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NEMATODES ASSOCIATED WITH MAMMALS IN THE GREAT AMERICAN BIOTIC INTERCHANGE (GABI)

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ABSTRACT

The Great American Biotic Interchange (GABI) is a large-scale zoogeographic event that illustrates the exchange and diversification of mammals between North and South America. This phenomenon was accelerated by the connection of both landmasses during the Pliocene. Support for this phenomenon includes the extant distribution of xenarthrans, didelphiomorph marsupials, hystricognath and cricetine rodents, sciurids and carnivores, as well as the distribution of fossils in the stratigraphic record and the coalescence of genotypes. Contrasting with the relatively well-documented role and history of mammals in GABI, the role of their parasites has been largely neglected. As a consequence, the reconstructions of the causes of diversification, extinction and dispersion of groups of mammals during the Pliocene (and Miocene) invoke changes in climate patterns and the role of competitors or predators, yet in most cases the lines of evidence are not direct. We posit that infections with parasites offer a direct form of evidence of the role of interactions among species, by considering that the successful establishment of species of parasites in new groups of vertebrates will result in a net effect on their adaptive immune system. Thus, the current distribution of nematode parasites of the families Aspidoderidae, Nippostrongylidae, Onchocercidae, Oxyuridae, Rictaluriidae and Viannaidae offers evidence that the historical associations of these nematodes and their hosts diverge from the expected cospeciation and codivergence. Thus, clades of parasites infect disparate clades of mammals and, by deviating from the expected cospeciation, represent a paradox. This paradox deters investigators from studying historical associations among symbionts, since researchers lose the compelling simplicity of testing coevolutionary associations through the congruence of their resulting phylogenies. However, the reconstruction of historical associations must acknowledge the differential survival of parasites in novel hosts. This consideration is part of the Stockholm Paradigm, which includes the hypotheses known as Ecological Fitting, Oscillations, Taxon Pulses and Mosaics of Geographic Coevolution. We introduce nine host-parasite systems that provide insights on the role of parasites in GABI. We posit that the conservatism of parasite resource use, heritability of the adaptive immune system, and the genetic structure of parasites make it possible to elucidate the role of these parasites in GABI.

Keywords: co-evolution; diversification; extinction; historical associations; neotropics.

INTRODUCTION

The Great American Biotic Interchange (hereafter GABI) is the asymmetric swapping of terrestrial biotas between North and South America (Webb 1978, Simpson 1980, Stehli & Webb 1985, Carrillo *et al*. 2015; Cione *et al*. 2015). GABI was consolidated by the closure of the Panamanian land bridge, which facilitated the flux of organisms otherwise restricted to their original landmasses (Webb 1978, Simpson 1980, Marshall 1985, O'Dea *et al.* 2016). The study of extant mammal diversity and distribution, in combination with the study of the rich fossil record throughout North and South America, has enabled biologists to document the net effects of GABI on mammalian dispersion, diversification and extinction (Webb 1978, Simpson 1980, Borrero 2008). In particular, scientists have estimated dates of the impressive adaptive diversification of South American Cricetidae (Parada *et al*. 2013, Leite *et al*. 2014); identified signals of mass extinction in Didelphiomorpha in the Miocene (Jansa *et al*. 2014); studied the Holocene expansion of South American species into North America (Arteaga *et al.* 2012, Feng *et al.* 2016);

tested the role of climate fluctuations on diversification of xenarthrans during the Paleogene (Delsuc *et al*. 2004), and estimated dates of mass extinction for the endemic South American megafauna (MacFadden 2006, Prado *et al*. 2015). In each of these examples either some sort of biological interaction (*i.e.*, predation) or a link to a physical change is invoked to explain the evolutionary outcome. Among the latter, the reconstruction of the paleoenvironments supports the establishment of links between drastic changes in climate, on one hand, and patterns of diversification and extinction, on the other. The establishment of these links is made possible by using a time-calibrated phylogeny that makes it possible to test the likelihood of association of said events with internal nodes of the phylogeny. However, the case of biological interactions relies more on extrapolation of the present interaction among associates and to some degree on their phylogenetic conservatism. As such, most mammals of the order Carnivora will be construed as predators of small mammals. In the case of GABI, predation by more efficient carnivores and competition (or lack thereof) are the most commonly invoked interactions that determine the fate of certain mammal groups (Jansa *et al*. 2014). Yet, the role of parasites and parasitism as a significant biological interaction is seldom considered as an important evolutionary force that shaped GABI.

Evidence of infection with micro- and macroparasites in extinct mammals and other vertebrates, although scarce, is available (Hugot *et al*. 2014, De Baets & Littlewood 2015, Poinar 2015). The scarcity of evidence is in part the result of the low chances of fossilization of the habitat of parasites; after all, most microparasites are systemic tissue-dwelling unicellular organisms (*i.e.*, they infect cells), thus they would replicate inside soft tissues that decay after death. Furthermore, their pathological effects on the hosts are mostly evident in these same tissues and seldom evident on the skeletal system, which has a greater chance of fossilizing. Internal macroparasites are no different in that these infect the intestine and other visceral organs that have low chances of fossilization. As a consequence, most of the evidence of the presence of parasites in Holocenic vertebrates consists of eggs of these parasites present in coprolites or fossilized feces (Araújo *et al*. 1989, Sardella & Fugassa 2009b, Sardella & Fugassa 2009a, Beltrame *et al*. 2010; Beltrame *et al*. 2013). These eggs have a greater chance of preservation due to the protective nature of the egg-shell and their inclusion in the fecal matter. Nevertheless, ectoparasites offer a different outcome in that there are sporadic findings of organisms attached to the remains of mummified wildlife (Dittmar 2000), or traces of infection on dried skins or osteoderms (Hammond *et al.* 2014 Tomassini *et al*. 2016).

The pervasive lack of direct fossil evidence has hindered the investigations of the evolutionary associations between parasites and mammals. This is because the lack of material evidence impedes both the unequivocal diagnosis and taxonomic assignation of a parasite into a taxonomic group and the establishment of the association among ancestral parasites and their ancestral hosts. Both of these are necessary because a precise taxonomic assignation and identification of a geological context facilitate the establishment of minimum ages of the association and are a prerequisite for calibration of a molecular clock used for phylogenetic reconstructions. Nevertheless, determination of both the origin of host-parasite associations is possible by using indirect methods, which include the increase of taxon and geographic sampling and the calibration of molecular clocks enforcing switches in geographic distribution or association with hosts. With the use of ancillary geological evidence, it is possible to estimate the age of associations, especially in those cases that involve an evident shift in the geographic distribution that is linked to a dated geological event (Ricklefs & Outlaw 2010, Badets *et al.* 2011, Outlaw &Ricklefs 2011). Thus, as in other organisms, the study of the evolution of parasites is possible through the analysis of their genetic structure (De Baets & Littlewood 2015), which again can be dated by correlating shifts in the distribution of parasites in their hosts or in new geographic areas.

The study of the diversification of parasites as a result of episodic geological/climatic changes, such as the closure of the Panamanian isthmus, is relevant because it makes it possible to establish the causality of these sudden changes in several ways, including: a) the current distribution of species, b) rates of species extinction, c) establishment and dispersion of invasive species, and d) exchange or transfer of pathogens among the faunal elements involved (Ricklefs & Outlaw 2010, De Baets & Littlewood 2015, Poinar 2015). Information derived from these phenomena may help in better understanding the consequences of the establishment and rapid dispersion of ecological invaders, which in the present time may result in the spread of novel emerging diseases that threaten wildlife and the human population (Brooks *et al*. 2014, Hoberg *et al*. 2015, Hoberg &Brooks 2015). The integration of ecological, micro- and macroevolutionary phenomena offers an optimal framework in which to reconstruct the effects of dispersal, cospeciation, host-switching and diversification of parasites into new hosts (Hoberg & Brooks 2015).

In this review, we identify the background information that may facilitate the study of parasites in this intercontinental exchange; we introduce case studies that account for the identification of clades with members in both land masses; we identify clades of parasites that switched among groups of mammals involved in GABI, and we identify the future directions in the research aimed at understanding the role of parasites in GABI. We posit that there are sufficient elements to act as the foundation for investigating the role of parasites in GABI.

What are parasites?

Parasitism is a symbiosis, a biological interaction among members of different taxa, in which the parasite will consume parts or the totality of the infected individual, the host. Parasitism has arisen independently in 223 animal lineages (Weinstein & Kuris 2016). Most of these events are concentrated among three phyla - Arthropoda, Nematoda and Platyhelminthes- which show a relatively successful diversification and association with vertebrates (Poulin & Morand 2000, Weinstein & Kuris 2016). In general, parasites are specialized consumers of resources available in their hosts, and as such they feature phylogenetic conservatism towards these resources and exhibit pronounced site specificity (Janz *et al*. 2006; Agosta *et al*. 2010). Parasites must gain access to these resources by evading or overcoming the immune response presented by their hosts and by becoming established in their specific site, in which they will have the chance to either undergo sexual reproduction or experience growth via asexual amplification.

What is a host?

The host is the individual organism that harbors the parasite and it features phenotypic traits that make the establishment, survival, and reproduction of the parasite possible. The host contains all of the resources that facilitate the survival, growth and reproduction of the parasite; thus, both (host and parasite) are said to be compatible (Combes 1991). This compatibility, when considered from the perspective of the host organism, includes an innate and an adaptive immune system. The immune system of vertebrates includes antibodies encoded by genes or gene families that may or may not be exaptations to a parasite or group of parasites. These genes are responsible for initially coding the immune system to recognize the parasites that are invading an individual host and for subsequent elaboration of the immune response against the variously invading parasitic or infective agents. Other elements of the phenotype of organisms, such as behavior and physiological traits increase their chances of encountering parasites and facilitate infection (Combes 1991). These phenotypic elements are likely inherited from a common ancestor, yet in some cases they may be the result of evolutionary convergence.

Distribution of parasites in vertebrates

In natural conditions, parasites will form large populations by concentrating several individuals in only a few hosts. These aggregations are in fact populations that feature their own dynamics (Nadler 1995). Generally, each of these populations concentrates sexual individuals, and their consolidation or grouping is regulated by biotic and abiotic factors that determine their mode and efficiency of transmission (Pavlovsky 1966). As a consequence, a cluster of populations may concentrate in areas that facilitate this transmission and this may not correspond with the entire distribution of the animal population that can serve as hosts.

Whereas the immediate effects of the parasite are in their host (*i.e.*, pathology), the evolutionary consequences of parasites in populations of vertebrates occur downstream through time and space; selection is occurring at the level of the individual but it is manifested by changes in gene frequencies through time in the host population (Anderson & May 1982, May & Anderson 1983). These associations are the result of the interactions among the parasites and the elements of the adaptive immune system of vertebrates, which can be identified in the hypervariable regions of the Major Histocompatibility Complex II, which encodes for antibodies that bind antigens presented by parasites. The signal for these associations has been identified in several groups of small mammals across South America (Meyer-Lucht *et al.* 2008, Meyer-Lucht *et al.* 2010)

Parasites may successfully infect several species of vertebrates

The phylogenetic conservatism of permanent parasites towards their resources has been considered as evidence of their pronounced taxonomic specificity towards their host (Fahrenholz 1913). However, this generalization seldom holds when one considers parasites that feature one or more free-living stages (Euzet & Combes 1980, Agosta *et al.* 2010). In natural conditions, the infective free-living stages are exposed to a myriad of potential hosts. The phenotype of the vast majority of these would be incompatible with the parasite and make the establishment of the parasite impossible. However, phylogenetically related organisms may offer the same resources and compatibility to parasites (Agosta *et al.* 2010). Furthermore, non-related organisms may also offer similar resources and compatibility to parasites, provided these organisms feature convergent behavioral or physiological characteristics (Janzen 1985, Agosta *et al.* 2010, Nylin *et al.* 2014).

Historical associations: Does cospeciation explain the distribution of all parasites?

Parasite diversification cannot be explained based on the process of strict cospeciation, since this would result in the extreme specialization of parasites and a narrow host spectrum (de Vienne *et al.* 2013). If cospeciation was the driving force of parasite diversification, one would expect that all mammals in a clade would be infected by parasites that are phylogenetically related, which is seldom the case (Light & Hafner 2008). The expectation of encountering mirroring or concordant phylogenies is based on two premises: (1) that species of permanent parasites are extremely host-specific, specializing in resources exclusively available on their host species; and (2) that parasites are able to transmit among potential hosts via contact and they are able to complete their life cycle without leaving the host body. As a consequence, these parasites would be a proxy of the phenotype of the host; thus the reconstruction of the relationships of these hosts necessitated the inclusion of parasites as an additional character (Fahrenholz 1913, Kellogg 1913). In spite of its circular reasoning (Klassen 1992, de Vienne *et al.* 2013), and the fact that most parasites are not permanent in or on their hosts, these premises have prevailed in the scientific literature up to the current time. The expectation of maximum cospeciation is not congruent with the restricted geographic distribution of several parasites. For example, to explain the distribution of *Schistosoma japonicum*, a trematode parasite that infects primates, rodents, artiodactyls, perissodactyls and carnivores, one would need to explain their extinction in the rest of mammalian lineages, including those present in the same geographic area (*i.e.*, pholidont pangolins). Both resource specialization and the restricted geographic distribution of clades of parasites combined with their ability to infect other hosts and diversify constitute the “parasite paradox”. This also suggests that the narrow geographic distribution of most parasite species is an artifact of a limited sampling (Agosta *et al.* 2010). After all, most species of parasites are known only from the original description, and extensive surveys of parasites have demonstrated that a species of parasite may be able to infect, grow and reproduce in several species of competent hosts (Notarnicola *et al.* 2010, Notarnicola *et al.* 2012). Cospeciation between parasites and their hosts, as in other symbionts, are expected to occur in nature; however, convincing cases that explain the diversification of entire clades of parasites are rare (de Vienne *et al*. 2013).

Independent events in parasites: The stockholm paradigm

The success of parasites as exploiters of reproducing resources (progeny of their host) can be explained by the interplay of four phenomena, which allow parasites to increase their host range by infecting new organisms and establishing viable populations in them; these populations then become isolated and undergo their own population dynamics by becoming fragmented. This complex interplay of hosts and parasites through evolutionary time is known as the Stockholm Paradigm (Hoberg *et al*. 2015, Hoberg & Brooks 2015), and it integrates the concepts of Ecological Fitting -ability of apparent specific parasites to infect a new host that features the conservative resource the parasite exploits- (Janzen 1985), the Oscillation hypothesis - consolidation of new host-parasite associations though the expansion of the host range of parasites that enable them to become generalists and give place to specialists- (Nylin *et al.* 2014), Taxon Pulses -diversification of a clade of organisms as a result of the invasion of a new area- (Erwin 1981) and the Geographic Mosaic Theory of Coevolution -persistence of the newly formed associations through reciprocal adaptations- (Thompson 2005). In conjunction, these phenomena explain the distribution of parasites in related and unrelated hosts as a consequence of three characteristics of the parasites. These include i) the ability of parasites to use inherent phenotypic plasticity in the characters that enable them to infect a host, ii) evade its immune response, and iii) access and exploit phylogenetically conserved resources present in their hosts. Once established into a new species of host, the ancestral population of parasites would experience rapid growth or expansion, followed by a subsequent contraction in geographic or host-range. The resulting fragments of the species or populations would be driven by the frequency of the host-parasite encounter, resulting in microevolutionary dynamics that determine the cohesion of a population. It is important to note that the expansion and contraction of the parasites may be geographical, that is through space and time; thus, the host-parasite associations may be modified by abiotic changes that affect the associations in punctuated geographic space.

The Stockholm Paradigm has not yet been widely accepted as a universal framework that helps to explain the origin of host-parasite associations. This is partly because the Stockholm Paradigm includes at least four different hypotheses, each with its own set of predictions that must be tested at micro- and macroevolutionary levels. Consequently, most times they require different lines of evidence, including observations derived from experimental infections. Furthermore, several host-parasite systems span different groups of animals over vast areas, and it is common that these groups of host animals feature different dynamics. This contrasts with the simplicity of the premise of maximum cospeciation, in which the apparent information derived from the host and parasite distributions, interactions and demographics seems to suffice to provide the necessary evidence to test the null hypothesis.

To this effect, the Stockholm Paradigm is a holistic approach that promotes the simultaneous study of micro- and macroevolutionary events in a single host(s)-parasite system, and forces researchers to determine compatible hosts in nature by surveying the presence of parasites, define the nature of the specificity of a parasite towards its host, characterize the population dynamics of the parasite, establish the effect of abiotic phenomena in the evolutionary history of the parasite lineage, and identify putative host-switching events, extinctions and instances of cospeciation. It is possible to detect most of these signals from a single dataset, yet again this dataset must include information that is useful at both the micro- and macroevolutionary levels (Peter & Slatkin 2013).

Parasites in geological history

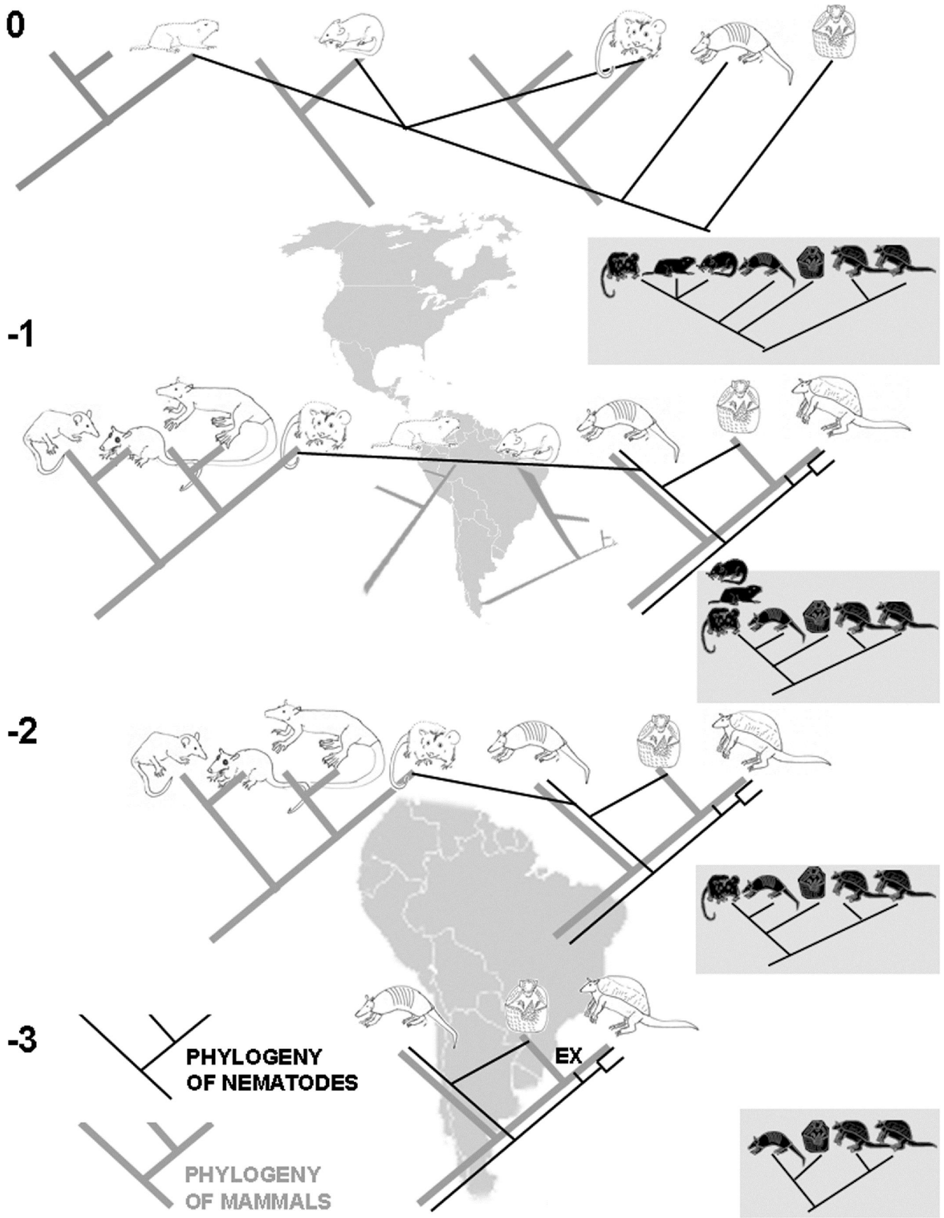
Evidence of a parasitic lifestyle in forms from ancient geological areas is scarce; yet, the scientific community recognizes that extinct animal forms would have been infected by parasites (Hugot *et al*. 2014, De Baets & Littlewood 2015, Poinar 2015). The role of pathogens and parasites has been acknowledged by paleontologists, some of whom invoked the putative role of pathogens in the extinction of the endemic megafauna of South America (Ferigolo 1999). In a series of at least 5 conjugations of Biotic Systems (expansions, contraction and switches of pathogens and their hosts) and Turning Points (abiotic crises or episodic events that affected the fauna) spanning from the early Oligocene to the Holocene, Ferigolo (1999) hypothesizes that the change in faunas may have exposed dispersing animals to different pathogens. This mixing, and subsequent exposure resulted in the establishment of parasites in new hosts, thus promoting a host-switch that may have resulted in the extinctions of the new hosts through geographic space. Furthermore, the pathogens may have been able to expand throughout the continent by infecting new organisms from different naïve species as they were encountered.

Interestingly, Ferigolo's hypothesis is in line with the Stockholm Paradigm in that it explains the expansion of the geographic range of mammals along with their pathogens/parasites and their ability to infect other endemic South American mammals through Biotic Systems and Turning Points. In this context, Biotic Systems are defined as expansions, contractions and switches of pathogens and their hosts, three phenomena that are consistent with Ecological Fitting and Oscillation; Turning Points consist of abiotic crises or episodic events that affected the fauna, these episodic events are also consistent with Taxon Pulses in cases in which the crises enabled the dispersion and diversification of taxa in new landmasses. Furthermore, Ferigolo's hypothesis even contemplates the Geographic Mosaic Theory of Coevolution, by acknowledging a long period of coevolution among parasites and mammals in the Northern Hemisphere prior to their southward dispersal. This coevolutionary period would have resulted in the acquired immunity to the current assemblage of Nearctic parasites infecting the mammals dispersing southwards after the continental connection. This phenomenon of coevolution has been amply documented for parasites and mammals in the Northern Hemisphere (Hoberg *et al*. 2012). The proper information necessary to build or to develop the adaptive immunity was not widespread in the South American Neotropical mammals, which in addition featured a relatively low fecundity (many, if not most, Hystricognath rodents, marsupials and xenarthrans have a relatively low intrinsic rate of natural increase relative to the invading sigmodontine rodents). In summary, the pathogens newly arrived in South America posed an insurmountable challenge to the immune system of the South American endemics, resulting in their decimation; furthermore, their low fecundity rate and slow growth may have resulted in their rapid extinction (Ferigolo 1999). The role of pathogens in the extinction of South American megafauna has yet to be evaluated using direct or indirect evidence. Although there is a limited number of fossilized parasites and those available render little information as to the timing of the diversification of parasite lineages, the framework of episodic or abiotic changes, and the dating of the extinctions and invasion of mammals are available. This would make it possible to test their effect on the evolution of parasites, by evaluating for signs of contraction or expansion in their genetic structure.

In the following, we present an interpretation of the studies that offer some insight into the role of nematodes in GABI (Summarized in Table 1). We attempt to dissect these studies and address the points they make relative to the Stockholm Paradigm. The goal is to help the reader in identifying the role of these parasite-host model systems in GABI, and in detecting strengths and weakness of each of the associations studied. Because of their limited taxon sampling, geographic distribution or methodology, none of the studies addresses all four tenets of the Stockholm Paradigm. However, with the aid of ancillary information, we hope to present a compelling case for the merits of the study of parasite-host associations in the study of GABI and to highlight the usefulness of intensive surveys of extant parasites, analyses of their distribution, genetic structure and tests of specificity to understand their impacts in the past events that determined the current distribution of mammals.

MATERIAL AND METHODS

The study of parasites involved in GABI includes manuscripts documenting the empirical evidence for the presence of fossilized parasites; systematic appraisals of parasite taxa associated with mammalian taxa involved in GABI; and the reconstruction of biogeographical patterns and historical associations with mammals through the phylogeny of the parasites.



BOX 1. The continuous evolution of nematodes of mammals in the New World is shaped by the geological events that bridged the North and South American landmasses. The reconstruction of the phylogeny of parasites and the mapping of their hosts reveal their ability to infect distantly related mammals that converge in habitat (gray rectangles).These interactions are shaped by biotic (mammal cladogenesis) and episodic events (Formation of the Panamanian Land Bridge): At present time 0, populations of parasites appear to be isolated in newly arrived mammals and diverge significantly one from the other by isolation. In -1, the closure of the Panamanian Land Bridge (episodic event) consolidated the exchange and flux of biotic elements between both landmasses. This event included the southward invasion and diversification of several groups of mammals originally from North America (Taxon Pulses of cricetid and geomyid rodents). The Ecological Fitting of local parasites enabled them to infect these newly arrived mammals. In -2, parasites from the group involved in host switching act as generalists and infect organisms from a disparate group of mammals; these parasites may become isolated in the newly acquired host, form a population and diverge genetically from the original population (Oscillation Hypothesis), thus completing a new event of host switching. In -3, the phylogeny of a fictional group of parasites is contrasted against the phylogeny of a group of mammals, events such as host switching, cospeciation, duplication and extinction are illustrated for the parasites (modified from Paterson & Gray 1997).

PARASITES IN GABI

Direct evidence of parasites in ancient times: Eggs in coprolites

In the first place, the empirical studies chiefly examine coprolites, which are the fossilized fecal matter, of cricetid or hystricognath rodents and enable the detection of parasite eggs (Araújo *et al*. 1989, Sardella &Fugassa 2009b, Beltrame *et al*. 2010, Beltrame *et al*. 2013, Beltrame *et al.* 2016). In most cases, evidence of parasites consists of only eggs or remains of eggs, which hinders the identification of parasites to a species level. This is due to their degraded nature, morphological conservatism and the fact that most characters with which species-level identifications can be made are located in the body of the adult; thus, identification is possible only to the family level. When it is possible to make identifications to the species-level from eggs only, the identification of species is largely based on the presence of a known species of parasite infecting the same host in the same or closely related areas (Araújo *et al.* 1989; Sardella & Fugassa 2009a); however, this may vary depending on the level of uniqueness of the parasite host association (Hugot *et al*. 2014). The identification to the species level of the parasite eggs in related hosts presupposes the specificity of the parasite and assumes that coprolites from the Holocene do belong to the same species as those we detect in the present day. Available studies to date provide records for parasites of different lineages across the continent, and evidence of range contraction of some species of parasites. For example, the nematode *Paraspidodera uncinata*, is a common parasite of extant hystricognath rodents in Argentina, with the documented southernmost edge of their extant distribution located in the southern end of Buenos Aires province (Rossin *et al.* 2004). Eggs of this species have been detected in coprolites from Patagonia, 1,480 km from the nearest known extant locality for this species (Sardella & Fugassa 2009a). This finding would suggest that the species expanded southward some time in the past and experienced a population contraction that resulted in its disappearance from present day Patagonia.

Biogeographical interpretation of systematic appraisals

In the tradition of the study, description and characterization of monophyletic groups, several systematists have hypothesized the origin of certain families of parasites in taxonomic monographs. Among the lineages of nematodes that appear to be associated with cricetid rodents, three were used to formulate reconstructions of their biogeographic origin. These include nematodes of the Helligmonellidae, Spiruridae and Syphaciinae (Quentin 1969, Quentin 1971, Durette-Desset 1985, Hugot 1988). Species of these taxa are associated with cricetid rodents, which are an important faunal element of GABI, in that they apparently invaded South America from North America once, and their diversification into approximately 400 species accelerated since the Miocene (Parada *et al.* 2013). The taxonomic decisions and interpretation of the evolutionary relationships of Heligmonellidae, Spiruridae and pinworms of the subfamily Syphaciinae (Quentin 1969, Quentin 1971, Durette-Desset 1985, Hugot 1988), was influenced by their putative specificity to their hosts, most of which were known only from their original description. Based on the analysis of the putative sister clades available to the authors, these parasites were postulated to be host-specific and their origin was hypothesized to be in North America.

Nevertheless, instances of putative host switching were identified in the study of *Pterygodermatites*, a group of intestinal spirurioid nematodes with a life-cycle that definitively requires the involvement of an invertebrate intermediate host (Quentin 1969). Species of this genus can be allocated to at least three lineages, recognized as subgenera, the monophyly of each supported by the configuration of the buccal capsule and orientation of their stoma along with the peculiar arrangement of body spines (Quentin 1969), which are rather rare in nematodes. In particular, species of *Pterygodermatites* (*Paucipectines*) have been recorded from bats, cricetid rodents, sciurids, didelphid marsupials and xenarthrans (Quentin 1969, Navone 1987, Jiménez &Patterson 2012). According to the hypothesis of Quentin, two lineages within this clade spread through Siberia and North America, with the species in North America subsequently dispersing into South America with their cricetid rodent hosts and then undergoing a host-switch -dubbed “host capture” or *phénomène du capture*- by both marsupials and bats (Quentin 1969).

A similar pattern was described for trichostrongylid nematodes in Heligmonellidae, and it occurs in species of the Nippostrongylinae (Durette-Desset 1985), nematodes of direct life cycle that infect their host via skin penetration. In this case, the lineage of the cricetid-dwelling Nippostrongylinae would have originated with rodents dispersing from Asia into North America, and these subsequently dispersed into South America with their cricetid hosts. In contrast, Durette-Desset (1985) identifies that at least two lineages of trichostrongylid nematodes, the Anoplostrongylinae and Viannaiidae, may have originated in South America and moved northward. In the case of Anoplostrongylinae these nematodes would have dispersed with bats and armadillos, and in the case of Viannaiidae their dispersion would be linked to didelphid marsupials. Nevertheless, the northward dispersion of species of Viannaiidae resulted in the presence of three extant species in mammals north of the isthmus of Panama, which presents a stark contrast to the presence of over 60 named species of Nippostrongylinae present in South America (Durette-Desset 1985). This is consistent with the asymmetric distribution of the mammal fauna associated with GABI.

Lastly, in the systematic appraisal of the Syphacinae, Hugot (1988) highlighted the close affinity of members of *Syphacia* towards their hosts that consist of both arvicoline and cricetid rodents. These nematodes feature a direct life cycle and infection is attained through the ingestion of the eggs. Here again, the putative pronounced specificity of these pinworms towards their hosts and the current distribution of extant species in the New World were used as an argument to postulate the origin of this genus in the Palearctic, dispersion towards North America, and subsequent dispersion into South America.

Unfortunately, none of these three hypotheses presented above were produced using a phylogenetic framework that allowed testing ancestor/descendant relationships by means of a test of ancestral character reconstruction. Furthermore, there is little or no information relative to the geographic distribution and host associations of most species of parasites. Thus, the interpretations were based largely on the frequency of host-parasite associations. Which were documented based on the sporadic encounter of a population of parasites in a single individual host.

Experimental tests of host specificity

Since most of the species of parasites that infect mammals of GABI are known from the original description, the evidence for their host specificity -the number of species of vertebrates infected by a given parasite- is rare. In several instances, surveys of mammal fauna in defined regions facilitate the detection of frequency of the association of a species of parasite with one or more species of mammals (Guerrero 1985, Kinsella 1991, Navone *et al*. 2009, Notarnicola *et al*. 2010, Simões *et al*. 2010, Solórzano-García *et al*. 2016). Yet, experimental evidence of the host specificity of these parasites is scarce; most of the empirical evidence derives from the study of the low host-specificity of rodent-dwelling species of *Litomosoides*, which rely on some species of arthropod as a vector (Bain *et al*. 1989, Bain &Philipp 1991). Experiments on the specificity of the adults demonstrate that microfilaria of this vector borne nematode can cause infections on rodents of several unrelated lineages, and that in some cases, the immune response of these rodents needs to be challenged so the adults become established (Hawking & Burroughs 1946, Pringle & King 1968, Dhar & Singha 1971, Siddiqui & Kershaw 1976, Babayan *et al*. 2003). Their low specificity has been used to investigate the ability of the nematodes to circumvent the immune system of their novel hosts (Pringle & King 1968).

The reconstruction of ancestral states using statistical tests

Species in the genus *Litomosoides* are distributed from southern Mexico to northern Patagonia in Argentina and Chile, totaling 42 species parasitizing didelphiomorph marsupials, bats, sciurids, hystricomorph and myomorph rodents (Notarnicola *et al*. 2010). Apparently, the ancestor of this clade originated in bats from South America and they switched to cricetid rodents when these dispersed into the continent roughly 5 mya according to the estimate by Bain and Philipp (1991). This group of nematodes shows frequent host-switching and invasions of mammals of different lineages, including hystricognath rodents and didelphiomorph marsupials. The group was studied using a phylogenetic analysis of morphological characters that resulted in a non-resolved phylogeny (Brant & Gardner 2000). Using this cladogram, the authors did not find support for the hypothesis of an origin in bats, but in their reconstruction, the topology was consistent with the origin of the group in the area of South America.

Furthermore, in an analysis of the morphological traits derived mostly from original descriptions of species, Pérez-Ponce de León *et al.* (2000), reconstructed the phylogenetic relationships of several species of *Stilestrongylus*, a genus of cricetid-dwelling Nippostrongylinae that have a geographic range that includes southern North America, Central and South America. The phylogenetic and biogeographic analysis of the species of *Stilestrongylus* revealed that this genus is constituted by two lineages: A) one lineage represented by species of *Stilestrongylus* distributed in the northern Neotropical region west of the Andes, with a range extending from central Mexico, south to Colombia, and west of the Andes to Chile, and B) a second lineage formed by species distributed to the east of the Andes representing the southeastern Neotropical lineage (Peìrez-Ponce de Leoìn *et al.* 2000). This reconstruction reveals that sister-group relationships are better explained by geographic proximity rather than by taxonomic affinities with their hosts (Pérez-Ponce de León *et al.* 2000). These results are concordant with the origin and subsequent diversification of cricetid rodents in South America. In addition, new records for species of *Hassalstrongylus* and *Guerrerostrongylus* appear to contribute to this hypothesis (Digiani *et al.* 2015; Weirich *et al.* 2016), in that the majority of the species are present in defined biomes of the South American continent and the parasites are frequently found in unrelated species of cricetid rodents.

Additional phylogenetic reconstructions have relied on DNA to infer the relationships among parasites, and these phylogenies have served to test biogeographic scenarios and patterns of historical association (Jiménez-Ruiz *et al*. 2008; Jiménez *et al.* 2012; Jiménez *et al.* 2013). The analysis of the Aspidoderidae led to the discovery of two clades that concentrate the events of host switching. In the first place, there is a South American clade that includes parasites that switched from armadillos to cricetid rodents and didelphiomorph marsupials; and a second clade that includes parasites that switched from armadillos to hystricognaths and then to geomyid rodents. The same analysis reveals that at least five lineages of parasites crossed northward the Central American isthmus independently. These results are consistent with the expectations of a clade of parasites in which the descendants demonstrate phenotypic plasticity to use resources available in different hosts, as well as the ability to evade their hosts' immune response. This enabled parasites to increase their host range and to expand their geographic distribution as their hosts dispersed into new areas (Box 1).

There are two studies that concentrate on a fraction of species of parasites that infect mammals of GABI. On one hand, the reconstruction of characters for Viannaiidae, a group of nematodes that occur chiefly in didelphiomorph marsupials and some hystricognath rodents, suggests a South American origin of the marsupial-dwelling parasites and their subsequent dispersion into North America (Scheibel *et al.* 2014). On the other hand, studies on the genetic structure of species of *Trypanoxyuris* (pinworms of New World primates) north of the isthmus of Panama, have revealed the presence of at least five species of pinworms occurring in three species of monkeys (*Ateles geoffroyi*, *Allouata palliata* and *Allouata pigra*) (Solórzano-García *et al.* 2015, Solórzano-García *et al.* 2016). Studies on these two systems show the persistence of groups of parasites that predated the faunal exchange and have been able to disperse northward with varying levels of success in adaptive diversification. The analyses presented in these studies reveal some level of coevolutionary history between the parasites and their putative ancestral hosts.

Table 1 summarizes 9 host-parasite systems that involve faunal elements of GABI. In this table we identify 7 systems that relied on datasets that could be expanded to include new evidence in the form of taxa or characters. Additional taxa from a larger geographic scale may facilitate the test and reconstruction of macroevolutionary phenomena. Alternatively, incorporation of additional characters that facilitate the detection of population expansion or contraction may provide evidence of microevolutionary phenomena, including but not limited to ecological fitting, oscillations and taxon pulses.

Table1. Summary of historical associations among mammals involved in GABI and their parasites. The columns represent a summary of information available for a particular mammal - parasite system, which may allow the reconstruction of the evolution of these associations as part of the Stockholm Paradigm. Ecological Fitting (ecological specialists infect other hosts without prior evolution of novel host-use capabilities) and Oscillation (interspecific ecological associations involves increase of host-range and subsequent isolation) are microevolutionary phenomena. Because they involve speciation, the Geographic Mosaic of Evolution (emergence of specialists from generalists) and Taxon Pulses (species diversity results from alternating episodes of biotic expansion and isolation due to an episodic change) are macroevolutionary phenomena.

Group of parasites	**Recorded hosts in the New World**	**Reconstruction of Macroevolution**	**Methods allow to include new data**	**Explicit test of biogeographic affinity / historical associations**	**Evidence of Ecological Fitting**	**Evidence of Oscillation**	**Geographic Mosaic of Evolution**	**Evidence of Taxon Pulse**
Spirurata								
Pterygodermatites	Cricetid rodents, bats, sciurids, didelphiomorph marsupials	(Quentin 1969)	NO	NO	YES (available in Kinsella 1991)	NO	NO	NO
Litomosoides	Geomyid and cricetid rodents, bats, sciurids, didelphiomorph marsupials	(Brant & Gardner 2000)	YES	YES	YES (available in Notarnicola *et al*. 2010; Simões *et al*. 2011; Notarnicola *et al*. 2012)	YES (available in Hawking & Burroughs 1946)	NO	NO
Oxyurida								
Syphacinae	Arvicoline and cricetid rodents	(Hugot 1988)	YES	NO	YES (available in Simões *et al*. 2011)	NO	NO	NO
Helminthoxys	Hystricomorph rodents	(Hugot 2003)	YES	YES	NO	NO	NO	NO
Trypanoxyuris	New World Monkeys	(Hugot 1999)	YES	YES	NO	NO	NO	YES
Trypanoxyuris	New World Monkeys	(Solórzano-García *et al*. 2015; Solórzano-García *et al*. 2016)	YES	YES	YES	YES	NO	YES
Trichostrongyloidea								
Nippostrongylinae	Cricetid rodents	(Durette-Desset 1985)	NO	NO	NO	NO	NO	NO
Stilestrongylus	Cricetid rodents	(Pérez-Ponce de León *et al*. 2000)	YES	YES	YES (available in Simões *et al*. 2011)	NO	NO	NO
Viannaiidae	Didelphiomorph marsupials, Hystricognath rodents	(Scheibel *et al*.2014)	YES	NO	YES (available in Jiménez *et al*. 2011; Byles *et al*. 2013)	YES	NO	NO
Heterakoidea								
Aspidoderidae	Armadillos, Hystrocognath and cricetid rodents, didelphiomorph marsupials, geomyids	(Jiménez-Ruiz *et al*. 2008; Jiménez *et al*. 2012)	YES	YES	YES	YES	YES	NO
Paraspidodera	Hystricognath and Geomyid rodents	(Gardner 1991)	YES	YES	NO	NO	YES	YES

DISCUSSION

Future directions

The case of species of *Pterygodermatites* is interesting, since some species of this genus are known to occur in a variety of mammals (*P. peromysci* is present in different species of *Peromyscus* and *Neotoma; P. elegans* in bats and marsupials). However, there is no comprehensive analysis of the distribution of the several species present in South America, which is a necessary prerequisite to understand the role of Ecological Fitting and Oscillations in the consolidation of any association.

In the case of Syphacinae (pinworms), some studies have documented that a single species is able to infect several species of rodents. This is consistent with Ecological Fitting and has been documented in both North and South America (Kinsella 1991, Simões *et al.* 2011). However, observations derived from surveys of akodontine rodents in Argentina suggest that this phenomenon is not universal, because it appears that species-specific pinworms are present throughout the South Cone (Robles, 2010). Similarly, the members of Nippostrongylinae appear to show high host-specificity. Nevertheless, Oscillations and Ecological Fitting are documented for several species in the eastern portion of South America (Simões *et al*. 2011, Simões *et al.* 2012, Digiani & Durette-Desset 2014). The use of genetic markers may perhaps shed some light on the distribution of a single lineage of parasites in several species of rodents.

In the case of vector-transmitted parasites, five of the 27 species of *Litomosoides* parasitizing rodents and marsupials and three of the 15 species parasitizing bats appear to exhibit low host-specificity, *e.g. L. brasiliensis* is recorded from six host species, *L. navonae* in five host species, *L. pardinasi* in four host species (including *Rattus* sp.), *L. hoplomys*, *L. sigmodontis*, *L. chandleri* and *L. hamletti* in two host species each (Notarnicola *et al.* 2010, Simões *et al.* 2011, Notarnicola *et al.* 2012). The detection of Oscillations should be possible in this group, especially because it is made up of clades that feature putative high host-specificity and clades that exhibit low host-specificity.

The case of Aspidoderidae provides different tests on the micro- and macroevolutionary phenomena that have shaped this association. First, the association of *Paraspidodera uncinata* and *Ctenomys* spp. in Bolivia offers evidence of a very localized Geographic Mosaic of Coevolution. This is concordant with the geographic isolation of each of the populations included in the study (Gardner 1991). Second, there is evidence of the dispersion of these parasites from South into North America, and evidence of host switches that are a result of the Taxon Pulses combined with Oscillations suffered by these worms. Nevertheless, this evidence is not supported by exhaustive sampling of the genetic structure of members of closely related populations. This evidence awaits to be produced and tested in the proper theoretical framework.

Moreover, the recent description of the geographic and genetic structure of four species of pinworms in two different species of New World monkeys offers evidence of a Taxon Pulse, and Oscillation. This is mainly because the system originated in South America but the evidence used in the study is present north of the Central American isthmus.

Finally, the presence of preserved eggs of parasites in coprolites highlights the notion of sustained infections throughout geological time. One may argue that the vast majority of these records belong to a recent age (Holocene); however these records assist in detecting variations in the distribution of the parasites and their association with particular groups of rodents (Sardella & Fugassa 2009a).

The study of the genetic structure of parasites makes it possible to elucidate the role of parasites in GABI, not only as a proxy of diversification, but also as evidence of a variety of infective agents that challenge the hypervariable regions of the adaptive immune system. To this effect, the interaction between these hypervariable regions and the parasite diversity is yet to be shown in these systems. We recommend a parasite-centered approach, in which the genetic structure of the parasite is framed on its own geographic distribution and biotic associations. This evidence should be analyzed for the proper signs of population expansion and contraction that suggest switches in distribution and biotic interactions (in this case infections and new host-parasite associations). Finally, the specificity of the host parasite association and their coevolutionary associations should be experimentally tested whenever possible. Since this experimental evidence will allow to pinpoint the role of host phenotype and distribution in the determination of the parasitic association.

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