

# Climate change and emerging infectious diseases: Evolutionary complexity in action

Daniel R. Brooks<sup>1,2</sup> and Walter A. Boeger<sup>3</sup>

## Abstract

More than a century of coevolutionary thought failed to anticipate the current crisis of emerging infectious diseases. This produced the *Parasite Paradox*: parasites are resource specialists with restricted host ranges, and yet shifts onto relatively unrelated hosts are common in the diversification of parasite lineages and directly observable in ecological time. An emergent framework, called the *Stockholm Paradigm*, resolves the paradox: ecological fitting - phenotypic flexibility and phylogenetic conservatism in traits related to resource use, most notably host preference - provides substantial opportunities for rapid host switching in changing environments, in the absence of the evolution of novel host-utilization capabilities. Host shifts via ecological fitting provide the fuel for the expansion phase of the recently proposed oscillation hypothesis of host range and speciation, and, more generally, the generation of novel combinations of interacting species within the geographic mosaic theory of coevolution. Large-scale environmental perturbations associated with climate change catalyze new oscillation cycles. The Stockholm Paradigm integrates emergent (Darwin's nature of the organism) and systemic (Darwin's nature of the conditions) properties characteristic of complex systems dynamics. The crisis of emerging diseases will continue so long as global climate change occurs.

## Addresses

<sup>1</sup> Evolutionary Systems Research Group, Centre for Ecological Research, Hungarian Academy of Sciences, 8237 Tihany, Hungary

<sup>2</sup> Institute for Advanced Studies Kőszeg, Kőszeg, Hungary

<sup>3</sup> Laboratório de Ecologia Molecular e Parasitologia Evolutiva, Universidade Federal do Paraná, Curitiba, PR, Brazil

Corresponding author: Brooks, Daniel R. ([dnlbrooks@gmail.com](mailto:dnlbrooks@gmail.com))

Current Opinion in Systems Biology 2019, 13:75–81

This review comes from a themed issue on **Systems ecology and evolution**

Edited by **Eörs Szathmáry** and **Ferenc Jordán**

For a complete overview see the [Issue](#) and the [Editorial](#)

Available online 23 November 2018

<https://doi.org/10.1016/j.coisb.2018.11.001>

2452-3100/© 2018 Elsevier Ltd. All rights reserved.

## Introduction

A century ago a global influenza outbreak sickened a quarter of the world's humans and killed 10% of them.

Ninety-one years later the World Health Organization issued its first global pandemic alert for swine flu. A decade after that, coping with emerging infectious diseases of humans, livestock and crops has become part of our daily news background. This is not a ringing endorsement of progress, but our failure is not due to a lack of effort. Rather, it is due to overly-simplified theories that have misdirected our efforts.

For more than 150 years, health specialists followed a triad of *medicate* (the ill), *vaccinate* (those at risk) and *eradicate* (the biodiversity responsible for transmission and persistence). Prior to WWII, evolutionary biology had made little impact on efforts to cope with disease, beyond the assertion – initially by orthogeneticists - that pathogens were so tightly bound to their hosts that they had no evolutionary life of their own. As a result, we would expect that for each group of pathogens, there would be one host – one pathogen. This seemed a perfect complement to Pasteur's simple and optimistic dictum “une maladie, un vaccin.”

Shortly after the end of WWII, however, there were indications that health goals were going to be more difficult to achieve than thought. In 1947, fewer than 20 years after the discovery of penicillin, the first documented appearance of microbial resistance to penicillin occurred. Two years later a potential turning point came and went, when the eminent British evolutionary biologist J.B.S. Haldane wrote about the need to study resistance to pathogens as an evolutionary problem [14]. Within a decade, the *coevolutionary arms race* paradigm (Mode [21–24]; popularized by Ehrlich and Raven [10]) strongly supported the health professionals' traditional approach. According to the paradigm, pathogens pursue specialized exploitation of their hosts which, in turn, try to eliminate the pathogens. Evolutionary innovations for mitigating pathogens (defense traits) are matched by ones that neutralize the host innovation (counter-defense). Pathogens become so tightly adapted to a single host that colonizing a new host requires the evolution of new genetic capacities, specifically allowing a given new host to be colonized. This meant that pathogens would be extremely unlikely to change hosts.

And yet, the last decade of the 20th century saw a marked increase in disease emergence worldwide.

Known pathogens appeared in new hosts, in new places, or in places where we thought they had been eradicated; previously unknown pathogens appeared in humans, and the plants and animals upon which we depend socio-economically. The costs of treatment and of lost production associated with emerging diseases now amounts to a trillion dollars a year globally, a figure that is certain to rise in the near future.

The Parasite Paradox summarizes the abject failure of evolutionary biology to anticipate the emerging disease crisis: how can ecologically specialized pathogens apparently tightly coevolved with one or a few hosts in a restricted geographical area nonetheless expand their host range and geographical distributions so rapidly? Or, to put it more simply, how can specialists become generalists [3]. The resolution of the paradox must reconcile deep-history evolutionary patterns that have been discovered in the past 40 years, since the emergence of studies integrating phylogenetic analysis and pathogen-host systems and must also explain the current emerging disease crisis.

In his seminal and influential book assessing evolutionary theory at the beginning of the 20th century [19], asserted that neo-Darwinism (which he associated with Herbert Spencer's influence on Darwinism), orthogenesis, and neo-Lamarckism all agreed on two things. First, the critical issue for evolutionary biology is explaining how the right adaptations show up at the right time to cope with environmental changes. Second, the traditional Darwinian explanation, that the critical adaptations must have existed before the environmental changes occurred was, in Kellogg's view, absurd. And yet, as we shall see, pre-existing capacities are the key to explaining the EID crisis and the role of climate change in it. So, let us quickly go.

### Back to the future

*... there are two factors: namely, the nature of the organism and the nature of the conditions. The former seems to be much more the important; for nearly similar variations sometimes arise under, as far as we can judge, dissimilar conditions; and, on the other hand, dissimilar variations arise under conditions which appear to be nearly uniform.*

– Darwin, 1872 [9]

From the beginning, Darwin proposed that evolution was an outcome, an emergent property in today's terminology, of asymmetrical interactions between two causal agents, each of which has its own properties relatively independent of the other, producing outcomes that are not readily predictable from knowledge of the properties of either one alone.

Darwin's conception of the Nature of the Organism was explicit: it is in the nature of the organism to produce

offspring; to produce offspring that are similar but not identical to each other; and to be able to act in their own behalf. The most important aspect of all this is that these aspects of the nature of the organism obtained regardless of the Nature of the Conditions. Nineteenth century philosophers believed organisms were perfectly "fit" to their surroundings, but Darwin recognized that the key to understanding evolution stemmed from the ways in which organisms were able to persist despite *misfits* between their surroundings and themselves. All species produced offspring exhibiting varying degrees of misfit with their surroundings and in far higher numbers than could be sustained by environmental resources.

This, Darwin reasoned, must lead to a struggle for survival on the part of those organisms *proportional to their degree of misfit*. When the inherent overproduction produced variety in traits critical for survival, organisms possessing traits that were functionally superior in that particular environmental context would survive best. Whenever an environment changed, those organisms that already had the capacity to survive in the new environment would do so, whereas those who lacked them would not; what is good today might not be good tomorrow. Natural selection was the *result* of the conflict created because the conditions of existence included the autonomy of the nature of the organism as well as the nature of the conditions. And the outcome of natural selection was partial or complete elimination of those variants that were so "misfit" that they could not survive. Evolution is thus a matter of both *capacity* and *opportunity*.

### The nature of capacity

Organisms that are both *exploiters* and *explorers* of their surroundings. The capacity to *exploit* (survive) stems from inherited information specifying ways that organisms impose themselves on "the conditions of life" in which they happen to find themselves to obtain the energy and materials need to sustain their lives. Inheritance is conservative, so each generation is likely to be comprised mostly of individuals with the same resource requirements; thus, if the previous generation was successful, the next one will most likely be as well. The capacity to *explore* (persist) stems from the fact that reproduction is both conservative and is produced without regard to the availability of the resources needed for successful exploitation. The capacity to cope with novel conditions based on pre-existing capacities is known as *Ecological Fitting* [18]; see also [8].

### The nature of opportunity

What counts as environmental opportunity for each organism is dependent on its inherited capacities. Opportunity is thus best thought of as the context of the nature of the organism rather than the nature of the conditions. This is the reason Darwin stated that the

nature of the organism is far more important than the nature of the conditions. The arena of opportunity is “function space.” The members of each species use a small, but predictable, portion of function space. Each species produces more offspring in each generation than there is available function space to allow their survival. The portion of function space for each species in which the differential survival takes place is *fitness space*. Fitness space contains all organisms that survive the struggle and reproduce; they have positive Darwinian fitness.

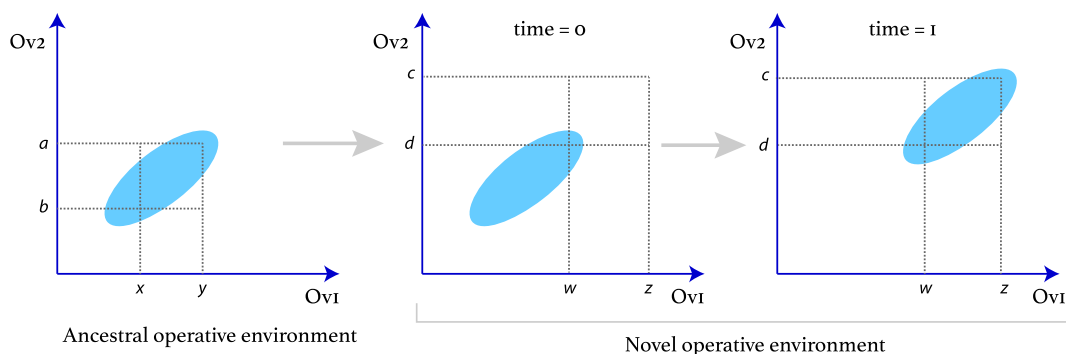
Even though fitness space for each species is a subset of function space determined by the nature of the organism, it is expansive. The *operative environment* of a pathogen species encompasses everything defining a host as a viable resource. Within that, not everything that could happen does happen. Not everything that does happen occurs all the time, or everywhere it could, or in equal proportions. And finally, not everything that happens provides optimal conditions for a given species. *Where organisms thrive is only a subset of where they can survive*. And because it is in the nature of the organism to explore as well as to exploit, variation allows organisms to investigate novel operative environments presented by the circumstances in which they find themselves.

Agosta [1–3] formalized this perspective (Figure 1). At a given point in space or time, the local or *realized* conditions are defined by the subset of environmental resources that exist. For any species, its *fundamental* fitness space is all combinations of all resources for which positive fitness can be achieved. *Realized* fitness space is that portion of fundamental fitness space that is accessed in the localized circumstances. The extent to which fitness space “fits” any particular set of realized

conditions will be a function of time and selection pressures, but the sum of all conservative elements of inheritance, called *evolutionary lagload* [20], ensures the fitness space will always remain in large part a function of retained history. The misfit between fundamental fitness space and realized fitness space at any given point in time or space is proportional to how “sloppy” the fitness space is. From large-scale environmental perturbations on regional or global scales to small-scale perturbations like local extinction of a host species, it is this “sloppiness” that provides the essential ability of life to cope with rapidly changing conditions (ancestral operative environment in Figure 1) and to explore new options across the physical landscape (novel operative environment in Figure 1). If a species’ RFS is restricted by selection at a particular place and time, other elements of its FFS will not be affected, so FFS cannot be optimized tightly. If a species’ RFS is a relatively large and more diverse portion of FFS, sub-groups will be responding to multiple selective forces at different places and times, so once again FFS cannot be tightly optimized.

We tend to think “specific and predictable” means “limited options.” But Darwin realized that the dualistic interaction between the nature of the organism and the nature of the conditions could produce predictable and specific outcomes without sacrificing options. That is because, in our terms, capacity is always greater than opportunity. And that is a good news/bad news situation. The bad news is that this means there will always be reproductive overrun and conflicts of interest among the members of each generation. The good news is that information is not distributed randomly, optimally, or maximally in fitness space. It is

Figure 1



Graphical representation of a hypothetical fitness space and the relationship with changing environmental conditions represented by two variables (Ov1 and Ov2). From left to right, despite the change in environmental conditions (i.e. the change on the rectangle describing the variation of the environment), the species illustrated in this example does not go extinct locally thanks to the overlap of its fitness space with the conditions of the new environment (or novel operative environment). With time (time = 1) and subjected to new selection pressures, the fitness space of the species will accommodate the new local conditions. (see Ref. [3]).

distributed functionally, and function is part of the nature of the organism. Information space is thus structured but variable — a system of indefinite variation. And while it is variable, it is far more conservative. That means there will be conflicts even if fitness space is sloppy; but the offspring that survive such conflicts will be variable because fitness space is sloppy. And what a pathogen is able to do, given the opportunity, can be as, or even more, important as how well it performs in explaining the reactions to climate change. Changes in the nature of the conditions are best understood by knowing the nature of the organism. *Survival in new environments allows, but does not require, new capacities specifically fit to that environment.* This is critical to understanding the rapid and widespread emergence of disease. At any given time, a pathogen is unlikely to inhabit all possible hosts in all possible places; therefore, its *current operative environment* will be a subset of its overall operative environment. No matter how specialized a pathogen's association is with a given host in a given place, it will always have some ability to survive in susceptible but currently unexposed, given the opportunity.

*Exploitation-biased activities* will tend to restrict realized fitness space and will be facilitated by discontinuities in fitness space. For a pathogen species, the ultimate exploitation-biased existence would be a species occurring in a single place, with a single host, and transmitted in a single way. These are the conditions under which opportunity acts as a filter, and such things as strong coevolutionary interactions would be favored if they arose, especially if they occurred in geographically isolated situations. A species living in such conditions would be highly specialized within realized fitness space. Because fitness space has been assumed to be highly optimized and limited, some believe that host changes could not occur without prior specific mutations permitting it. But given the enormous potential capacity provided by plasticity, co-option and evolutionary conservatism, strong local coevolutionary interactions may restrict realized fitness space locally without affecting fundamental fitness space.

*Exploration-biased activities*, by contrast, occur when the nature of the conditions changes in such a way that connectedness among elements of fitness space increases, amplifying opportunity. In such circumstances, opportunity acts as facilitator. Exploration can be as subtle as reproduction but that is apt to be mostly unsuccessful if available fitness space is occupied and no new connections can be made. But if there is always reproductive overrun, there will always be offspring produced that are not the fittest. Add to that plasticity, co-option and phylogenetic conservatism and you have a system in which no matter how limited the realized fitness space is at any one place or time, capacity will always be greater than opportunity.

### The oscillation hypothesis: generalizing and specializing and back again

Organisms are capable of exploiting and exploring fitness space. They will tend to be biased towards exploitation, because survival always requires exploitation. When opportunities are limited, ecological fitting in sloppy fitness space leads to exploitation-biased evolution, in part because exploring the boundaries of fitness space generally fails. When opportunities abound, by contrast, ecological fitting in sloppy fitness space leads to exploration-biased evolution and exploring the boundaries of fitness space is more often successful. The proportion of realized fitness space to fundamental fitness space determines — in a relative sense — how generalized or specialized you are. And temporal trends determine if a species is specializing (exploitation-biased) or generalizing (exploration-biased) in fitness space. In this view, the ability to generalize or specialize within fitness space is a built-in feature of living systems, so the members of any species can oscillate between generalizing and specializing themselves in fitness space as their surroundings change, no matter how specialized their previous situations.

The *Oscillation Hypothesis* [16,17] postulates that species, as inheritance groups of organisms, should exhibit oscillating behavior that emerges from the collective oscillating tendencies of individual organisms. On relatively short time scales and small spatial scales, oscillations appear as localized changes in host range associated with fluctuations in environmental conditions. Large-scale evolutionary diversification of pathogens involves an initial phase in which host range increases, as opportunities allow the pathogen to generalize itself in fitness space, which in turn sets the stage for the emergence of new pathogen lineages, each specializing itself in fitness space. There are four ways to initiate host range oscillations: (1) altering existing trophic structure so previously inaccessible but susceptible hosts become apparent to the pathogen; (2) bringing new susceptible hosts that have never encountered the pathogen into the ecosystem; (3) expanding the pathogen into new geographic locations where susceptible but previously unexposed hosts live; and (4) expanding pathogen capacity by the accumulation of evolutionary novelties through time. These factors provide opportunities to establish new associations through episodes of generalizing in fitness space, which then set the stage for diversification through subsequent specializing in fitness space. The geographical and temporal extent, and the biological magnitude of such oscillations depend on the circumstances causing increasing or decreasing connections in fitness space.

Ecological fitting in sloppy fitness space explains why coevolutionary arms races cannot be effective on more than the local scales envisioned by the Geographic Mosaic Theory of Coevolution [26]. In other words, if

there is an arms-race locally, it will not affect the pathogen or the host globally, and any interactions that affect all associations cannot be a restricted case of mutual modification, so there cannot be an effective arms race beyond the local association. Therefore, the more the local coevolutionary interactions restrict realized fitness space, the larger fundamental fitness space becomes (Figure 2). Fitness space becomes sloppier, increasing the chances for ecological fitting. When generalized by new opportunity, local coevolutionary arms races become global Red Queen dynamics in which the pathogen has the decided advantage [4,5].

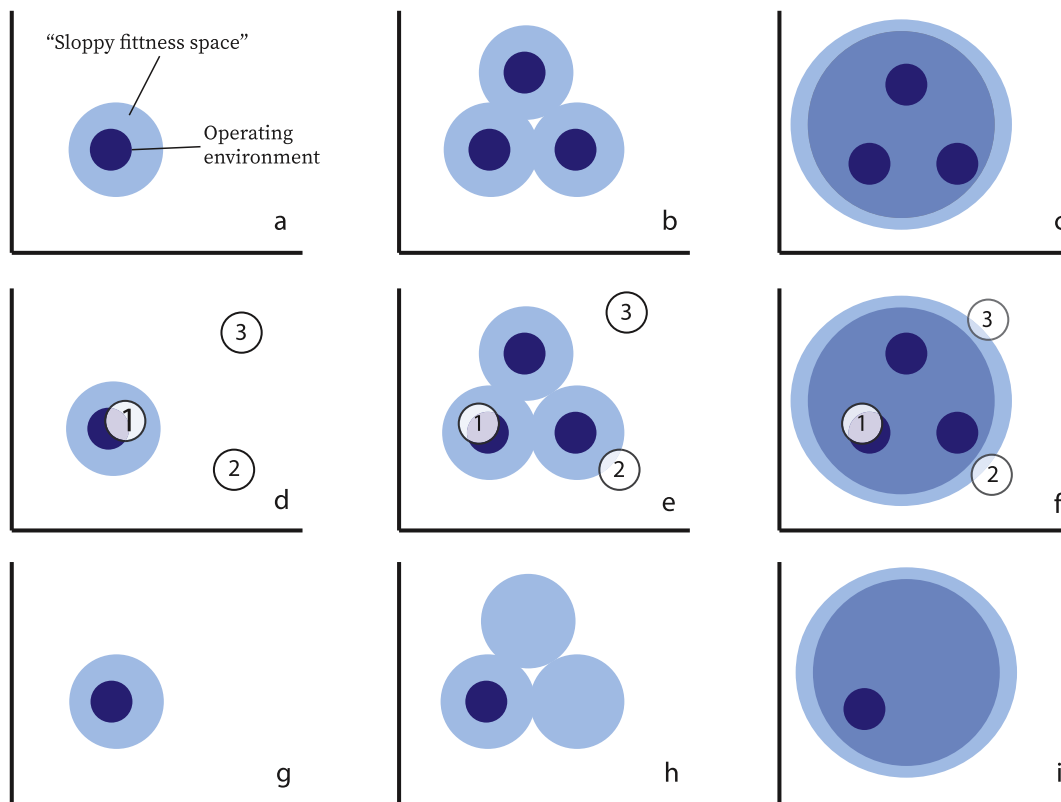
### Repeating oscillations: taxon pulses and emerging disease

Computer simulations [4,5] allow us to understand how generalized species can diverge into more than one specialized species, but specialized species remain specialized. In other words, there should be only one

oscillation cycle. We know this cannot be the case, because we find little support for co-speciation in long time-scale studies and see evidence of rapid and rampant host range expansions – emerging diseases – in real time. This implies that oscillation cycles recur. What determines *that*?

If fitness space is sloppy, there will always be places where pathogens could exist that are not accessible. Inaccessibility can be due to local trophic constraints (the pathogen is transmitted by a vector or intermediate host that does not feed on, or is not eaten by, all susceptible hosts) or geographic isolation (susceptible hosts live in geographic areas where the pathogen does not). Pathogens may exist in a stable host community, but they continue to accumulate variability in isolation, limited to the realized fitness space, increasing the capacity to explore whenever opportunity space changes in such a way that new susceptible hosts become

Figure 2



Depiction of two dimensions of the operative environment associated with hypothetical host resources. Sloppy fitness space comprises fitness in an area outside the operative environment to which the parasite is adapted (light grey circles). Panels a, d and g illustrate a specialist, adapted to a single host resource, panels b, e and h illustrate a poly-specialist that has adapted independently to three different resources, and panels c, f and i illustrate a true generalist with a more general host recognition and tolerance system that allows it to utilize any resource that falls within the dark grey area. The open circles in panels d–f represent three novel resources. The specialist in panel d can colonize resource 1 which is more or less identical to the ancestral resource but not resource 2 or 3. The poly-specialist in panel e can colonize resource 1 but also resource 2 that falls within its sloppy fitness space, and the generalist in panel f can colonize all three resources. In panels g–i only one host is available, so all 3 pathogen species will appear to be specialists, but their ecological and evolutionary potential will be very different. (see Ref. [3]).

accessible. Even if specialized pathogens retain the capacity to survive in hosts other than the ones they “see,” how do they find them, setting off a new round of generalizing leading to the emergence of new specialize associations? How do we get new diversity if the “internal dynamics” of the Oscillation Hypothesis are not sufficient? We think that repeating oscillations require perturbations in the nature of the conditions to open up new opportunities for oscillation modules.

*Taxon Pulses* [11–13] occur over relatively long periods of time and are characterized by expansion into suitable habitat when previous barriers break down, altering previous source-island relationships. During an expansion phase, different species within a biota encounter additional geographical heterogeneity, including range contractions. Such heterogeneity may: (1) stop the expansion of some species, resulting in species of restricted distributions; (2) affect only the rate of expansion for some species, producing widespread species; or (3) act as barriers to dispersal of sufficient magnitude to produce new species. Geological evolution, operating on longer time scales than biological evolution, may also produce relatively static or impermeable barriers, resulting in episodes of speciation by geographic isolation affecting members of these same biotas similarly (*vicariance*). Taxon pulses are historically repetitive, meaning that biotas resulting from them are made up of species that have been associated with each other for varying lengths of time, and arrived under varying circumstances. Biotas assembled in this manner are complex mosaics resulting from the mixture of episodic expansion, isolation and mixing during new expansion [15].

Periods of climate stability are times of specializing in largely disconnected fitness space. Environmental changes following such episodes create new opportunities by connecting fitness space, leading to biotic expansion events. Species that cannot tolerate the changes in the place where they have been living leave as fast as they are able, changing from exploitation to exploration mode as they seek familiar conditions. As they leave, they pass other species that have vacated their abodes and are in the process of discovering that they like the newly-vacated territory. Biotic mixing is underway. A few species survive staying in place, but they must cope with the loss of old neighbors and the arrival of newcomers. In some cases, the new arrivals will be functional replacements for species that have recently left, maintaining pre-existing trophic structures. In other cases, the combination of departures and arrivals will produce novel trophic linkages. This produces an enormous amount of potential fitness space to be explored and exploited. Hosts arriving from adjacent areas will often be closely related to the residents, increasing the ease of host range expansion by ecological fitting. Resident hosts not accessible to the pathogen

before biotic expansion may find themselves apparent. This is why most host range expansion occurs in evolutionary bursts during episodes of increasing connectivity in fitness space associated with biotic expansion catalyzed by climate change.

## Summary

The Stockholm Paradigm resolves the parasite paradox. Environmental perturbations causing a change in the nature of the conditions lead to biotic expansions based on existing capabilities (*Ecological Fitting*); this leads to generalizing (*Ecological Fitting in Sloppy Fitness Space*). When climate stability returns, local isolation reduces connectivity in fitness space, leading to specializing with or without strong coevolutionary interactions (*The Geographic Mosaic Theory of Coevolution*). These emergent properties set the stage for survival when the next environmental perturbations occur (the *Oscillation Hypothesis* and *Taxon Pulses*). Those new perturbations are systemic properties, leading to a repetition of the sequence, this time with new players, producing complex evolutionary diversification of inter-specific associations, including pathogen-host systems [25].

The Stockholm Paradigm also provides a direct link between climate change and emerging disease. The planet is a minefield of evolutionary accidents waiting to happen so long as climate change perturbations continue, and that will continue indefinitely. Each new emerging disease exacts a cost and persists as *pathogen pollution* after its initial acute outbreak, always having the potential to break out anew. Coping with emerging infectious diseases of humans, livestock and crops is already a trillion-dollar a year enterprise – greater than the GDPs of all but 15 countries - the costs borne disproportionately by those that can least afford them [6].

There is hope, however. We can anticipate and mitigate the effects of these EID. The historical conservatism and specialization that gives pathogens the capacity to take advantage of opportunities that make new fitness space available allows us to anticipate where pathogens may go and what they will do when they get there. Proactive policies of “finding them before they find us” (the DAMA [document, assess, monitor, act] Protocol: Brooks et al. [6,7]) can buy time and lower costs, allowing humanity to better cope with a dangerous future.

## Conflict of interest statement

Nothing declared.

## Acknowledgements

We thank Eors Szathmari for the invitation to present these ideas in this forum. WAB acknowledges funding by CNPq (grant numbers 471165/2009-3 and 404344/2013-5).

## References

1. Agosta Salvatore J: **On ecological fitting, plant-insect associations, herbivore host shifts, and host plant selection.** *Oikos* 2006, **114**:556–565.
2. Agosta Salvatore J, Klemens Jeffrey A: **Ecological fitting by phenotypically flexible genotypes: implications for species associations, community assembly and evolution.** *Ecol Lett* 2008, **11**:1123–1134.
3. Agosta Salvatore J, Janz Niklas, Brooks Daniel R: **How generalists can be specialists: resolving the “parasite paradox” and implications for emerging disease.** *Zoologia* 2010, **27**: 151–162.
4. Araujo SBL, Braga MP, Brooks DR, Agosta S, Hoberg EP, von Hahnel F, Boeger WA: **Modeling the Stockholm Paradigm: ecological fitting facilitates host switching in sloppy fitness space.** *PLoS One* 2015, **10**:e0139225, <https://doi.org/10.1371/journal.pone.0139225>.
5. Braga MP, Araujo SBL, Agosta S, Brooks DR, Hoberg EP, Nylin S, Janz N, Boeger WA: **Host use dynamics in a heterogeneous fitness landscape generates oscillations and diversification.** *Evolution* 2018, **72–79**:1773–1783, <https://doi.org/10.1111/evo.13557>.
6. Brooks DR, Hoberg EP, Boeger WA: *A perfect storm: climate change, emerging disease and the future of humanity.* Chicago: University of Chicago Press; 2019.
7. Brooks, Hoberg DREP, Boeger WA, Gardner SL, Galbraith KE, Herczeg D, Mejía-Madrid HH, Rácz SE, Tsogtsaikhan A: **Finding them before they find us: informatics, parasites and environments in accelerating climate change.** *Comp Parasitol* 2014, **81**:155–164.
8. Brooks Daniel R, McLennan Deborah A: *The nature of diversity: an evolutionary voyage of discovery.* Chicago: University of Chicago Press; 2002.
9. Darwin Charles: *The origin of species.* 6th ed. London: Murray; 1872.
10. Ehrlich Paul R, Raven Peter H: **Butterflies and plants: a study in coevolution.** *Evolution* 1964, **18**:586–608.
11. Erwin Terry L: **Thoughts on the evolutionary history of ground beetles: hypotheses generated from comparative faunal analyses of lowland forest sites in temperate and tropical regions.** In *Carabid beetles.* Edited by Erwin Terry L, Ball George E, Whitehead Donald R, Halpern Anne L, Dordrecht: Springer; 1979: 539–592.
12. Erwin Terry L: **Taxon pulses, vicariance, and dispersal: an evolutionary synthesis illustrated by carabid beetles.** p. 159–196. In *Vicariance biogeography: a critique.* Edited by Nelson Gareth, Rosen Donn E, New York: Columbia University Press; 1981.
13. Erwin Terry L: **The Taxon pulse: a general pattern of lineage radiation and extinction among carabid beetles.** p. 437–472. In *Taxonomy, phylogeny, and zoogeography of beetles and ants.* Edited by Ball George E, Dordrecht: W. Junk; 1985.
14. Haldane JBS: **Disease and evolution.** *Rice Sci Suppl* 1949, **19**: 68–76.
15. Hoberg EP, Brooks DR: **A macroevolutionary mosaic: episodic host-switching, geographic colonization, and diversification in complex host-parasite systems.** *J Biogeogr* 2008, **35**: 1533–1550.
16. Janz Niklas, Nylin Soren: **The oscillation hypothesis of host-plant range and speciation.** In *Specialization, speciation, and radiation: the evolutionary biology of herbivorous insects.* Edited by Tilmon Kelley J, Berkeley: University of California Press; 2008: 203–215.
17. Janz Niklas, Nylin Soren, Wahlberg Niklas: **Diversity begets diversity: host expansions and the diversification of plant-feeding insects.** *BMC Evol Biol* 2006, **6**:4.
18. Janzen Daniel H: **On ecological fitting.** *Oikos* 1985, **45**: 308–310.
19. Kellogg Vernon L: *Darwinism today.* New York: Holt; 1907.
20. Maynard Smith John: **What determines the rate of evolution?** *Am Nat* 1976, **110**:331–338.
21. Mode Charles J: **A mathematical model for the Co-evolution of obligate parasites and their hosts.** *Evolution* 1958, **12**: 158–165.
22. Mode Charles J: **Generalized model of a host-pathogen.** *Biometrics* 1961, **17**:386–404.
23. Mode Charles J: **Some multi-dimensional birth and death processes and their applications in population genetics.** *Biometrics* 1962, **18**:543–567.
24. Mode Charles J: **A stochastic model of the dynamics of host-pathogen systems with mutation.** *Bull Math Biol* 1964, **26**: 205–233.
25. Nylin S, Agosta S, Bensch S, Boeger WA, Braga MP, Brooks DR, Forister ML, Hambäck PA, Hoberg EP, Nyman T, Schäpers A, Stigall AL, Wahlberg N, Wheat CW, Österling M, Janz N: **Embracing colonizations: a new paradigm for species association dynamics.** *Trends Ecol Evol* 2018, **33**:4–14.
26. Thompson John N: *The geographic mosaic of coevolution.* Chicago: University of Chicago Press; 2005.