the advantage conferred by increasing propagule sizes during colonization appears to be associated with demographic issues, most likely stochastic, as we did not model social collaborative processes nor limitation in the encounter of mates during reproduction (see Hufbauer et al., 2013). Nevertheless, the increased success of establishment associated to increasing propagule size does not vary linearly since its effect is less noticeable at larger simulated propagule sizes (Fig. 2c).

Although less evident than the simulations with variable propagule size, increases in reproductive rate in less than 10 – fold (from 1.5 to 7.5) resulted in a more significant increase in the probability of successful colonization than 1000-fold increases in the rate of emergence of novelties (from $\mu=10^{-6}$ to $\mu=10^{-3}$). This is an unexpected result, especially considering that the

emergence of new associations – such as infectious diseases - is often linked by many to high mutation rates of the consumer associate (Pepin et al., 2008; Selman et al., 2012; Viana et al., 2015). Hence, our results indicate that the rate of emergence of evolutionary novelties alone (e.g. mutation rates for simple organisms such as viruses) has secondary importance in the colonization of new host species, as suggested in Araujo et al. (2015) and implicitly by the Stockholm Paradigm (Brooks & Hoberg, 2007; Brooks & Boeger, 2019; Brooks et al., 2019; Agosta & Brooks, 2020). The accumulation of accessible historical information - termed the *information space* by Brooks & Agosta (2012) or *capacity space* by Agosta & Brooks (2020) - is of greater importance for the events of host-repertoire expansion (i.e. the evolutionarily process that precedes what is known as host-switching; see Braga et al., 2018). It is the accumulation of heritable information by preceding generations (and ancestors) and its retention in the biological entities (i.e. populations, species) through time (=phylogenetic conservatism) that will determine the ability of lineages to endure ecological and environmental changes or to take advantage of opportunities (e.g. explore new resources, new habitats). Since compatibility (i.e. the distance to the actual host optimum) varies within individuals of a diverse pathogen population, regions of suboptimal fitness in the ancestral host - albeit potentially at low frequency in the population - may contain pathogen variants that are capable of reaching more distant (= more different) resources (new hosts) than originally higher-fitness variants (see also Araujo et al., 2015; Brooks et al., 2019). Consequently, under this scenario, actual rates of emergence of new inheritable evolutionary novelties (e.g. mutations) are less important than the number of individuals colonizing the new host (=propagule pressure), the rate of reproduction, and the degree of the variability in the original donor population.

When all three parameters considered are maximized, the simulations generate pronounced synergism (grey line in Fig. 2). The fact that this combination of values likely compares to those observed for viruses, particularly among RNA-viruses (Holmes, 2009), is especially significant in understanding the evolution of this group of organisms and the corresponding emergence of infectious diseases. This outcome is compatible with the conclusions of Geoghegan et al. (2017) that "cross-species transmission is a near universal feature of the viruses …, with virus-host co-divergence occurring less frequently..." For instance, continuous oscillations of host species were suggested as an intrinsically biological feature of coronaviruses (Menachery et al., 2017), but it is likely a property of viruses in general and perhaps of pathogenic bacteria as well. It is, thus, understandable that viruses and bacteria are the most common groups of organisms associated with emergent infectious diseases (Cleaveland et al., 2001; Duarte-Neto, 2019; Gubler, 2010; Pękala-Safińska, 2018; M. Woolhouse & Gaunt, 2007).

Since we expect that in the real-world representatives of the variants of pathogens are continuously exploring accessible resources (e.g. host species) (Brooks et al., 2019; Agosta & Brooks, 2020) the emergence of new associations - or colonization of new environments - is expected when suitable matching (likely imperfect rather than perfect) between requirements of the pathogen, the resource (i.e. host properties), and/or environmental conditions occur. Therefore, the original host species represents an imperfect reference - but, perhaps, the only one accessible at this time - to describe the relative quality and the distance of the new resources to the pathogen. Phylogenetic distance between the host species involved in the host range expansion appears, within limits, to estimate the multidimensional space of traits that influence the compatibility of host and a specific pathogen lineage (Martiny et al., 2013; Braga et al., 2015;

Streicker et al., 2010; Gilbert & Webb 2007). Since the resources defining compatibility vary according to both host and pathogen species, phylogenetic distances appear to be the only accessible proxy for the value of d_0, but it should be considered parsimoniously because evolutionary convergence of resources (Brooks & McLennan, 2002) and the variability of the pathogen and hosts may influence also the outcome of the colonization attempts (see for instance Boeger et al. 2005; Araujo et al. 2015).

The results of the present simulations are also fundamental to expand the understanding of the role of ecological fitting (Janzen, 1985; Agosta, 2006; Agosta & Klemens, 2008) on the evolution of ecological changes. As suggested previously by Araujo et al. (2015), newly established populations of pathogens may survive for many generations in a host even in the absence of adaptations. By surviving under these "suboptimal" conditions, pathogens may expand their temporal window for the "right" novelty to present itself and allow an increase in the population's fitness (adaptation) following the ecological change. For instance, Antia et al. (2003), modeling a scenario of colonization similar to the present simulations, suggested that early values of R_0 of a new pathogen may evolve towards an $R_0>1$ subsequently, under the selective pressure of the newly colonized host. However, the emergence of evolutionary novelties (e.g. mutations) in the pathogen is random and, hence, these new features are most likely not adaptive. These emerging novelties, in the absence of favorable selection, will likely remain at very low frequencies in the population of the pathogen. These emerged novelties compose the genetic load of the pathogen (Wallace, 1987). It is unlikely that the "perfect match" (i.e. a perfectly fit association) may ever happen despite the influence of selection and the pathogen may remain in a situation of continuous suboptimal fitness regarding its host species, a scenario proposed by Sax et al. (2007) derived from studies of invasive species. However, while these accumulated features may not result in the "perfect fit" to the host species, they represent important assets to cope with future ecological challenges (e.g. host-range increase) (Brooks et al., 2019).

Another additional perspective is that the newly established population of pathogens, although unchanged in its diversity due to the absence or limited emergence of novelties (phenotypic or genetic), may also expand the window of opportunity to encounter additional hosts (=resources) by utilizing a host species with distinct ecological interactions with the surrounding environment. The newly colonized host species may increase the likelihood of the specific pathogen to encounter other potential hosts, not previously available. Simply put, the new host can increase the opportunity for the pathogen to explore a greater extent of its *fitness space*. This is an empirically recognized process associated with many cases of emergence of new symbiotic associations - contemporary (Brown, 2001) and historical (Braga et al., 2015). This process was named *host switching by stepping stone* (Braga et al., 2015), and includes one of the possible pathways of SARS-CoV-2 during its emergence in humans (Ji et al., 2020; Zhang et al., 2020).

In the case of SARS-CoV-2, the scenario is even more worrisome since humans became one of the "stones" in the process of host-repertoire expansion. COVID19 has rapidly expanded to almost every part of the planet, providing opportunities for the virus to colonize other human populations and animal species. Presently, pets – ferrets, cats, and dogs – and captive wild animals – such as minks, tigers, lions, macaques, Syrian hamsters, tree shrews, marmosets, and Egyptian fruit bats (Gryseels et al., 2020; Lin et al., 2020) - are known empirically to be compatible hosts while a much greater range of host species has been suggested through

modeling (Damas et al., 2020) - from old-world monkeys to anteaters. While many of the presently known compatible hosts are not seriously affected by the virus, they certainly represent unique selective pressures and opportunities for broader dissemination through ecological fitting (as suggested above). Hence, we may anticipate that the acquisition of new host species may influence the genetic make-up of SARS-CoV-2 and result on the emergence of unique haplotypes in isolated host populations (as suggested also by Franklin and Bevins 2020). Indeed, the nature of RNA-viruses replication influenced by host and geographic expansion and isolation are already known to generate new variants (Franklin & Bevins, 2020) with dissimilar potential virulence to humans. Such evolutionary changes may result in new strains of the viruses with the ability to generate diseases with symptomatic, virulence, and epidemiological characteristics distinct from the original strains (see Jerzak et al., 2007; Bordería at al., 2011). This epidemiological scenario is complicated by the accumulation of evidence suggesting that SARS-CoV-2 may take the opposite path (retro-colonizing humans), a situation already recorded among other coronaviruses for the Siberian musk deer *(Moschus moschiferus)* and ferrets (*Mustela lutreola*) (Hadfield et al., 2018; Van Der Hoek et al., 2004). Hence, despite the recognition that these retro-colonization events are likely rare (de Morais et al., 2020), they cannot be simply ignored in epidemiological surveillance systems.

The simulations revealed yet another aspect of this host-exploration dynamics that makes the above-proposed scenario of retro-colonization of humans particularly important in health surveillance for EIDs. The simulations strongly suggest that at higher values of the rate of emergence of evolutionary novelties (e.g. mutation rates for viruses), the phenotypic profile of the pathogen (=capacity space), although changing qualitatively and quantitatively under the selective pressure of the new host resource, putatively retain ancestral variants at low frequency in the new host (Fig. 4; Fig. S2). This outcome provides theoretical support for the retention of the capacity of fast-evolving pathogens to retro-colonize their previous host species by ecological fitting (Janz & Nylin, 1998; Brooks et al., 2019; Haan et al., 2021). RNA viruses, such as SARS-CoV-2, are well known to evolve rapidly through mutation and hybridization (Holland et al., 1982), and the retention of variants may facilitate retro-colonization of humans from other animal species. Hence, retro-colonization should be an important element in epidemiological monitoring (as suggested by Favoretto et al. 2019, Franklin & Bevins,, 2020, and González-Salazar et al., 2017), especially in cases of recent emergence and re-emergence of EIDs.

The combined results of this study provide further theoretical support for the assertion that "emerging infectious diseases are evolutionary accidents waiting to happen" (Brooks & Ferrao, 2005). An increase in host-repertoire by pathogens, potentially associated with the emergence of a new infectious disease, is most likely to occur among closely related species of hosts, but it is also possible among distantly related hosts when the resource(s) is(are) convergent (see discussion on specilization in Brooks and McLennan 2002). **Capacity** is much larger than we can anticipate, and it is the **opportunity** of encounter (i.e. the breakdown in mechanisms for ecological isolation) that is a more essential determinant to the emergence of new associations (Araujo et al., 2015; Brooks et al., 2019; Agosta & Brooks, 2020). Opportunity is more frequent during periods of environmental disruptions, many of which are associated with climatological fluctuations in the past (Hoberg & Klassen, 2002; Brooks & Hoberg, 2007; Hoberg & Brooks, 2008, 2015; Hoberg et al., 2017).

Climatological fluctuations may change the permeability of pre-existing ecological

barriers and promote shuffling in the composition of organismic communities, augmenting the rate of encounter of different host lineages fostering intense exchange in pathogens. Indeed, climate fluctuations and independent or accompanying environmental disruptions over evolutionary time have been a central determinant of opportunities for faunal mixing and pathogen exchange that have structured complex associations (Hoberg & Brooks, 2008). Climate and environmental disruptions occur across temporal and spatial scales and historically have had a substantial episodic behavior in the past (Hoberg et al., 2017). However, during what is now characterized as the Anthropocene, the outcomes of environmental disruption have become significantly more prevalent due to globalization, other human-associated actions, and also to climate change, which promote movements of wildlife, humans, and domestic species into new geographic range (Wilson, 1995; Brooks & Boeger, 2019). As a consequence, we expect EID's to become even more frequent in the years to come (Brooks et al., 2014). We have little control over capacity, but we can, to a certain level, monitor, avoid, and minimize the opportunity of encounter between parasites and compatible host species. This is the principle of the D.A.M.A. protocol (Brooks et al., 2014; Hoberg & Brooks, 2015; Brooks & Boeger, 2019; Brooks et al., 2019).

However, even with an effective D.A.M.A. protocol established, the task to avoid the emergence of new diseases is especially difficult, considering available empirical information. Many of the most significant events in the history of life, and in the history of EID's, are likely the result of unpredictable incidents when compatible biological entities unexpectedly meet (opportunity). Attempts to generate new associations (hosts and pathogens, in this case) likely occur continuously, most being unsuccessful. However, a single successful event may perpetuate the emerged association through evolution and have a significant influence on the future diversifications of the associates. That was likely the case for well-known symbioses, such as those of proto-eukaryotic cells and mitochondria, eukaryotic cells, and chloroplasts but also for many recent EIDs, such as HIV, Ebola, Dengue, Zika, Chikungunya, and, of course, Covid19.

Perhaps the final message from the empirical information accumulated from the recent emergence of infectious diseases and the dynamics revealed from the theoretical framework of the Stockholm Paradigm (Brooks et al., 2019) and associated evolutionary models (Araujo et al., 2015) is that we cannot "lower our guard". These events are evolutionarily dynamic processes, with pathogens incessantly exploring the space of compatible host species (Brooks et al., 2019). And we and domesticated species are among the most abundant, available, ecologically diverse, and widespread species of potential hosts on this planet.

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Conflict of interest statement

The authors report no conflict of interest.

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Table 1. Parameters, with a short definition, and all the values analyzed during simulations. The underlined values are the fixed values used in the presented results, while the other parameters varied.

Parameters	Short Definition	Investigated values
G	Compound phenotype size; Length of the binary characters that define each pathogen.	30, 40, 50, 60, 70, 80, <u>100</u>
K	Carrying capacity; The pathogen's maximum population size the host can support	<u>1000</u>, 2000, 3000, 4000, 5000
σ	Deviation rate for survivor probability; the higher its value the lower the selection pressure imposed by the host on pathogens	<u>10</u>
b	Reproduction rate; average population growth per reproduction step	<u>1.5</u>, 3.5, 5.5, 7.5 and 2^{n*}
μ	Novelty rate per locus, probability of trait state change	10^{-7},10^{-6},10^{-5},<u>10^{-4}</u>, 10^{-3}, 10^{-2},10^{-1}, 0.5,0.0.
p_h	Optimum Phenotype imposed by the host	<u>G/2</u>
p_0	Propagule phenotype. It defines the phenotype distance d_0 between propagule and host in the first generation of the colonization (see Eq.1)	$0<d_0<G/20$
N_0	Propagule size	<u>1</u>, 10, 50, 100, 200 and 2^{n*}
	Maximum number of generations that each simulation was run	<u>1000</u>
	Number of simulation repetitions of a given set of parameters.	<u>700</u>

* n={0, 1,2,3,4,5,6,7}

Legends to figures

Figure 1. Flowchart of the model dynamics. The initial population, with individuals of identical compound phenotype, is subjected to the *Selection* in the newly-colonized host. Upon survival, the simulated pathogen population will then undergo *Reproduction*. The descendent compound phenotype will differ from the parental phenotype according to a pre-defined rate of emergence of evolutionary novelties (μ). Descendent populations are subjected to these cyclic sequences for a pre-determined number of generations

Figure 2. Probability of establishment of the pathogen population as a function of the propagule phenotype distance (d_0). The graphs present the effect of (*a*) reproduction rate, (*b*) evolutionary novelty rate, and (*c*) propagule size (N_0) on the probability of establishment for varying resource distances (d_0). Except for the specifically tested parameter in each graph, the remaining simulation parameter values used are defined in Table 1. The black line in every graph represents the probability of a single pathogen individual of surviving the first reproductive event following colonization at each d_0 - Eq (1). The grey line represents the probability of establishment of the pathogen when b=7.5, μ=0.1, N_0=200.

Figure 3. Evolution of compound phenotype diversity/frequency and population size over generations. Left vertical axis indicate the distance of the pathogen compound phenotype from the optimum value imposed by the host, ($d_{i,n}$), whereas the horizontal axes indicate generation time in simulations. The orange palette depicts compound phenotype frequency in the given generation, warmer colors indicate greater phenotype frequency in the population. The right vertical axis represents the population size, drawn as a blue line - carrying capacity = 1,000 (Table 1). The vertical lines in the last two plots correspond to the respective generation time (same colors) depicted in Figure 3. The respective rates of novelty emergence for each graphic are the following: (*a*) $\mu = 0.0$; (*b*) $\mu = 10^{-4}$; and (*c*) $\mu = 10^{-2}$ - the remaining parameter values are those underlined in Table 1.

Figure 4. Maintenance of original phenotypes according to the rate of evolutionary novelties. Relative frequency of each compound phenotype as a function of the distance of the pathogen compound phenotype from the optimum value imposed by the host, ($d_{i,n}$) for two levels of evolutionary novelty rates and propagule size: (*a*) $\mu=10^{-4}$ and (*b*) $\mu=10^{-2}$, N_0=1 (*c*) $\mu=10^{-2}$, N_0=200, *b*=7.5). Each curve represents specific generation times as follow: (*a*) 45 (yellow line), 120 (dark-orange line), 200 (red line), 500 (brown line); (*b*) and (*c*) =10 (yellow line), 13 (light-orange line), 25 (dark-orange line), 35 (red line), 500 (brown line). The first four temporal elements (colored lines) of each list are highlighted by the vertical lines in Figure 3b and 3c, respectively.