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Bibliography

Methods for detecting interactions between macroparasites with abundance data

Glossary

Introduction

What is macroparasitism?

Crofton (1971) defined macroparasitism as “an equilibrium between individuals hosts and their parasites based on evolutionary adaptation which, under real conditions, ensures continuity of the relationship by the survival of the unharmed host.”. Macroparasites regroup parasitic helminths and arthropods (Wilson et al. 2002).

Within wild ecosystems, there are numerous interactions between macroparasites and other organisms (hosts or other parasites) and their environment (Behnke 2008, Luttermann et al. 2015). Indeed, parasites are parcelled within hosts in infrapopulations and infracommunities (Bush and Holmes 1986, Bagge et al. 2005). This close relationship has then been a central point for researcher in macroparasitism.

Why is it important to analyse?

Macroparasitism is important to quantify the risks of infection and the intensity related to these risks. These risks can be determined in a wide range of populations. Veterinary or environmental studies often analyse risks within livestock such as the salmons against sea-lice (Krkosek et al. 2005) or wild animal communities such as wild rodents (Benhke 2008) or stray cats (Nursheena et al. 2013). Concerning medicine studies, they focus on human health risks (Bundy et al. 1988, Gurarie et al. 2010). A direct study on parasites is also possible to focus on one parasite species that is less specific of one order. For example parasitic helminths (MacDonald 1965, Bush and Holmes 1986, Poulin 2001) or ticks (Monello and Gompper 2007, Segura et al. 2018).

Once risks are quantified, parasitologists aim to model macroparasitism in order to control and manage efficiently these risks. According to the results, a strategy can be designed to control diseases or morbidity caused by macroparasitism within livestock (Morgan et al. 2014) or human populations (Gurarie et al. 2015, Gurarie et al. 2016).

Comparison with microparasitism

Studies on microparasitism is based on the number of individuals that are infected or not (Yakob et al. 2014). However, for macroparasitism studies have to focus on aggregation models. Indeed, host mortality and morbidity is dose-dependent and it is important to determine

not only if individuals are infected or not but also the intensity of this infection (Wilson et al. 2002).

Questions

The aim of this report is to determine the main issues of macroparasitism and then what are the main models to analyse them. Finally, what conclusion modelling has drawn from parasitology studies?

What are the main issues of macroparasitism?

The study of aggregation

Shaw and Dobson highlight macroparasite aggregation across a host population, with the majority of the parasite population concentrated into a minority of the host population (Shaw and Dobson 1995, Shaw et al. 1998). For example in human communities, less than 20% if individuals harbour 80% of the helminth parasite population (Wilson et al. 2002).

What are the patterns of macroparasite aggregation and how parasitologists model this phenomenon?

The study of heterogeneities

Heterogeneities is the variation between individuals in exposure to parasite infective stages and in susceptibility to infection when encountered (Isham 1995, Wilson et al. 2002). Heterogeneities are an important of observed aggregation patterns within a host community (Shaw and Dobson 1995). Numerous factors can induce changes in exposure to parasite or susceptibility to infection such as intrinsic factors (host age, sex, diet, genetic or acquired variation, immune resistance, social position) or environmental ones (variation in distribution of parasites in time or space, climate) (Shaw and Dobson 1995, Behnke 2008, Poulin 2012).

Which factors are the main causes of heterogeneities? What are the relationships between intensity of infection and these factors?

The study of interactions

Interactions can be between members of the same species (intraspecific) or between two populations of different species (interspecific). It has been demonstrated that intensity of infection and intra/inter-specific interactions are correlated (Simkova et al. 2001). Indeed, each

parasites can affect the host in different ways, what will also affect other co-infecting species throughout host immune system, pathology or nutrient/space limitation (Behnke 2008). Nevertheless, interactions are easy to observe in laboratory with controlled confounding factors but still difficult in natural ecosystems (Poulin 2001).

What are the possible interactions between host-parasites and between parasites themselves? What factors are influencing these interactions? What are the consequences in the intensity of infection?

How to analyse these issues?

Phenomenological model (statistics-based)

General method

Bliss and Fisher (1953) first popularized the Negative Binomial distribution fitting, which has been described as the most widely adaptable and generally useful method for analysing causes and consequences of aggregation. However, the most widely used method was described by Shaw and Dobson (1995). It consists in the analysis of two parameters of aggregation: the variance to mean ratio and the parameter k of the Negative Binomial distribution. The first one is analysed with a linear regression between the log-transformed mean and the log-transformed variance of parasite burden. The ratio is then compared to the mean/variance ratio of a Poisson distribution to determine if the parasite population is randomly distributed or aggregated within its host population. The second parameter of aggregation is obtained by fitting the log-transformed abundance data with a Negative Binomial distribution and use the parameter k (number of failure). This parameter is then inversely proportional to the degree of aggregation. Moreover, the 'tail' of the Negative Binomial distribution is a good representation of the most heavily infected individuals who is representing the less proportion of the population. Numerous factors can be taken into account into analyses to determine the influence of heterogeneities across host populations.

Interactions are more difficult to analyse, but some general methods are also used. The Levin's niche width is useful for studying interspecific occupancy of a niche while Ives intraspecific index aggregation is used for intraspecific ones. (Yves and May 1985, Simkova et al. 2001, Bagge et al. 2005). Moreover, cross-sectional studies are the main methods for analysing interspecific interactions but not for intraspecific ones (Luttermann et al. 2015).

Source of errors:

The statistics-based methods rely mainly on abundance data. Nevertheless, many errors can be made while collecting or analysing these data and this can affect the conclusions that has been drawn concerning macroparasitism (Wilson et al. 2002).

While collecting data, sampling methods can skew the statistics and misrepresent the population. Indeed, opportunistic methods and behavioural changes induced by parasitism can lead an over-representation of one category of the population, compared to another one (depending on age, sex, diet…). The specificity and sensitivity of the methods of counting have to be taking into account while sampling to determine with more precision the number and characteristics of parasites within their host (Wilson et al. 2002). Moreover, the sampling size has a significant effect on variability in mean host burden (Poulin 2013). That is why a large sampling size and with equal size across categories is necessary to avoid underestimation, a decrease in accuracy and approximations of the real population.

Many errors can also be done while analysing data. Statistical tests are very sensitive to pseudoreplication, when observations are dependent of each other's (spatial or temporal correlations). To avoid this errors, the sampling design is important, but during analysis, nested ANOVA or mixed models can overpass this (Paterson and Lello 2003). Poulin and Guégan (2000) use a phylogenetically independent contrast method to remove pseudoreplication from data. A wrong null model can also skew analysis of data. An appropriate null model has to be found to observe a departure and find the real cause of this departure (Poulin 2001). Finally, it is important to take into account the possible confounding factors into the model such as host age, predictable patterns of seasonal or spatial variation (Behnke 2008).

Limits

This phenomenological model has limitations. Indeed, fitting depends a lot on data: the Negative Binomial distribution is especially consistent for intermediate degree of aggregation (Gaba et al. 2005) and classical linear models fail to fit data to a normal distribution if population is highly aggregated of mean parasite load is low (Wilson et al. 1996). However, the main problem is the contested parameter k, which is hard to link with biological processes (Calabrese et al. 2011, Yakob et al. 2014) compared to mechanistic methods where we can express k or other parameters according to biological processes without losing important details (Kretzschmar 1993, Calabrese et al. 2011, Rabajante et al. 2020). Then, Rabajante et al. (2020) contest the a priori assumptions done by statistical tests such as independence of individuals.

Finally, the specificity and sensitivity of statistical tests where the null hypothesis can incorrectly be rejected or accepted can bring to false conclusions (Wilson et al. 1996, Wilson et al. 2002).

Alternatives

Thus, the use of the Negative Binomial distribution to fit the abundance data is more and more challenged (Gaba et al. 2005, Calabrese et al. 2011, Yakob et al. 2014, Rabajante et al. 2020). That is why other fits has been proposed: a Negative Binomial distribution but allowing k to vary with age (Quinnell et al. 1995), a Weibull distribution for heavily infected host and with a flexible 'tail' (Gaba et al. 2005) or a Normal distribution for low degrees of aggregation (Gaba et al. 2005).

The use of classical linear models is also challenged by parasitologists. Generalized linear models are an alternative to linear regression model without assuming normal data/error data distributions (Wilson et al. 1996, Wilson and Grenfell 1997, Jackson and Tinsley 2003, Luong et al. 2011). Mixed models are more and more used across modern studies. They allow understanding the causes and consequences of variability between hosts and their susceptibility/exposure to infection by avoiding pseudoreplication and allowing adding random effects specific to each group of observation (Paterson and Lello 2003, Luong et al. 2011, Krkosek et al. 2012, Poulin 2013, Luttermann et al. 2015). Then, Shaw and Dobson (1995) use tree-based models as a graphical alternative to linear regression and generalized linear models. It is a binary division of data into categories with an automatic selection of the most important predictor. According to Wilson et al. (2002), it is easy to interpret, it handles missing data better and it captures non-additive behaviour and multiplicative interactions.

Overwhelming majority use both parameters described by Shaw and Dobson (1995) but other studies tried to search other indexes of aggregation. Lloyd (1967) has presented the index of mean crowding of Patchiness and Poulin (1993) the index of discrepancy D. Nevertheless, statistic models still opt for the Show and Dobson's ones.

Mechanistic model (mathematics-based)

Mathematical models focus on elucidation of principles rather than exact predictions, compared to statistical ones (Cornell 2005). Nevertheless, mechanistic models are very few compared to phenomenological ones (Rabajante et al. 2020).

Methods

Anderson and May (1978) described the more common mathematical infinite model of macroparasites interactions with host as differential equations. This work is the starting point of mathematical models of macroparasitism and many different models derivate from this latter.

Some models mix mechanistic and phenomenological (mathematics and statistics based). Calabrese et al. (2011) built a Poisson-Gamma mixture model with a simple tick accumulation model with Gamma distribution of the estimation of intrinsic and extrinsic host's variables. A Negative Normal distribution was used to fit to this modelled data. Morrill et al. (2017) used a parasites-centric model with one population of host infected by more than one parasite species and fitted data with a Negative Normal distribution.

Nevertheless, mathematics-statistics mixed models are not very common because works based on mathematical models often questioned the statistics used to analyse aggregation. Thus, many models are principally constructed to replace the Negative Binomial distribution while fitting data. Indeed, they try to find a model that fit optimally with abundance data. The bottom-up models are the more common used model for a mechanistic point of view. It exists models that are similar to Anderson and May's one (1978) by modelling parasite and host abundance with mathematical equations. Isham (1995) has constructed a model based on the effect of immunity in macroparasites-host interactions, adding an age component. Frazer (2008) took into account the host mortality, lice clumping and macro-stages in its sea-lice abundance model, and sea-lice induce increasing host mortality. However, other studies has focused on modelling the number of parasites that each hosts harbour. Gurarie et al. (2010, 2015, 2016) modelled a stratified worm burden with age-structured communities, geographically distributed and adding biological components) into a population strata. This model is based on the mean worm burden model of MacDonald (1965). Finally, a very recent study by Rabajante et al. (2020) model each class of host that harbour at least i parasites ($0 \leq i < +\infty$). The infection parameter is a probability of being in one class, easy to calculate with abundance data and which is linked with biological processes.

Individual based models have recently seen its popularity rise since computers can resolve very important and heavy mathematical problems. These models trace the birth and death of individuals with biological components, roaming into a specify environment and allowing each other to interact (Cornell 2005).

Limits

However, mechanistic models have limits. It is still hard to find a general mathematical approach for all systems (Rabajante et al. 2020). Despite the fact that mathematical model can link with biological process, it requires a fine balance between biological and mathematical tractability (Cornell 2005). It can be very difficult to compute these infinite models and solve them: statistical one are an issue to simplify them (Anderson and May 1978, Kretzschmar 1993). Then, in many models, there is a parameter Beta for identifying the strength of infection. It could be hard to choose the best value for this parameter, even with data (McCallum et al. 2017, Rabajante et al. 2020). Thus, for Cornell (2005), mathematical models are more illustrative than predictive and there is so a lack of confidence over these models.

Other model

Pedersen and Fenton (2007) proposed to inspire from ecology models and apply them to parasitology. They proposed to expend from one-host-one-pathogen to multi-host-multi-parasite communities. Thus, many ecology-inspired models are reproducible such as network of interactions (trophic networks), scale-free networks, community stability and perturbations, tool predictors (CVA, strength estimators, loop analysis, Fuzzy cognitive maps).

Conclusions on these analyses

Aggregation

Shaw and Dobson (1995) demonstrated, confirmed by Poulin (2013), that mean parasite burden explains 87% of the variability in burden between hosts. Poulin (2013) tried to search for the 13% left of the variability and found that in this 13% left, 8% of the variability was due to sampling efforts (sampling size) and 65% by random effects (species-specific or study-specific) idiosyncrasies (unique behaviour of an individual). Nevertheless, 3% of the total variability still unexplained.

Bagge et al. (2005) hypothesized that aggregation of parasites of crucian carp is first a stochastic event of attachment on a gill arch and after positive intra-specific interactions result in a move of parasite towards conspecifics individuals. However, a random distribution of parasites within their host population is possible, for example the parasite *Pterygodermatites peromysci*. This parasite cannot be aggregated within white-footed mouse population because the prevalence of infection is density-dependent. The parasite load is capped at a very low level, with very little variation.

Heterogeneities

Heterogeneities is the variation between individuals in exposure to parasite and susceptibility to infection. In absence of heterogeneities in exposure, even a small difference in susceptibility can produce non-random distribution (Wilson et al. 2002).

First, susceptibility to infection is highly affect by host age. Indeed, there is a tight relationship between abundance and host age (Monello and Gompper 2007, Nursheena et al. 2013, Segura et al. 2018, Nielsen et al. 2020). There is different patterns of age-infection curve (Figure 1). The type I curve (linear increasing of parasite load with age) occurs when there is no transmission and no reproduction within host and parasites are acquired from the environment while the type II curve (increasing towards an asymptote) is drawn when the rates of parasite acquisition and parasite mortality are constant (the ratio determine the asymptote) (Wilson et al. 2002). Then, the type III curve (convex age-intensity curve) is due to acquired immunity, age-related changes (in predisposition to infection, exposure to parasite), death of heavily parasitized hosts or age-dependent of sampling methods (into faecal eggs) (Wilson et al. 2002, Monello and Gompper 2007, Segura et al. 2018). The first pattern is rarely observed in wild systems, but the type II and III curves are widely observed, the latter depending a lot on characteristics of host-parasites system (Nielsen et al. 2020). Many convex age-intensity curve has been studied (Bundy et al. 1988, Cattadori et al. 2005, Monello and Gompper 2007, Lello et al. 2018, Nielsen et al. 2020). Woolhouse (1998) described the peak shift of this pattern and Park and Ezenwa (2019) have created a model to generate a convex curve with the force of infection and the clearance rate depending on age. Then, there is also a significant relationship between abundance and sex (Monello and Gompper 2007, Segura et al. 2018, Nielsen et al. 2020) where male infection are more important than female one (Wilson et al. 2002, Segura et al. 2018). This difference between males and females can be explained by ecological and physiological differences (Wilson et al. 2002) or by a hormone-linked suppression of the immune system among breeding males (Nielsen et al. 2020). Moreover, the host genetics also affects host's susceptibility to infection. Indeed, the loss of heterozygosity induces a reduction in parasite resistance (Wilson et al. 2002). The concept of the Red Queen between hosts and parasites is also applicable to parasitology (Wilson et al. 2002). Karnoven et al. (2004) observed that fishes developed resistance to infection after repeated exposure.

Secondly, heterogeneities can be caused by a variation in exposure to infection. The host body characteristics, especially the body size, are correlated with prevalence and intensity of infection. Poulin (1999) observed, for endoparasitic helminths, a positive relationship with

prevalence and a negative one with intensity. In like manner, he determined a positive relationship for both intensity and prevalence in ectoparasitic copepods. Then, external heterogeneities like the spatial distribution of external stages, the seasonality or the environment (temperature, humidity) can bring to variation in exposure (Wilson et al. 2002).

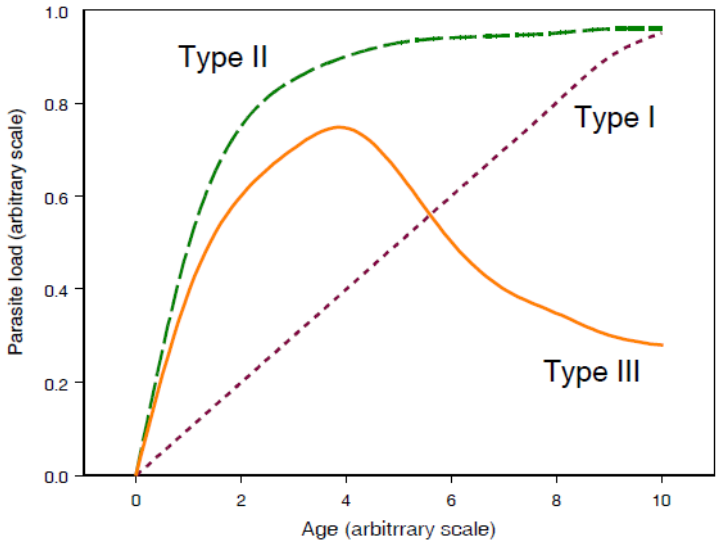

Figure 1: different age-intensity patterns (Wilson et al. 2002)

Interactions

Morrill et al. (2017) have demonstrated that aggregation increases the probability of parasitizing by the same species (conspecific) but decreases the probability, intensity and diversity of heterospecifics depending on the mean abundance. Some patterns within parasite infracommunities have been drawn such as nestedness or anti-nestedness (parasite species are always present/absent from infracommunities richer than the most depauperate one) (Poulin and Guégan 2000). However, broad generalization on interactions among or within species are difficult to predict, so case-by-case studies have to be conducted (Poulin 2001). Behnke (2008) has seen a robust significant relationship between H. polygyrus and the species richness of other helminths in wood mice, which demonstrates interspecific interactions.

Many studies have shown an intra-specific density-dependence within a parasite infrapopulation. Aggregation and high densities could increase interactions between conspecifics positively (mate finding or cross-fertilization) or negatively (competition) (Bagge et al. 2005). Indeed, Allee effect could monitor parasite abundance (Krkosek et al. 2012) and Simkova et al. (2001) stated that aggregation brings evolutionary advantages by increasing the survivorship of the group or the reproductive success of individuals. Aggregation can also

facilitate subsequent attacks within some mite species but there is a strong variation between species (Krasnov et al. 2009). However, negative intraspecific interactions are also possible within species, especially throughout competition (Monello and Gompper 2007). Thera are direct intraspecific competition for space (realised niche) and resources and indirect competition mediated by host immune response (Jackson and Tinsley 2003, Luong et al. 2011). Space restriction is in general more severe among large-bodied parasites (Poulin and Morand 2000). However, for the crucean carp, Simkova et al. (2001) hypothesize that intraspecific competition for space was not a limiting factor for niche distribution of parasites among gill arches. Positive interactions are more important than negative ones (Bagge et al. 2005).

Conclusion

The study of macroparasitism is a key point for scientists to control and manage parasitic-caused diseases. Aggregation, heterogeneities and interactions are the main issues. Many different models exist to explore these issues but there still have no consensus between deterministic and phenomenological modelling. Mathematical models are used to elucidate principles whereas statistical ones are more efficient for precise predictions (Cornell 2005). However, statistical models such as mathematical ones try to find an “ecological law” for studying macro-parasitism and apply it to fit to all systems (Rabajante et al. 2020).

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