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SYMPOSIUM

Host Competence: An Organismal Trait to Integrate Immunology and Epidemiology

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Synopsis The new fields of ecological immunology and disease ecology have begun to merge, and the classic fields of immunology and epidemiology are beginning to blend with them. This merger is occurring because the integrative study of host–parasite interactions is providing insights into disease in ways that traditional methods have not. With the advent of new tools, mathematical and technological, we could be on the verge of developing a unified theory of infectious disease, one that supersedes the barriers of jargon and tradition. Here we argue that a cornerstone of any such synthesis will be host competence, the propensity of an individual host to generate new infections in other susceptible hosts. In the last few years, the emergence of systems immunology has led to novel insight into how hosts control or eliminate pathogens. Most such efforts have stopped short of considering transmission and the requisite behaviors of infected individuals that mediate it, and few have explicitly incorporated ecological and evolutionary principles. Ultimately though, we expect that the use of a systems immunology perspective will help link suborganismal processes (i.e., health of hosts and selection on genes) to superorganismal outcomes (i.e., community-level disease dynamics and host–parasite coevolution). Recently, physiological regulatory networks (PRNs) were cast as whole-organism regulatory systems that mediate homeostasis and hence link suborganismal processes with the fitness of individuals. Here, we use the PRN construct to develop a roadmap for studying host competence, taking guidance from systems immunology and evolutionary ecology research. We argue that PRN variation underlies heterogeneity in individual host competence and hence host–parasite dynamics.

> "Models are where the theoretical rubber meets the empirical road"—Zamer and Scheiner (2014).

Introduction

For most of its history, immunology has favored reductionism over holism, conceiving host defenses as decomposable, linear processes. This directive probably persisted because reductionism was so successful, providing such strong causal inference. Reductionism, while unquestionably valuable, has at least two limitations (Kohl et al. 2010; Yuste 2015). First, reductionism misses that many infections are of importance to the whole organism, not just the cells and tissues proximal to the problem. Indeed, many infections have implications for host reproduction, social behavior, and other traits (Sheldon and Verhulst 1996; Martin et al. 2008), but these effects have only recently gained attention. The second limitation of reductionism is that it rarely leads to generalizations. Systems immunology, by contrast, uses -omics approaches to capture the complexity of immune responses (Zak and Aderem 2009; Shapira and Hacohen 2011; Diercks and Aderem 2013). Such holistic research is poised to change our understanding of host–parasite interactions because no longer are we constrained to study just a few cells or proteins, which is especially limiting when novel host–parasite interactions are of interest (Adelman 2014; Jackson 2015). Indeed, we can now collect data on processes we might never have thought to consider from a purely reductionist

perspective. Right now though, the strength of systems approaches lie in their ability to generate and describe large datasets (Kohl et al. 2010). Rarely have they instigated *a priori* hypothesis testing, and when they were used to guide research programs, most such work minimally involved ecology and evolution (Li et al. 2011; Arazi et al. 2013).

By contrast, many evolutionary biologists have asked, with little emphasis on mechanistic details, i) how mobilization of resources can help combat infections (Shudo and Iwasa 2001, 2002), ii) how body size constrains defense architectures (Cohn and Langman 1990; Wiegel and Perelson 2004; Savage et al. 2007), iii) how host life history strategies shape immune defenses (Lee 2006; Martin et al. 2007), and iv) how collateral damage selects for optimal, not maximal, immunity (Graham 2002; Graham et al. 2005). Because those studies typically caricaturize the immune system, it is not always obvious how they feed into basic immunology. Many have claimed that it will be beneficial to merge eco-evolutionary ideas with the tools of systems immunology (Turner and Paterson 2013; Jackson 2015), but we as yet lack a way to do so, particularly one amenable to the diverse hosts that circulate parasites in natural communities (Downs et al. 2014). An immediate benefit of such an approach would be that immunology and epidemiology become unified. Because the former has tended to focus on individual host health and the latter is directed at understanding the movement of parasites through communities, both have developed their own lexicons and research agendas. Beyond vaccination immunology and a few, more recent efforts (Ezenwa and Jolles 2015; Handel and Rohani 2015; VanderWaal and Ezenwa 2016; Vazquez-Prokopec et al. 2016), cross-talk between epidemiology and immunology is just beginning.

One concept that has fostered such cross-talk is parasite tolerance (Raberg et al. 2007). Parasite tolerance, distinct from the concept of self-antigen tolerance (Medzhitov et al. 2012), is a host defense strategy whereby hosts cope with the effects of parasites on health or fitness, not parasite burden itself. Tolerant hosts cope well with even high parasite burdens whereas intolerant individuals suffer even with low burdens (Jackson et al. 2014; Råberg 2014). Tolerant hosts might be much more common than we currently recognize, as emphasized by the moniker "reservoir species," which recognizes hosts that carry parasites but seem to suffer little from them. Critically, these and other tolerant hosts might be threatening to other hosts (Guivier et al. 2014), especially if their high tolerance is correlated to their ability to amplify and/or transmit parasites (Tompkins et al. 2011; Barron et al. 2015; VanderWaal and Ezenwa 2016). Historically, so much immunological research has focused on understanding the reduction of parasite burden even though parasite eradication seems to have rarely been an evolutionary solution to infection (Stearns and Koella 2007). A concerted focus on parasite tolerance might provide us novel and even more practical methods of disease mitigation (Venesky et al. 2012).

In the present paper, we describe a generic approach to characterizing host competence that merges the tools of systems immunology with the conceptual foundations of ecology and evolution. We define host competence as the ability of a host to transmit parasites such that they effectively infect another host or vector. We focus on this trait because it links what happens inside a host to what happens among hosts in a community (Gervasi et al. 2015). Most disease researchers have some explicit or implicit interest in host competence. In fact, heterogeneity in aspects of host competence has been characterized and its implications mapped on higher biological scales (Paull et al. 2011). So far though, we still lack a measureable trait that captures accurately host competence. We propose a physiological regulatory network (PRN) framework to serve this task (Cohen et al. 2012a; Martin and Cohen 2014). The advantage of the PRN perspective is that it will be informative to biologists interested in any host–parasite system at any level of analysis (Downs et al. 2014), yet we make our case here using West Nile virus (WNV) as an example, as it is a system of substantial consequence for humans and wildlife (Marra et al. 2004; Kilpatrick et al. 2007; LaDeau et al. 2007).

Defining host competence

Heterogeneity in host competence occurs across genotypes, individuals, populations, and even species (Paull et al. 2011; Gervasi et al. 2015). At the species level, the competence of the white-footed mouse (*Peromyscus leucopus*) for nymphal ticks infected with *Borrelia burgdorferi* bacteria partly explains Lyme disease dynamics in rural parts of New York state (Brunner et al. 2008; Ostfeld et al. 2014). Around Washington, DC, the competence of American Robins (*Turdus migratorius*) for attracting the bites of *Culex* sp. mosquitoes is a major explanatory factor in the spatiotemporal cycles of WNV (Kilpatrick et al. 2006a, 2006b). At the level of individuals, heterogeneity in competence also affects

disease dynamics (McDade 2005; Quintana-Murci and Clark 2013). Broad differences in individual behavior and physiology influence exposure to and subsequent burden and transmission of various parasites (Ferrari et al. 2004; Beldomenico and Begon 2010; Hawley and Altizer 2011). Variation in individual competence is also thought to explain partly why parasite prevalence varies over space and time in so many populations and species (Hawley et al. 2011; Coon et al. 2014). Most relevant to the remainder of this paper, variation in individual competence is the basis of the 20:80 rule (Woolhouse et al. 1997), which highlights that 80% of infections are caused by 20% of members of a host population. In general, host infectiousness is rarely randomly distributed (Lloyd-Smith et al. 2005); some hosts are disproportionately responsible for transmission for parasites with diverse life histories, transmission modes, and evolutionary legacies. Consider for example Mary Mallon, a cook in New York City around 1906 (Soper 1939) who was responsible for numerous cases of typhoid fever but suffered little herself from the bacterium. Superspreaders such as Mallon are implicated in multiple microparasite disease systems (e.g., SARS, HIV, influenza). Many macroparasites (e.g., ticks and helminths) exhibit aggregated distributions among individual hosts, suggesting similar superspreading dynamics (Lloyd-Smith et al. 2005). Super-receivers, animals more likely to contract infections (Hamede et al. 2013; Adelman et al. 2015), are also being discovered, and these individuals too might have important impacts on disease dynamics (Raffel et al. 2008). Overall, individual heterogeneity in host competence appears to be a key trait to understanding the ecology and evolution of host–parasite interactions.

Host competence and PRNs

Heterogeneity in host competence can take many forms and hence contribute to disease dynamics by many pathways (e.g., death, immune memory, parasite shedding, attractiveness/value to vectors) (Hawley et al. 2011; Barron et al. 2015). Broadly, host competence can be split into two parts: behavioral and physiological. Although behavioral aspects will no doubt be critical to understanding competence, and physiological and behavioral elements of competence are apt to covary in important ways (Korte et al. 2005; Hawley et al. 2011), due to space constraints, we do not discuss the behavioral dimensions of host competence here. We instead refer readers to recent papers on the topic (Barber and Dingemanse 2010; Hawley and Altizer 2011; Barron et al. 2015). We focus here on the physiological basis of competence. If parasites cannot overcome defensive barriers and infiltrate the appropriate tissue or cell, or if hosts die before they can transmit a parasite to a new host, hosts are by definition incompetent. The more interesting hosts to consider, then, are those that vary in the propensity to pass parasites to other susceptible hosts and vectors when such opportunities arise.

The immune system is an obvious and likely critical aspect of host competence. However, many other systems will be important too. Reproductive hormones can suppress immunity (Foo et al. 2016), the nervous and endocrine system are intimately intertwined with lymphoid cells and tissues (Demas et al. 2011), and food amount and nutrient composition can strongly shape a host's defense portfolio (Klasing 2007). In other words, host competence is probably best understood as an integrated, organismal trait directed at maximizing host reproductive fitness (Martin et al. 2014), not just the outcome of weak immune functions. In the last 15 years, systems immunology (Kohl et al. 2010) has allowed us to start capturing the complexity inherent to such a trait, and another field, psychoneuroimmunology (PNI), has already been studying host defenses as integrated traits. To date though, PNI has attended mostly to non-infectious (or not obviously infectious) diseases such as depression and anxiety-like disorders (Bilbo et al. 2008; Galic et al. 2009). Among the PNI studies that have focused on viral and bacterial infections, most have stopped at the level of individual health (Bailey et al. 2003, 2009). Only a handful has considered how neuroendocrine-immune interactions might impact parasite transmission (Cohen and Hamrick 2003; Cohen et al. 2012b). However, as the few collaborations among traditional, PNI, and eco-evolutionary immunologists have been fruitful (Ferreira et al. 2011; Medzhitov et al. 2012; Brock et al. 2014; Regoes et al. 2014; Torres et al. 2016), it would likely be very valuable to develop a measureable form of competence, amenable to the interests of biologists working at different levels. Such was partly the motivation developing PRN theory (Martin et al. 2011; Cohen et al. 2012a; Martin and Cohen 2014).

PRN theory takes lessons from realms of biology that demonstrably have dealt well with complexity: community ecology and gene network biology. These disciplines recognize that epistasis and species interactions play strong roles in i) phenotypic variation and ii) community stability and productivity, respectively. What is unique about these fields is that the above effects (items i and ii) are not expected to be

decomposable to network components. Indeed, these traits are understood as emergent properties of networks. In the case of host competence then, variation at higher biological levels (i.e., cells, tissues, and whole organisms) arises from quantitative variation among nodes (e.g., cytokines, chemokines, steroids, various receptors), but especially direct and indirect interactions (edges) among nodes (Fig. 1). Other bionetworks, natural communities of plants and animals (Dunne et al. 2002) and gene networks (Wagner et al. 2007), exhibit power-law distributions in node connectivity. This means that if PRNs resemble other bionetworks, they might be more empirically tractable than they at first would seem. Indeed, a concerted focus on particular PRN molecules (i.e., date hubs or integrators; Fig. 1) and their linkages might be a good place to start learning about the mechanistic basis of host competence. Even though whole-organism traits will often be emergent, high connectivity of some nodes suggests that some molecules might act at the level of whole organisms as master regulatory genes (e.g., *Hox*) do within gene regulatory networks (Martin et al. 2011).

PRN theory also takes guidance from behavioral and evolutionary endocrinology (Sinervo and Calsbeek 2003; McGlothlin and Ketterson 2008; Wingfield 2013). For years, those fields have emphasized that some steroids and other hormones can act as physiological "keystone" molecules (Wagner et al. 2007). Such date hubs are highly connected to other nodes and thus might play particularly integral roles in regulating developmental plasticity and phenotypic flexibility (Martin et al. 2011). By contrast, other PRN nodes are highly connected but only locally (party hubs), coordinating small-scale functions. Yet other PRN nodes are minimally connected and predominantly perform physiological work. Digestive enzymes, heat shock proteins, and other active molecules fall into this group. From an immunological perspective, additional PRN nodes serve as detectors of threats (e.g., Toll-like receptors) and effectors of parasite control (e.g., antimicrobial peptides, acute phase proteins) and collateral damage, healing and recovery mitigators (e.g., antioxidants, clotting factors) (Medzhitov 2008).

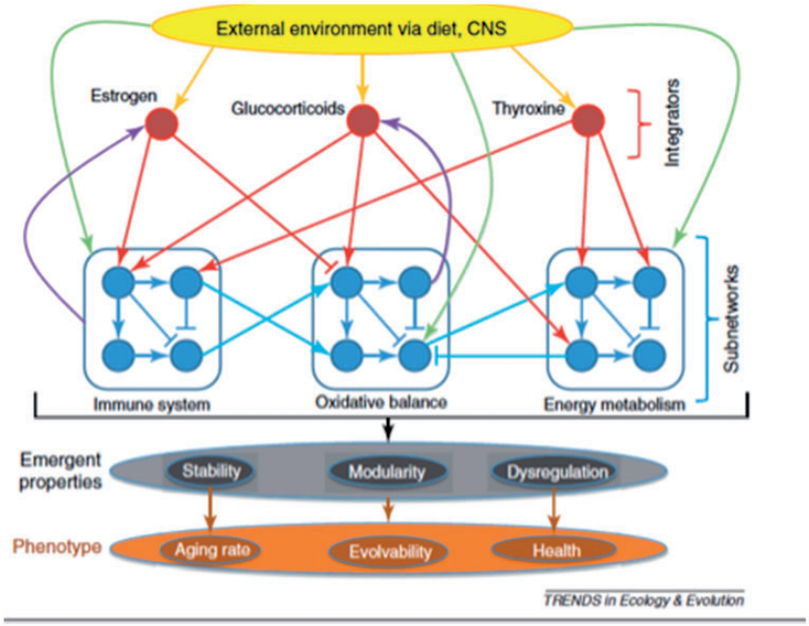

Fig. 1 A simplified, partial schematic of physiological regulatory network (PRN). Red arrows indicate top-down control, such as steroid hormone modulation of immune function. Purple arrows indicate feedback effects such as antioxidant effects of glucocorticoids. Light blue arrows indicate direct interactions among subnetworks, yellow arrows indicate environmental regulation of integrators, usually via the central nervous system (CNS). System-level properties of the PRN exist at different levels, including state within individuals (e.g., dysregulation) and species-level structure (modularity). Likewise, phenotype can include individual—or species-level traits (e.g., health and evolvability, respectively). Modularity is determined by the proportion of potential light-blue arrows present; interconnectedness by the total number of arrows relative to molecules; and robustness by the density of purple arrows resulting in negative feedback effects. Temporal dynamics and metabolite flux (not shown) can also be important determinations of system-level properties, such as dysregulation. The particular structure of connections, as well as their strengths and interactions, will determine how the PRN responds at an individual level and evolves at the species level in response to a changing environment.

For the PRN construct to be a useful measure of host competence, another currently understudied phenomenon must also be addressed: plasticity. Plasticity in competence can alter the contributions of hosts to community disease dynamics to a similar degree as better-studied ecological drivers such as host density and diversity (Gervasi et al. 2015). Whereas systems immunology approaches have the potential to describe plasticity simply by repeated sampling across contexts, they have rarely done so. There are experimental and statistical approaches available for generating representative datasets across many tissues and relevant environmental gradients, but the financial challenges of such work are large (Li et al. 2011; Qu et al. 2011; Williams et al. 2011; Cohen et al. 2013). Perhaps by attending more to the details of a host–parasite system of interest, studies of plasticity could be limited to the particular set of factors that have impacted natural populations the most for the longest time. For instance, hosts living at high latitudes face more diverse and more consistent infection threats across the year than hosts living at tropical latitudes (Guernier et al. 2004). Similarly, small hosts face different parasite challenges than big ones (Dobson and Hudson 1986), and males and females of the same species are differently likely to encounter parasites and differently abled to deal with them (Nunn et al. 2009). PRN theory accommodates well these observations and could help guide the incorporation of plasticity into systems immunology.

An "eco-systems" perspective on WNV competence

As an example of the promise of merging PRN theory and systems immunology, consider vertebrate interactions with WNV. WNV is a vector-borne zoonosis of the genus, *Flaviviridae*, that has spread to six continents since its identification nearly 80 years ago (Kramer et al. 2007). The transmission cycle typically occurs among various passerines and *Culex* spp. mosquito vectors (Kramer et al. 2007), yet WNV also poses a significant threat to humans and horses in the form of West Nile fever and encephalitis. Incompetent hosts, including humans, some birds, and many other vertebrate species become infected but not infectious when exposed to WNV, maintaining titers below the critical minimum threshold to facilitate transmission to vectors (Komar et al. 2003). Competent hosts, by contrast, amplify virus to sufficient levels to pass it to susceptible mosquitoes (Kramer et al. 2007). In domesticated mice, following inoculation via mosquito bite, WNV initially replicates in dendritic Langerhans cells before migrating to lymph nodes for further replication (Johnston et al. 2000; Byrne et al. 2001; Lim et al. 2011). The virus then disseminates to peripheral tissues (e.g., spleen), where additional replication occurs (Suthar et al. 2013). In individuals with high viremia, the virus may cross the blood–brain barrier to infect the central nervous system (Samuel and Diamond 2006), sometimes having pathogenic effects (Suthar and Pulendran 2014).

A fuller understanding of WNV competence will require much more work in birds, asking whether the above domesticated mice research represents well naturally competent hosts (Babayan et al. 2011; Maizels and Nussey 2013). So far, very little avian WNV immunology has occurred (Pérez-Ramírez et al. 2014), and the majority involves immunoglobulin responses, which are not obviously relevant to the framework discussed here. Still, high-throughput, systems-level research on model organisms and humans has been useful to understanding infection by and dissemination of many viruses (Suthar and Pulendran 2014). Few so far have focused on WNV though. In one such study, gene expression was compared between human patients that had previously experienced severe or asymptomatic infections (Qian et al. 2015). A WNV susceptibility signature was developed using a combination of microarray and Deconvolution analyses and Nanostring gene expression. Variation in the expression of a few genes characterized a WNV-susceptible profile (Qian et al. 2015). A second study sought to identify the role of specific innate immune responses in controlling WNV infection and tissue tropism in mice (Suthar et al. 2013). Through a series of comparative survival and viral burden analyses, whole-genome microarrays, and bioinformatics in wild-type and immunologically suppressed (via gene knock-out) animals, a network of immune genes was discovered. Intriguingly, this network also regulated WNV replication and spleen and liver tropism (Suthar et al. 2013), important aspects of host competence. In light of these advances as well as other shortcomings of current research approaches (i.e., little consideration of network plasticity), we advocate that future WNV systems immunology focus particularly on PRN date hubs, as these nodes interlink PRN subnetworks and thus coordinate organismal responses to similar risks and opportunities (Martin and Cohen 2014).

Many date hubs warrant attention, but here we focus on the role of glucocorticoids (namely cortisol and corticosterone [CORT]) as host competence date hubs because these steroids have extensive effects on

vertebrate immunity (Martin 2009); long-term elevations tend to enhance susceptibility to and mortality from many infections (Sapolsky et al. 2000) whereas short-term CORT elevations can be protective (Dhabhar 2009). CORT also affects host growth (Hull et al. 2007), cognition (Schoech et al. 2011), reproduction (Wingfield and Sapolsky 2003), and various behaviors (Martins et al. 2007), implicating them as major drivers of heterogeneity in host competence because of their impacts on so many organismal processes. As just one example, consider the tendency for CORT to damp inflammation. These effects protect hosts from over-zealousness of the innate immune system (Råberg et al. 1998; Sapolsky et al. 2000). Whereas some hosts might still die from infection (Warne et al. 2011), other hosts might cope reasonably well with infection and high CORT (Sternberg 2006).

Still, we know little as yet about the role of CORT in host competence in the animals with the propensity to circulate it in the wild. In one study, WNV-exposed Northern Cardinals (*Cardinalis cardinalis*) experimentally implanted with CORT exhibited greater mortality than controls although there was no difference in viral burden (Owen et al. 2012). Another study found that CORT-manipulated domesticated chickens (*Gallus gallus*) shed more virus for longer and had higher antibody titers than controls (Jankowski et al. 2010). In mice, multiple stressors elevated CORT, or CORT was surgically elevated, which increased permeability of the blood–brain barrier, allowing easier entry of attenuated WNV and subsequently more risk of neuropathological death (Ben-Nathan 2013). We have no such data for avian species even though many seem to die from similar pathology. We expect that these studies have just scratched the surface to revealing the role of CORT in WNV dynamics. Unsurprisingly, there is a growing interest in CORT as a mediator of wildlife responses to anthropogenic effects such as climate change, pollution, and urbanization (Martin et al. 2010). Many of these conditions alter community-level disease risk, and it is plausible that some such effects arise because of the effects of CORT on host competence (Martin and Boruta 2014). Presently, we do not yet know how CORT affects interactions among susceptible and infected hosts and vectors, nor do we know much about how CORT affects host propensity to transmit WNV. Altered CORT regulation could change PRN configurations and thus lead some hosts to impose greater risk on other susceptible individuals by passing more parasites for longer to their habitats, conspecifics, or vectors (Cohen et al. 2012b), but this hypothesis remains to be tested.

Besides CORT, some cytokines are implicated as date hubs for WNV competence. Many cell types produce interferons in response to viral infections (Samuel and Diamond 2006). Type I interferons mediate innate and adaptive immune responses through the actions of interferon stimulated response elements (ISREs), antiviral interferon stimulated genes (ISGs; e.g., protein kinase R [PKR]), and T- and B-lymphocytes (Samuel and Diamond 2006). Mice deficient in IFN-γ (IFN-$\gamma^{-/-}$), a type II interferon, experienced greater mortality, higher viremia, and faster dissemination of WNV to peripheral and central nervous tissues (Shrestha et al. 2006). Type I interferons (IFN-α/β) display similar effects: WNV-exposed IFN-α/βR$^{-/-}$ mice had higher mortality and altered tissue tropism compared with wild-type mice (Samuel et al. 2005). Critically, interferons and another putative cytokine date hub, interleukin (IL)-1β, affect the ability of the immune system to control WNV (Ramos et al. 2012). These cytokines also impact reproductive, behavioral, and other host processes (Galic et al. 2009), and as with CORT, these putative date hubs, as well as IL-6 (Hunter and Jones 2015), would be great starting points for research on PRNs and host competence for WNV (Weil et al. 2006; Adelman and Martin 2009).

Host competence as an emergent property

CORT, IFNs, and other date hubs help regulate host responses to WNV by recruiting and coordinating various subnetworks and thus mediating changes in host phenotype. It is therefore probably the state of the collective PRN, not single nodes, that underlies organismal resistance, tolerance, and competence for parasites (Martin et al. 2011). Figure 2 depicts a very simplified PRN for vertebrate responses to WNV; the actual nodes and edges are vastly more numerous, and edges especially are likely to differ among species and even individuals. What is probably important for capturing host competence, though, is the connectivity (i.e., number of edges), modularity (i.e., distribution of edges), degree distribution (i.e., distribution of edges from date and party hubs), and other aspects of the whole PRN across environments. Figure 3 highlights such a PRN reaction norm, or in other words, changes in PRN states, changes in parasite burden, and thus changes in host health and competence. In the absence of WNV exposure, many PRN edges will be absent, making connectivity low, allowing physiological sub systems to operate

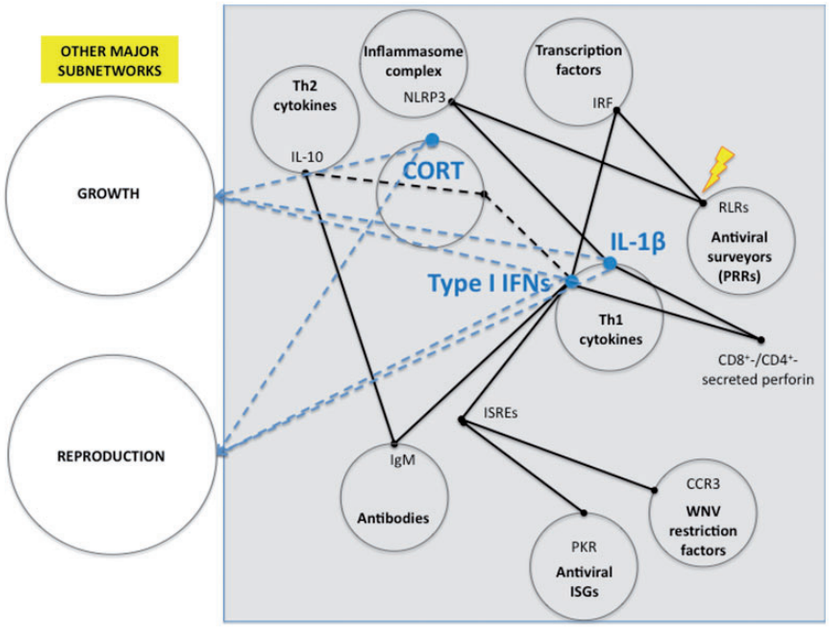

Fig. 2 PRN for West Nile virus infection. Example PRN for WNV responses in vertebrate hosts, highlighting CORT, type I interferons (IFNs), and interleukin (IL)-1β as date hubs (small, filled black symbols). Pattern recognition receptors (PRRs) detect the presence of WNV (represented by the lightning strike) and then propagate information across the PRN. Date hubs links the immune system subnetwork to other major subnetworks within the host (i.e., growth and reproduction). Circles and plain text represent subnetworks within the broader immune network, whereas dots and bolded text identify example nodes. Solid and dashed lines depict stable and labile edges, respectively; see Fig. 3 for details on lability. Abbreviations: CORT = corticosterone, Type I IFNs = interferons α/β, PKR = protein kinase R, ISGs = interferon-stimulated genes, IgM = immunoglobulin M, IRF = interferon regulatory factors (e.g., IRF3, IRF7), ISREs = interferon-stimulated response elements, RLRs = RIG-I-like receptors (e.g., MAVS). References: Quicke and Suthar (2013), Elenkov (2004), Daffis et al. (2007, 2008, 2009), Lazear et al. (2013), Horvath (2004), Purtha et al. (2008), and Pinto et al. (2011).

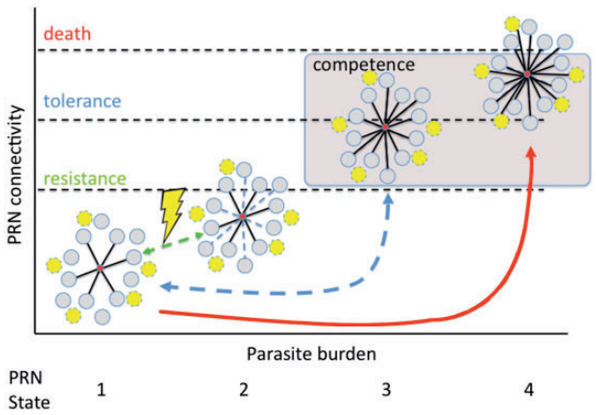

Fig. 3 PRNs and plasticity in host competence. In the absence of parasites (state 1), host PRN characteristics are set by genetic and epigenetic variation within the host individuals. In response to parasite exposure (lightning bolt; state 2), PRN connectivity (i.e., number of edges, black lines) and modularity (i.e., distribution of edges among nodes, not depicted) change, with date hubs (small filled symbol) becoming highly connected to other nodes and subnetworks (large, dark black circles). Note that edges can be fixed (solid black lines) or induced (dashed black lines). If hosts are able to resolve an infection by the initial change in PRN state, the PRN state reverts to an unexposed (or further modified (i.e., immune memory) condition. Alternatively, if the host is unable to resolve the threat, an altogether different PRN state may ensue. Different PRN states result in different (emergent) outcomes. Parasite tolerance (state 3) is one possibility, but death too is a possible endpoint (state 4). Death and disease too might result from the recruitment of typically unconnected subnetworks (light grey circles). The gray shaded rectangle emphasizes that only some PRNs will support competence, as many PRNs will eliminate parasites (through host death, resistance, or insufficient amplification) before they can be transmitted.

relatively autonomously. Upon exposure to WNV, however, PRNs should change state, inducing the formation of edges and hence regulatory relationships among subnetworks. Contingent on i) the initial state of the PRN (as mediated by health, condition, prior exposure, age, or time of year for an individual host), ii) network characteristics shaped by life history priorities [fast versus slow pace of life (Ricklefs and Wikelski 2002)], and iii) the evolutionary legacy of the species, PRNs will reconfigure plastically, determining host responses to and hence competence for WNV.

These predictions for relationships between PRN dynamics and host health are consistent with basic immunology. For instance, Th1 and especially Th17 cytokines engender strong inflammatory responses (Sears et al. 2011). Individual hosts in which such pro-inflammatory cytokine connectivity increases rapidly upon exposure would be expected to take a highly resistant defense strategy (Diaz and Allen 2007). Such hosts would be relatively incompetent. Conversely, hosts that experience high Th2 or T regulatory cytokine connectivity upon parasite exposure or with changing burden would manifest a robust anti-inflammatory response. Depending on further PRN state changes over the course of the infection, some individuals might become particularly competent because they cease trying to resist infection and instead activate particular PRN subnetworks facilitating tolerance (i.e., they become biased to a particular Th cell phenotype (Diaz and Allen 2007]). As we hinted above, changes at date hubs (e.g., CORT, IFNγ) might strongly influence such outcomes (Sapolsky et al. 2000; Jankowski et al. 2010). If individuals with high CORT-driven connectivity do not resist or die from infection, changes in their PRN states might lead them to impose great transmission risk to others, especially in some environments (i.e., transmission hotspots [Paull et al. 2011]). Figure 4, borrowed from an effort to encourage neuroscience to move from a cell- to a systems mindset (Yuste 2015), depicts the possible role of CORT for changes in PRN states and host competence. Different environments alter CORT regulation, which instigates movement of the PRN, and hence the phenotype, across the landscape (i.e., PRN structure). CORT (and other date hubs), due to their actual and potential connectivity with other nodes, alters the depths of ''basins'' of resistance and tolerance, ultimately determining whether individuals will be competent.

This PRN competence framework promises to work well for WNV, but it should apply to myriad host–parasite systems. Examples include murine malaria in which low inflammatory signaling (TNF-α) ameliorates individual suffering from infection (i.e., increases tolerance), and also increases parasite transmission to mosquitoes (i.e., increases competence) (Long and Graham 2011). In many vertebrates, TNF-α has been implicated as a PRN date hub because of its effects on various non-immune targets (Dantzer 2001). Similar arguments can be made for the emerging pathogen, *Mycoplasma gallisepticum* (*Mg*). In house finches (*Haemorhous mexicanus*), disease severity (i.e., reduced tolerance) is positively correlated with inflammatory signaling (IL-1β to IL-10 ratio) (Adelman et al. 2013b); these cytokines too seem to act as date hubs. In this system, PRN state might underlie individual competence in a different way than above; animals with more severe pathology (and presumably higher inflammatory signaling) shed more *Mg* onto bird feeders, potentially increasing transmission to other susceptible hosts (Adelman et al. 2013a).

Where do we go next?

The value of our framework lies in its ability to describe how we can measure and thus describe well traits such as resistance, tolerance, and competence as emergent properties of an organismal network. This framework thus captures the complexity and plasticity inherent to suborganismal phenomena, but it will also be effective at describing competence heterogeneity in the interest of population-level processes too (Downs et al. 2014). With the advent of new, fairly inexpensive technologies (Jackson 2015), we stand poised to collect enormous amounts of information about host–parasite interactions. Weighted gene-coexpression network analyses and other computational approaches will facilitate the use of our PRN framework with such large datasets (Li et al. 2011). The path ahead is still fraught with challenges, though, particularly in terms of performing experiments and establishing causality. One now has the option of manipulating single date hubs, collections of date hubs, or whole PRN traits (i.e., connectivity, modularity), and most such efforts will be challenging. Perhaps fields with more experience with such hurdles can guide us. Research on the development of morphological traits and bioelectric networks might help us learn how whole organisms are coordinated toward the same task (Levin 2014; Newman 2014). Likewise, we might reconcile problems associated with level-spanning (e.g., molecular network effects cascading up to organ function) from work on the assembly of tissue structures from protein interaction networks (Hunter and de Bono 2014).

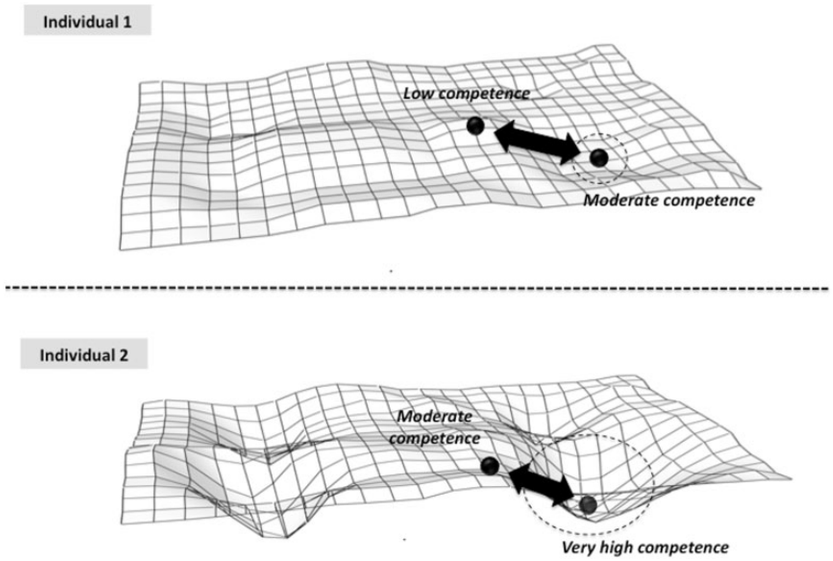

Fig. 4 PRN date hubs as drivers of plasticity in host competence. The grids depict competence landscapes for two individual hosts of the same species. The topography is determined by the underlying PRN structure, which is set by the genotype and/or epigenotype (inherited or induced; Jalbonka, Lamb and Zeligowsk [2014]). Each point on the grid reflects a different PRN state and hence a different (potential) competence. Black balls represent example PRN states, and basins depict the relative likelihood (i.e., stability) of particular PRN states. Importantly, the deeper the basin, the more stable the PRN and hence the more competent is a host. Plasticity in competence occurs when a change in the environment induces changes in CORT (and other date hubs) connectivity within PRNs (black arrow). The PRN then moves across the landscape, following contours into basins of attraction (dashed circles). Here, in response to a stressor (black arrow), competence increases in both individuals as the PRN takes a more stable form. Two important things should be noted though. First, the same magnitude stressor (length of black arrow) induces dramatically different effects on competence between individuals; individual 1 is shifted into a shallow basin (moderate increase in competence) whereas individual 2 is shifted into a deep basin (extreme increase in competence). Second, recovery from the stressor (i.e., escape from the attractor basin) will be much more challenging for individual 2 than individual 1.

Eventually, it will also be in our interest to evaluate the impacts of physiological and behavioral covariation regulated by PRNs. There is a growing interest in coupled heterogeneities in many disease systems (Vazquez-Prokopec et al. 2016), and shared regulatory pathways underlie many of these relationships (Demas et al. 2011). It will also be important to determine the influence of various epigenetic mechanisms on PRN structures and states (Jablonka and Raz 2009; Jablonka et al. 2014; Noble et al. 2014). We recognize that PRN theory will not perfectly capture host competence, but this framework lends itself to quantitative analysis and empirical manipulation (Zamer and Scheiner 2014), something not yet offered by other hypotheses directed at understanding organismal health and performance such as allostasis (McEwen and Wingfield 2003) and reactive scope (Romero et al. 2009). Given the extensive movement of parasites across the globe and the exorbitant costs of their control (Heesterbeek et al. 2015), creative yet practical interventions are needed, especially in non-Westernized areas where access to healthcare and hygienic infrastructure will remain modest (Ewald 2000).

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