Title: Resource competition and host feedbacks underlie regime shifts in gut microbiota

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Abstract

The spread of an enteric pathogen in the human gut depends on many interacting factors, including pathogen exposure, diet, host gut environment, and host microbiota, but how these factors jointly influence infection outcomes remains poorly characterized. Here, we develop a model of host-mediated resource-competition between mutualistic and pathogenic taxa in the gut that aims to explain why similar hosts, exposed to the same pathogen, can have such different infection outcomes. Our model successfully reproduces several empirically observed phenomena related to transitions between healthy and infected states, including (1) the nonlinear relationship between pathogen inoculum size and infection persistence, (2) the elevated risk of chronic infection during or after treatment with broad-spectrum antibiotics, (3) the resolution of gut dysbiosis with fecal microbiota transplants, and (4) the potential protection from infection conferred by probiotics. We then use the model to explore how host-mediated interventions, namely shifts in the supply rates of electron donors (e.g., dietary fiber) and respiratory electron acceptors (e.g., oxygen), can potentially be used to direct gut community assembly. Our study demonstrates how resource competition and ecological feedbacks between the host and the gut microbiota can be critical determinants of human health outcomes. We identify several testable model predictions ready for experimental validation.

Introduction

The human large intestine, hereafter referred to as the gut, harbors hundreds of microbial taxa, some of which interact mutualistically with the host, while others, such as pathogens, thrive at the host's expense. The relative success of beneficial and harmful taxa in the gut depends on their relative ability to compete for shared resources, which is modulated by gut environmental parameters, most notably the concentration of strong electron acceptors such as oxygen (Rivera-Chávez et al. 2017). Disturbances (e.g., antibiotics; Looft and Allen 2012), immigration events (e.g., fecal transplants; Kang et al. 2019), and pathogen exposure (Black et al. 1988; Beatty et al. 2014) can all lead to swift changes in gut community composition (e.g., transitions from healthy to infected states) that may persist indefinitely (Beatty et al. 2014). While such community shifts in the gut are well documented, the mechanisms behind them remain poorly understood.

Progress in understanding community assembly of the gut microbiota has been limited in part because host-microbial interactions are multifactorial and difficult to isolate, and in part because experimentation in anaerobic guts is logistically challenging, especially in humans. One way around these obstacles is to use mathematical modeling to explore how infection dynamics are influenced by ecological interactions among the gut microbiota, pathogens and the gut environment. An understanding of how key ecological parameters of the gut could be manipulated to achieve particular community assembly outcomes may lead to novel treatments that are complementary or even superior to traditional medical approaches. More broadly, a more mechanistic framework for the relationship between infection and host-associated microbial community assembly would add to our general understanding of the ecology and evolution of microbial symbioses.

Enteric infections are underappreciated examples of species invasions, in which a rare taxon undergoes rapid population growth and quickly becomes a dominant member of the local community. As such, efforts to understand and treat enteric infections are opportunities to draw upon the concepts and tools of invasion ecology and restoration. Invasiveness in well-studied macrobiological systems is affected by several factors including the propagule pressure of the invading species (Wilson et al. 2009), the local disturbance regime (Hierro et al. 2006; Liu et al. 2012) and local community structure (Miller et al. 2002; Von Holle and Simberloff 2004). In one grassland, the establishment of an invasive species altered the local fire regime, necessitating a qualitatively different management strategy (Brooks et al. 2004; Suding et al. 2004). Changes in the abiotic conditions or resource supply rates in a community can even affect the range of possible community assembly outcomes, transforming communities from uninvasible to invasible, or from monostable to bistable (Meijer et al. 1994; Scheffer et al. 2001). It remains to be seen which principles from invasion ecology and restoration ecology will extend to enteric infections and other community imbalances in the human gut.

While the community assembly rules of the gut remain murky, the biochemical processes underlying gut homeostasis are relatively well understood. The gut communities of healthy individuals are generally dominated by two phyla, the gram-positive Firmicutes and the gram-negative Bacteroidetes (The Human Microbiome Consortium 2012). Both phyla contain obligately anaerobic taxa that form long-term relationships with their mammalian hosts and are often transmitted vertically from parent to offspring, reflecting their close evolutionary associations (Peeters et al. 2016). These anaerobic groups proliferate in the gut soon after birth (Guittar et al. 2019) due in part to positive feedbacks with the host environment that deplete the concentration of strong electron acceptors that can be used in respiration, such as oxygen, to

favor their continued dominance. For example, many taxa in *Clostridia*, a class of Firmicutes, catabolize dietary fiber and release butyrate (Rivera-Chávez et al. 2016); host epithelial cells then use this butyrate in aerobic respiration, consuming the oxygen that would otherwise diffuse from the bloodstream into the lumen, thereby reinforcing the hypoxic conditions preferred by *Clostridia* (Rivera-Chávez et al. 2016). Likewise, many taxa in Bacteroidetes encode cytochrome *bd* oxidase, which reduces ambient oxygen levels (Wexler and Goodman 2017) and thereby reinforces the hypoxic conditions preferred by Bacteroidetes.

Enteric pathogens, meanwhile, initiate countervailing positive feedbacks in the gut that increase the concentration of respiratory electron acceptors (i.e., those used in aerobic or anaerobic respiration, rather than fermentation), subverting gut homeostasis and promoting their rapid expansion. For example, pathogens are known to trigger the host to release respiratory electron acceptors (e.g., oxygen, nitrate, sulfur or nitrogen oxides) into the gut environment, which are then used by the pathogens to gain an energetic advantage while simultaneously imposing oxidative stress on anaerobic gut mutualists (Abt et al. 2016; Lopez et al. 2016; Rivera-Chávez et al. 2016; Brooks and Mansfield 2017; Sorbara and Pamer 2019). Bacterial gastroenteritis, a leading cause of child mortality and morbidity worldwide (Pires et al. 2015), occurs when an enteric pathogen outcompetes resident gut mutualists for resources and the gut system shifts from healthy to a diseased, pathogen-dominated state. An expansion of pathogens is one manifestation of gut "dysbiosis," a general term that describes a disruption to the structure of the host microbial community that is associated with human health problems (Petersen and Round 2014).

Previous modeling efforts to understand and predict the arrival and proliferation of enteric pathogens in human hosts have used one of two approaches. The first, found primarily in

the microbiological literature, is a detailed and highly mechanistic approach that draws on laboratory experimental data to carefully reveal the cellular and biochemical steps enabling pathogen transmission and rapid growth within a host. Such *microbiological models* (Fig. 1A) are invaluable for understanding virulence factors and the granular mechanics of infection, but poorly suited for predicting system dynamics over time or how infections might play out differently among individuals due to historical contingencies. The second approach, found primarily in the community ecology literature, is more phenomenological and uses classical mathematical models like Lotka-Volterra competition (Stein et al. 2013; Fisher and Mehta 2014; McGeachie et al. 2016) or network analysis (Wang et al. 2019) to study infection dynamics in highly simplified ecological communities. Such *competition models* (Fig. 1C) capture the dynamical nature of a system, but are too abstract to be of applied use in predicting and preventing infections in a given host, as they include no mechanistic basis for species interactions and do not account for how the gut environment modulates competitive outcomes (O'Dwyer 2018).

Here we develop a modeling framework that strikes a balance between these two approaches (Fig. 1B), with enough microbiological detail to meaningfully inform applied work on the treatment and prevention of bacterial gastroenteritis, but not so much detail that it cannot be modelled dynamically and understood by a general audience. We use our model to ask how enteric infection outcomes can differ so strikingly even when hosts are similar. One possible answer to this question is that the gut system has alternative stable states, such that minor differences in the history of the system can cause hosts to diverge towards healthy or infected states (Beisner et al. 2003; Scheffer and Carpenter 2003). If this is the case, it leads immediately to another question: what ecological and physiological processes would underlie a system with

alternative stable states, and what triggers would induce switches between them? With this line of inquiry in mind, we ask the following specific questions: (1) Under what assumptions do alternative stable states arise in the gut, such that ecological dynamics can drive similar hosts to experience divergent infection outcomes? (2) Under what circumstances do common perturbations to the gut microbiota like pathogen ingestion, antibiotic treatment, fecal transplants, and probiotic supplements lead to shifts between healthy and pathogen-infected states? (3) How do shifts in resource supply rates, such as changes in oxygen availability or dietary fiber, affect the likelihood of infection and/or recovery, and what implications does this have for preventing and treating enteric infections?

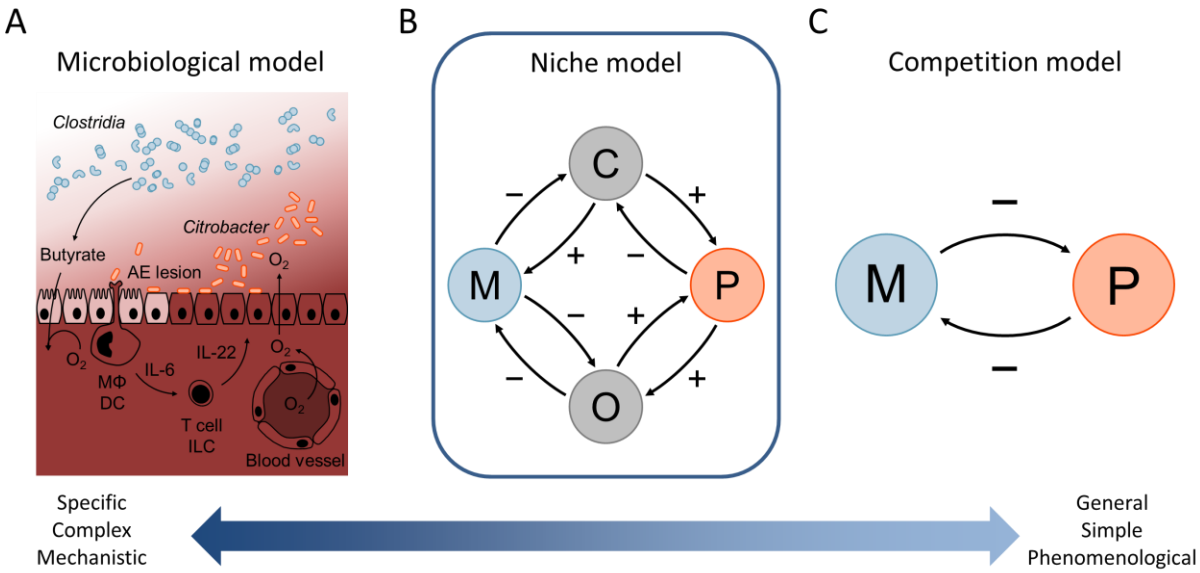

Figure 1. A continuum of modeling approaches. Gut community modeling approaches range from **A)** a microbiological perspective that focuses on specific genes, regulatory networks, and biochemical reactions; **B)** a resource-competition-based model – our approach – that focuses on population dynamics, environmental state variables (e.g., resource concentrations), and their interactions, using generalized ecological mechanisms instead of physiological mechanisms; and **C)** a Lotka-Volterra model of two-species competition where environmental parameters are implicit and do not influence competitive dynamics. **A** is specific to *Citrobacter rodentium* (Rivera-Chávez et al. 2016, 2017), while **B** and **C** are general to many enteric pathogens. Consistent with model variables, M and P are the abundances of anaerobic mutualist and pathogens, C is shared carbon substrate, and O is pathogen-preferred electron acceptors.

Model

Our model is rooted in resource competition theory (Tilman 1982; Smith 1993) and contemporary niche theory (Chase and Leibold 2003) and explicitly incorporates the roles of resource supply and environmental feedbacks in gut community assembly. Niche theory is based on the idea that interactions between organisms are shaped by how they both respond to and affect their biochemical environment (Chase and Leibold 2003). Our use of the term "resource" includes both electron donors (e.g., dietary fiber) and respiratory electron acceptors (e.g., oxygen). We model the coupled dynamics of the gut community and its chemical environment (i.e., local resource concentrations) using ordinary differential equations, tracking changes through time in the abundance of anaerobic mutualists M and pathogens P, and concentrations of shared carbon substrate C and pathogen-preferred electron acceptors O. To do so, we make three key simplifying assumptions, justified below.

Biological justifications for key model assumptions

Assumption 1: Pathogen success is determined by its ability to compete for carbon with a broad group of anaerobic mutualists. Although the carbon substrates that reach the large intestine comprise various forms of indigestible fiber (Sawicki et al. 2017), which are generally unusable by enteric pathogens, these diverse fibers are broken down by anaerobic mutualists into monosaccharides (Wexler and Goodman 2017), which are then usable by pathogens. Rapid cell turnover due to viral lysis of anaerobic mutualists, as well as pathogen interception of intermediate metabolic products (i.e., cheating; Allison et al. 2014, Welch et al. 2017), together ensure that a substantive fraction of the fiber-derived carbon pool ultimately becomes available

to pathogens in more labile forms (Weitz and Wilhelm 2012). While there is a broad range of enteric pathogens with different life history traits (e.g., pathogenic strains in *Salmonella*, *Escherichia coli, Shigella, Campylobacter*, etc.), their success generally hinges on their ability to compete for carbon substrate with a broad group of anaerobic mutualists (e.g., Firmicutes and Bacteroidetes). Hence, for modeling purposes, their populations are combined and designated "mutualists" and "pathogens."

Assumption 2: Competition for carbon between anaerobic mutualists and pathogens is mediated by the availability of host-derived electron acceptors. Under hypoxic conditions, anaerobic mutualists ferment carbon substrates for energy, outcompeting pathogens (Bäumler and Sperandio 2016). However, unlike most anaerobic mutualists, which lack the ability to respire, many enteric pathogens can use oxygen as a terminal electron acceptor for aerobic respiration, and/or use nitrate, S-oxides, and N-oxides as terminal electron acceptors for anaerobic respiration (Bäumler and Sperandio 2016; Lopez et al. 2016; Rivera-Chávez et al. 2016; Wexler and Goodman 2017). Because respiration is more energetically efficient than fermentation, pathogens gain a competitive edge over anaerobic mutualists in the presence of these potent electron acceptors.

Assumption 3: Anaerobic mutualists and pathogens modify the gut environment to favor their own growth while hampering the growth of the other. As described above, anaerobic mutualists have direct and indirect methods of promoting hypoxia in the gut, favoring their competitive dominance. Conversely, many enteric pathogens use virulence factors that result in the release of host-derived respiratory electron acceptors that enable swift population growth while exposing anaerobic mutualists to oxidative stress (Lopez et al. 2016; Rivera-Chávez et al. 2016, 2017; Zeng et al. 2017), thus favoring their competitive dominance. These environment-

modifying mechanisms work as opposing positive feedbacks and each constitute forms of "niche construction" (Odling-Smee et al. 1996; McNally and Brown 2015; Goldford et al. 2018).

Model Description

The mutualist M and pathogen P grow following classic population dynamics:

$$\frac{dM}{dt} = [g_M(C) - \beta_M O - m_M]M \quad (1a)$$

$$\frac{dP}{dt} = [g_P(C, O) - m_P]P \quad (1b)$$

where g_M and g_P are the substrate-dependent growth rates, m_M and m_P the background mortality rates, and the term $\beta_M O$ models the extra mortality of the mutualist as a consequence of oxidative stress at a rate β_M. We model substrate-dependent growth of the two microbial populations as being controlled by classic microbial uptake kinetics and substrate limitation (Tilman 1982; Saito et al. 2008):

$$g_M(C) = \min(\mu_M, \alpha_{CM} C) \quad (2a)$$

$$g_P(C, O) = \min(\mu_P, \alpha_{CP} C, \alpha_{OP} O) \quad (2b)$$

where μ_M and μ_P are the maximal growth rates, α_{CM} and α_{CP} the growth affinities for carbon substrate of the mutualist and pathogen bacteria, respectively, and α_{OP} the growth affinity for the respiratory electron acceptors O of the pathogen. The minimum function returns the metabolic rate – either substrate uptake or maximal growth rates – that most limits population growth, a modeling assumption commonly referred to as Liebig's Law of the minimum (Tilman 1982, Chase 2003, Saito 2008). Because it contains both the substrate-limited uptake rate and maximal

growth rates, the minimum function effectively behaves like an extension of the classic Monod function to multiple limiting resources (refer to Supplementary Information).

In turn, population growth affects C and O concentrations:

$$\frac{dC}{dt} = a_C(C_{\text{in}} - C) - q_{CM} \cdot g_M(C)M - q_{CP} \cdot g_P(C,O)P \tag{3a}$$

$$\frac{dO}{dt} = a_O(O_{\text{in}} - O) - q_{OP} \cdot g_P(C,O)P + \frac{\gamma_{OP}\kappa_{OP}}{\kappa_{OP} + O}P - \frac{\gamma_{OM}O}{\kappa_{OM} + O}M \tag{3b}$$

C_{in} is the concentration of carbon substrate entering the gut through diet and mucus secretions (Li et al. 2015) at rate a_C. Similarly, O_{in} is the concentration of respiratory electron acceptors entering the gut with diffusion rate a_O. Conversion coefficients q_{CM}, q_{CP} and q_{OP} relate bacterial growth and nutrient uptake according to mass balance. Mutualists deplete O at rate γ_{OM} with a saturating efficiency given by the half-saturation constant κ_{OM}. The pathogen induces gut inflammation, triggering the host to release the respiratory electron acceptors (Zeng et al. 2017) at a maximal rate γ_{OP}, with decreasing efficiency as respiratory electron acceptor concentrations approach κ_{OP}. Different pathogens have different mechanisms for triggering the release of different respiratory electron acceptors, but they all depend on the same fundamental positive feedback dynamic, so can be treated generally. Refer to Supplementary Information for a more detailed justification of our mathematical approach to modeling the host release of respiratory electron acceptors, including an example of how to mechanistically derive γ_{OM} and κ_{OM} in the butyrate-producing *Clostridia* pathogen system. Importantly, we constrained our model parameter estimates to fall within realistic ranges based on published literature; for a full list of model parameters and their values refer to Table S1.

Model analysis

We used two complementary approaches to study and represent the dynamics and equilibrium states of the gut ecosystem described by eqns. (1–3), and their response to shifts in resource supplies by the host. In the first, we assume that the dynamics of the carbon substrate C and terminal electron acceptors O in the gut happen faster than the population dynamics of the mutualist and pathogen, a mathematical approach called Quasi-Steady State Approximation (QSSA). When applied to eq. (3), QSSA reduces the model to a simplified competition system in which its dynamics and equilibria can be represented and studied in the mutualist-pathogen abundance phase plane (Fig. 2; refer to Supplementary Information for a more detailed explanation of QSSA). The QSSA-reduced model is similar to Lotka-Volterra dynamics because it focuses on the dynamics of the two competing species while abstracting the gut environment. It differs from Lotka-Volterra in that it accounts for the changing states of the gut environment, i.e., the concentrations of gut resources. The QSSA approach produces non-linear interactions between the mutualists and pathogens that vary depending on the environmental context.

In our second, more graphical approach, we present equilibria between the bacterial community and its physiochemical environment under a range of different resource supply rates using tools and concepts from contemporary niche theory (Chase and Leibold 2003; Koffel et al. 2016; Fig. 3). Within this graphical framework, we delimit the biochemical niches of mutualists and pathogens as regions of potential persistence (i.e., the red and blue shaded areas in Fig. 3). These niches delineate the biochemical conditions under which each species can be found. Furthermore, the baseline rates of resource supply (i.e., points a-e in Fig. 3), as determined by host diet and host physiology, are graphically linked using solid lines to their corresponding set

of realized gut environmental conditions at equilibrium (i.e., the filled red and blue circles in Fig. 3), after accounting for feedback with the gut microbiota. For a more rigorous exploration of this graphical modeling approach and the community-level consequences of positive feedbacks, refer to the Supplementary Information and Koffel et al. (in press). Mathematica 9.0 software was used for all numerical calculations and to generate figures.

Results

Our model, based on ecological feedbacks between the gut microbiota and the host gut environment, reproduces many observed phenomena related to gut homeostasis and enteric infections. In particular, a core outcome of the model is a dynamical system with two alternative stable states in which similar individuals can exhibit starkly divergent community assembly outcomes. These two outcomes – a mutualist-dominated healthy state and a pathogen-dominated gastroenteritic or dysbiotic state – can be visualized using a mutualist-pathogen abundance phase plane (Fig. 2). In this phase plane, both mutualist-dominated and pathogen-dominated community states are resistant to small perturbations because system dynamics create basins of attraction that draw each community back towards its original equilibrium state. When perturbations are sufficiently large, the system will traverse a critical boundary (i.e., a separatrix, shown as a grey line in Fig. 2) into an alternative basin of attraction.

A gut system with alternative stable states provides a mechanistic explanation for how common perturbations, such as the four described below, can lead to transitions between healthy and pathogen-infected states. First, imagine a set of humans with similar gut communities exposed to different quantities of a foodborne bacterium. In each individual, the influx of pathogenic bacteria would result in an increase in their relative abundance (i.e., an upward shift

in the phase plane of Fig. 2A), but only the individuals exposed to a sufficiently large inoculum would become infected (i.e., those in which the community was pushed across the separatrix and into a new, pathogen-dominant basin of attraction). Such a scenario would explain why the rates of host infection increase with pathogen inoculum size (Black et al. 1988). An alternative scenario with the same outcome would occur if individuals were exposed to the same influx of pathogens but differed in the sizes of their mutualist populations. The size of the mutualist population modulates community resistance to infection by increasing the distance between equilibrium and the separatrix (Fig. 2A; see insets b and e in Fig. S7).

Second, a gut system with alternative stable states can explain why broad-spectrum antibiotics sometimes have the paradoxical effect of increasing the risk of infection (Faber et al. 2016; Rivera-Chávez et al. 2016). Broad-spectrum antibiotics are prescribed by physicians to eliminate an offending pathogen (not necessarily an enteric pathogen) and have the unwanted side effect of decimating resident mutualist populations, drawing the community closer to the origin of the mutualist-pathogen abundance phase plane (Fig. 2B). Increased proximity to the origin makes the system more likely to traverse the separatrix into the infected basin of attraction (Scheffer et al. 2012; Ng et al. 2014; Faber et al. 2016). That is, a regime shift into a pathogenic state is now more likely to be triggered by exposure to a new pathogen, the presence of an antibiotic-resistant pathogen, a minor disturbance, or potentially even demographic stochasticity.

Third, a gut system with alternative stable states can explain how fecal microbiota transplants can swiftly rescue chronically dysbiotic systems (Kang et al. 2019), by first reducing pathogen population density with a pre-procedural colonic purgation, and then increasing mutualist population density with a large immigration event from a healthy stool donor, placing the gut community into a new, healthy regime (Fig. 2C). Fourth and finally, a gut system with

alternative stable states provides a mechanistic explanation for why probiotics may decrease the risk of and/or promote recovery from gastroenteritis (McFarland 2007; Ritchie and Romanuk 2012); increasing the mutualist population density through mass effects (Leibold et al. 2004) increases the number of pathogen immigrants needed to cause an infection in a healthy individual, and makes it easier to clear the pathogen in an uninfected individual (Fig. 2D).

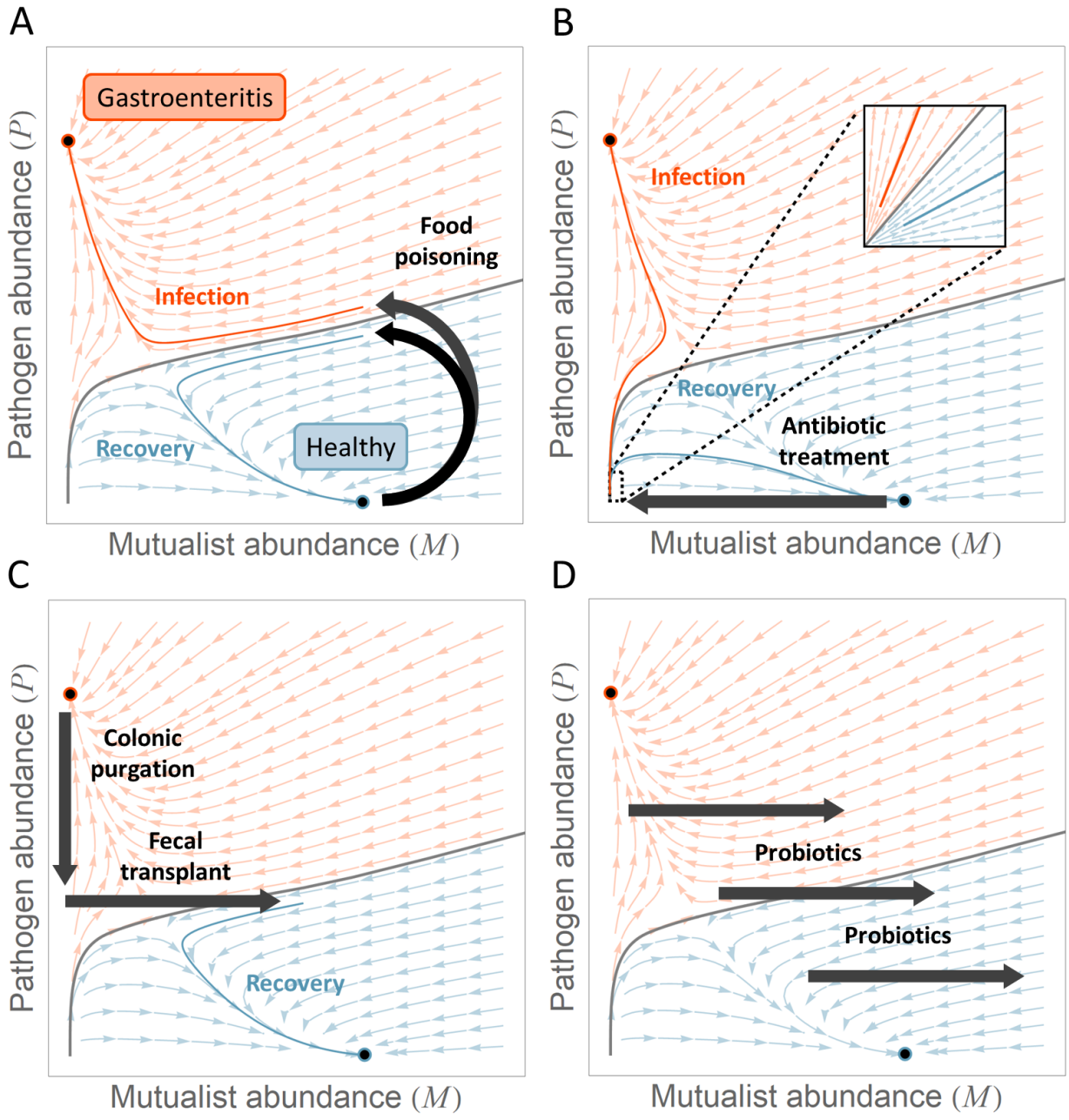

Figure 2. Disturbances and immigrations underlie regime shifts. In a gut community with bistable dynamics, immigration events or disturbances can qualitatively alter community assembly outcomes, moving the system to a different state (e.g., between healthy and gastroenteritis). **A)** A pathogen immigration event must be sufficiently large to lead to an infected state. **B)** Antibiotics decimate mutualist populations, increasing the proximity to the boundary between basins of attraction and thus sensitivity to

infection. **C)** Fecal microbiota transplants show promise in resolving chronic infection by reducing pathogen abundance through a pre-procedural colonic purgation, and then increasing mutualist populations with a large immigration from a stool of a healthy donor. **D)** Probiotics promote recovery and/or increase resistance to infection by increasing mutualist population density through mass effects. Note that the bistable dynamics displayed here are only one of three possible dynamical outcomes that depend on resource supply rates – in this case, the supply rates (C:35; O:1.375) are similar to those of **d** in Fig. 3A.

Not only does our model detail how sudden shifts in the abundances of pathogens or mutualists can trigger regime shifts under fixed environmental conditions (Fig. 2), but it also provides an opportunity to explore how changes in the underlying parameters of the gut environment can alter the behavior of the system. Changes in resource supply rates can affect both quantitative behavior (e.g., a change in the resistance to a regime shift) and qualitative behavior (e.g., a conversion of a bistable system to a monostable one). Fig. 3 provides a visual summary of how changes in resource supply affect the number of possible community assembly outcomes. For example, in the white region of Fig. 3A, there are no non-trivial stable state outcomes; in the red region, the pathogen always dominates (i.e., monostability); in the blue region, the mutualist always dominates; and in the area with overlapping red and blue, either the pathogen or the mutualist can dominate depending on the history of the system (i.e., bistability). If the supply rate of dietary fiber is increased, the size of the shared carbon pool increases and the system becomes more resistant to change because it is now further from a tipping point (e.g., moving from **b** to **c** in Fig. 3A, B). This is easily visualized using a bifurcation diagram, wherein moving from **b** to **c** increases the environmental distance between the two alternative stable

states (Fig. 3B), also pulling the two equilibria further apart in their associated phase planes (Fig. S7) and making the transition from one state to the other less likely. In a healthy individual, such a shift would lower the risk of infection by supporting larger mutualist populations and depleting oxygen concentrations, thereby depriving pathogens of respiratory electron acceptors.

Even when the supply rate of carbon substrate is held constant, variation in the supply rate of respiratory electron acceptors, such as oxygen, can qualitatively alter gut community dynamics in a similar fashion (Fig. 3C, D). For example, an increase in the supply rate of oxygen (e.g., a shift from **b** to **d** in Fig. 3C, D and S7) increases susceptibility to infection in a healthy individual, and increases resistance to recovery in an infected individual. Our model suggests that the supply rate of respiratory electron acceptors can – at least in theory – be so high that obligately anaerobic mutualists cannot invade an infected gut due to oxidative stress, and so low that pathogens cannot invade a healthy gut due to competitive inferiority in hypoxic conditions (**e** in Fig. 3C and D).

Discussion

Returning to our central motivating question, our model provides a mechanistic explanation for how similar individuals can differ dramatically in their responses to pathogen exposures and medical treatments. Individuals that differ in their densities of resident gut mutualists and/or pathogens – potentially due to differences in dietary fiber intake, oxygen diffusion from the bloodstream, and/or epithelial mucin production (Hansson 2012) – will have different tipping points or system equilibria, and thus will differ in their resistance to shifting into alternative stable states. Even small differences in the numbers of arriving pathogens or mutualists (e.g., after exposure to an infected food source, or a fecal microbiota transplant), or in the ecological

parameters of the gut system, can lead to highly divergent responses if some gut communities are pushed over tipping points into alternative basins of attraction while others are not. It is important to note that our model seeks to explain why individuals differ in their response to ecological events like immigrations, disturbances, or shifts in resource supply rates; we do not seek to understand why individuals differ in their rates of autonomous recovery from gastroenteritis, which are likely governed by slower-acting immunological mechanisms that defend the gut system from infection through more targeted means, e.g., through the use of antimicrobial peptides and secretory immunoglobulin A (Muniz et al. 2012).

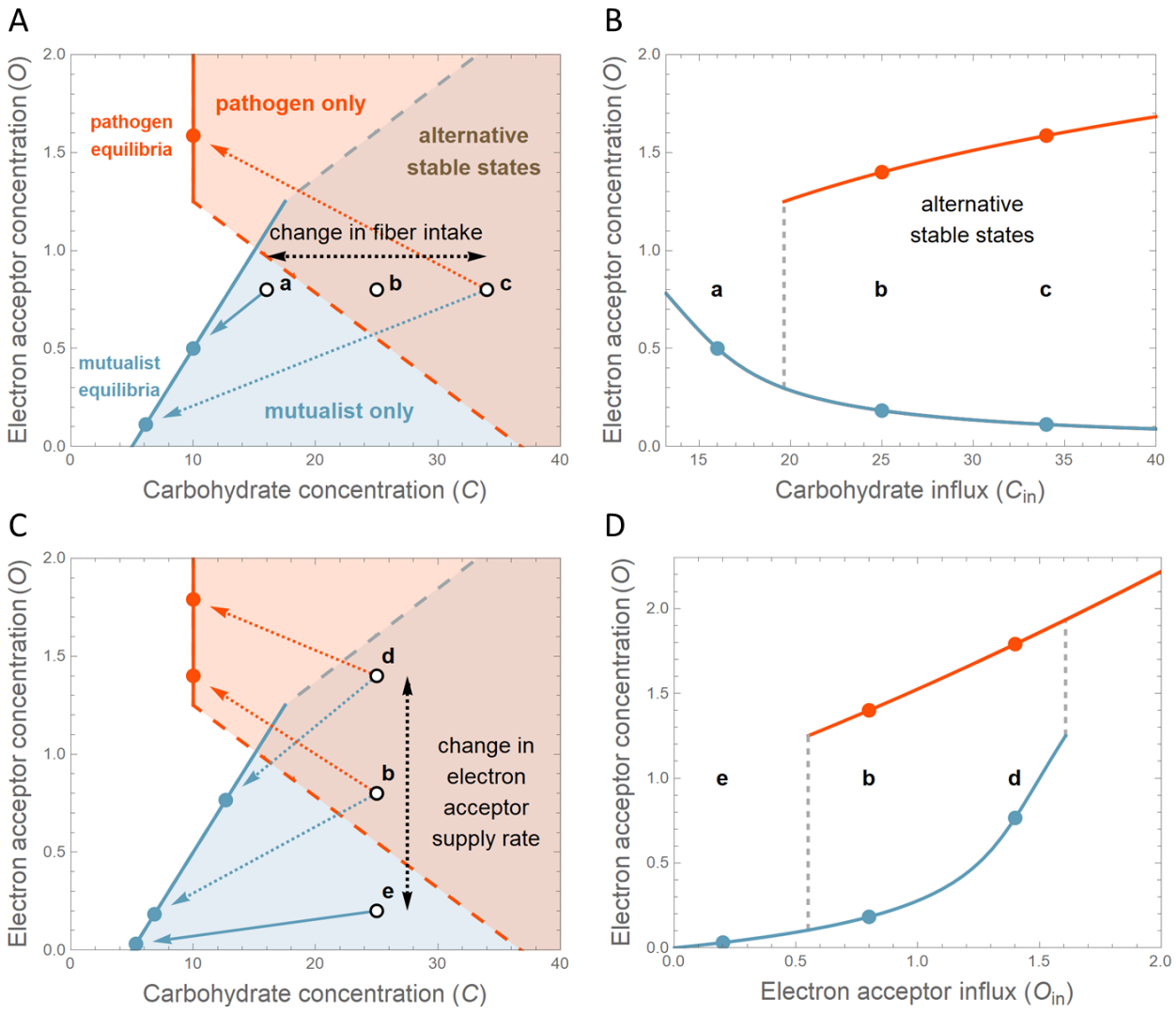

Figure 3. Resource supply rates shape community assembly. In the gut, pathogen-preferred respiratory electron acceptors O and carbon substrate C enter the gut at baseline supply rates, which can be subsequently altered through host physiological mechanisms and/or diet. Each supply point leads to a community with different characteristics and different underlying dynamics, and its corresponding phase plane. For example, Fig. 2 is associated with a supply point qualitatively similar to supply point **d** (see Fig. S7 for the phase planes corresponding to supply points **a** – **e**). The red areas in panels A and C delineate the combinations of O and C that allow the pathogen to persist, and the blue areas delineate where mutualists can persist. The areas with overlapping blue and red are bistable regions, i.e., those in

which either mutualists or pathogens dominate, depending on the history of the system. Red and blue arrows are the impact vectors on O and C exerted by pathogens and mutualists, respectively. O and C are drawn towards the specific equilibria that are shown as filled circles on the Zero Net Growth Isoclines (solid lines); these equilibria are also shown in panels B and D. Note that for many given values on the x-axis, there can be two equilibria, with either pathogen or mutualist dominance (i.e., alternative stable states). **(A, B)** An increase in dietary fiber (e.g., from **b** to **c**) increases the stability of both healthy and pathogenic equilibria by shifting the oxygen concentration of the gut to be further from the preferred oxygen concentration of its competitor, and a large decrease in fiber (e.g., from **b** to **a**) can eliminate the pathogen altogether. The y-axis reflects the percent composition of the gut environment that comprises respiratory electron acceptors; the x-axis reflects the percent composition of the gut environment that comprises the shared pool of carbon substrate. **(C, D)** A decrease in the supply of respiratory electron acceptors such as oxygen (e.g., from **d** to **b**) can reinforce stability in healthy systems, or, more dramatically (e.g., from **b** to **e**), eliminate the pathogen entirely.

Our results show how resource manipulation offers a distinct and possibly complementary approach to preventing and treating enteric infections, in concert with traditional approaches that directly attack the pathogen (Smith 1993). An increase in dietary fiber, for example, increases the stability of both healthy and pathogenic equilibria by shifting the oxygen concentration of the gut to be further from the preferred oxygen concentration of its competitor (**b** to **c** in Fig. 3A, B). This prediction is supported by experiments showing dietary fiber to benefit healthy mice but exacerbate colitis in mice with enteric pathogen infections (Miles et al. 2017), demonstrating the context-dependent effects of fiber addition on gut function. Meanwhile, a decrease in fiber would decrease the stability of both healthy and pathogenic equilibria. Corroborating this theoretical prediction, healthy mice deprived of dietary fiber proved to be

more susceptible to pathogen colonization and subsequent epithelial tissue damage (Desai et al. 2016). Counterintuitively, our model also predicts that an infected person could reduce their resistance to recovery by decreasing their dietary fiber (e.g., **c** to **b** in Fig. 3A, B), and even more intriguingly, that a very large decrease in fiber could eliminate the possibility of infection altogether (**b** to **a** in Fig. 3A, B).

Such predictions, along with the assumptions of our model, warrant further experimental validation. In particular, one important experiment could be to expose a cohort of healthy mice to a low but steady immigration rate of a foodborne pathogen, and then vary dietary fiber; if the system is bistable, the tipping point of runaway infection should increase monotonically with fiber intake. Conversely, pathogen-infected mice could be provided a range of dietary fiber; if fiber derivatives are indeed used by the pathogen, then the duration and/or severity of infection should increase monotonically with fiber intake.

Although the supply of respiratory electron acceptors like oxygen in the gut is less easily manipulated than fiber intake, there are still some important considerations for human health. Patients with ileostomies (i.e., feeding tubes inserted into their small intestines), for example, are one instance in which oxygen exposure can be directly controlled and observed. In one study, Hartman et al. (Hartman et al. 2009) observed that the gut communities of patients with ileostomies exhibited persistent shifts from obligate anaerobes to facultative anaerobes, until the ileostomies were removed and the communities returned to being dominated by obligate anaerobes. Such observational studies underscore the medical relevance of basic niche theory and illustrate how changes in the supply rates of resources lead to dramatically different gut community assembly outcomes. Intriguingly, the mammalian body appears to leverage these same ecological principles to defend itself against enteric infection. For example, shortly after a

pathogen is detected in the gastrointestinal tract, the host deploys a localized burst of neutrophils which temporarily lowers the concentration of oxygen through NADPH oxidase activity (Campbell et al. 2014), preventing pathogens from using oxygen to gain a competitive advantage and reducing the risk of transitioning to an infected state (Fig. 3A, B). Over longer time scales, mice have been shown to directly reduce oxygen diffusion rates into the lumen through unknown physiological mechanisms, possibly to promote colonization of benign anaerobic mutualists during gut primary succession (Friedman et al. 2018). Indeed, healthy individuals evidently may tolerate small populations of facultative anaerobes (e.g., some taxa in *Enterobacteriaceae*) because they consume oxygen released after community disturbances, thus impeding pathogen expansion and/or expediting the recovery of gut mutualists populations (Palleja et al. 2018; Litvak et al. 2019).

In this study we show how ecological theory can be applied to better understand the drivers of infection and dysbiosis in the human gut. Niche theory, in particular, offers a productive framework to think about how microbial fundamental niches, i.e., the physiochemical conditions required by each microbial species to thrive, combine with the abilities of microbes to modify these conditions to their liking through niche construction (Odling-Smee et al. 1996; McNally and Brown 2015; Goldford et al. 2018). In addition to modifying the concentration of respiratory electron acceptors such as oxygen, microbes are known to manipulate other aspects of their environment to affect their fitness relative to their competitors. For example, some microbes can elicit an immune response against their competitors, similar to how plants draw herbivores to their competitors, a phenomenon known as apparent competition (Holt 1977). Alternatively, some microbes produce allelopathic compounds, such as narrow-spectrum antibiotics, that directly attack other community members (Garcia-Gutierrez et al. 2019). In the

gut, the ability of key microbial populations like *Clostridia* to enhance their growth while suppressing the growth of their competitor contributes to the overall strength of homeostasis. Ecological models like ours offer the opportunity to identify the mechanisms driving community assembly as well as the resulting physiochemical state of the gut, simultaneously elucidating gut ecological functioning and its consequences for the host (Smith and Holt 1996).

Our model comes with limitations that could be addressed in future studies. First, it omits biochemical details involved in substrate usage differences among taxa; explicit consideration of additional niche differentiation among gut microbial taxa could shed light on microbial community assembly and community response to infection (Levy and Borenstein 2013; Goldford et al. 2018; Dubinkina et al. 2019). To this end, future work could consider more than two functional groups of microbial taxa, e.g., by subdividing facultative anaerobes into benign taxa and pathogenic taxa. Second, we considered only two resources (respiratory electron acceptors and shared carbon substrate), even though other environmental parameters (e.g., pH, toxins, viral dynamics, other electron acceptors) may significantly affect community dynamics. Third, spatial structure and environmental heterogeneity could be considered; the gut has a radial gradient in oxygen from the epithelium to the center of the lumen (Albenberg et al. 2014), and longitudinal gradients in carbon substrate availability and quality along the digestive tract (Donaldson et al. 2015). Future modeling work could explore how these gradients may affect system-wide competitive dynamics between mutualists and pathogens, and their consequences for shifts between alternative stable states.

The ecological perspective of bacterial gastroenteritis developed here provides a simple yet robust set of explanations for many empirical observations related to enteric infection and recovery, and advocates for an increased focus on managing resource availability in the gut. Our

ecological model further emphasizes the risks of broad-spectrum antibiotics (Faber et al. 2016; Rivera-Chávez et al. 2016), and how they paradoxically increase host vulnerability to enteric infection by placing the community closer to a tipping point. Finally, our framework constitutes an ecologically informed and mathematically rigorous starting point for developing guidelines for the prevention and treatment of a range of enteric pathogens, including rare and emergent pathogens with mechanisms of infection and transmission not yet fully understood.

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Statement of Authorship

JG and TK worked together closely at all stages of manuscript development. JG, TK, and EL conceptualized the study. TK developed the model, with feedback from JG, CK and EL. TK designed the figures, with feedback from all authors. JG and TK wrote and revised the manuscript, with feedback from all authors.

Data and Code Accessibility

Code for all figures is publicly available at https://github.com/guittarj/gut_regime_shifts (DOI:10.5281/zenodo.4599835).

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