The emerging medical ecology of the human gut microbiome

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Abstract

It is increasingly clear that the human gut microbiome has great medical importance, and researchers are beginning to investigate its basic biology and to appreciate the challenges that it presents to medical science. Several striking new empirical results in this area are perplexing within the standard conceptual framework of biomedicine, and this highlights the need for new perspectives from ecology and from dynamical systems theory. Here, we discuss recent results concerning sources of individual variation, temporal variation within individuals, long-term changes after transient perturbations and individualized responses to perturbation within the human gut microbiome.

A new scientific connection: medicine meets ecological theory

The complex ecology of the human gut microbiome is of great medical importance, but researchers are only beginning to investigate its basic biology and to appreciate the challenges that it presents to medical science. The gut bacterial community has been implicated in a range of human health issues extending far beyond the gastrointestinal (GI) tract. Those issues that do directly involve the GI tract include inflammatory bowel disease [1], gastric ulcers [2], obesity and diabetes [3,4], and cancers, including esophageal [5] and colorectal [6]. Moreover, the gut microbiome is also implicated in diseases not obviously linked to the GI tract, including disorders of the central nervous system [7], as well as autism [8] and major depressive disorder [9]. The shared mechanism linking these disparate diseases to the gut microbiome is apparently the immune system and its interactions with the gut microbiome during development [10,11]. In particular, lack of interaction with normal gut bacteria that are mutualistic and developmentally appropriate has been suggested as a cause of immunological dysregulation leading to chronic inflammation and various resulting pathologies [3,7,9,11,12]. This is of special interest for cancer prevention, because it appears that chronic inflammation drives oncogenesis in many organ systems [10,12].

Understanding the human gut microbiome adequately will require new perspectives because it is quite unlike most systems studied in medicine. Rather than involving only human physiology and human cells, it is a complex ecological community involving interactions among hundreds of bacterial species. Traditionally, medicine has emphasized reductionist approaches, in which subunits of a system are analyzed in isolation, ignoring complex interactions and focusing on simpler causal relationships. Other fields of scientific research have increasingly been forced to go beyond this approach and grapple directly with complex networks of nonlinear interactions among many entities. The resulting 'complex systems' orientation entails fundamentally different observations and assumptions about causality (Table 1). The techniques developed for studying complex systems are increasingly mature and formalized, and are available for the study of any system in which pure reductionism cannot adequately address the phenomena of interest (e.g. [13]).

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Several striking new empirical results on the human gut microbiome are perplexing and so highlight a need for new perspectives. These challenging recent observations arose from genetic analysis of the presence and abundance of bacterial species in the human gut, and include: (i) individual gut microbiomes are not fixed, but instead show sustained change over many months within each individual, with no apparent external cause [14]; (ii) even a brief disturbance of the gut microbiome often causes lasting change in its make-up [14]; (iii) when multiple individuals are subjected to the same kind of disturbance, the lasting changes that result are not shared, but are unique to each individual [14]; and (iv) a large number of individuals surveyed all fell into just three distinct types, as defined by the presence and abundance of bacterial species in their guts [15]. This is surprising because of the continuous range of possible variation in the abundance of each bacterial species in the gut; because of ongoing changes observed within individuals, and because the observed types did not correlate with any known external factors that might have explained them.

The human gut microbiome is an ecosystem comprising, in preliminary estimates, on the order of 1000 bacterial species [16], with little-known ecological interactions. In ecological theory, interactions among species, including bacteria, are typically modeled using the Lotka–Volterra equation to represent the effects (either negative or positive) of species on each other. The equation has been well-studied mathematically[*], supporting a body of ecological theory on the properties of large and complex ecological communities (Box 1).

Box 1

Stability, dynamic attractors and multistability

In population dynamics with a large number of species, a steady state in which all the numerous antagonistic tendencies are perfectly balanced (making all population sizes constant), as expressly demonstrated in the seminal paper by R.M. May [22], is almost impossible[†]. However, another scenario of stability, called 'asymptotic dynamic stability' [23], is more feasible. In this type of stability, the system continues to change; however, it is trapped within a closed domain of possible states. This closed domain is called a 'dynamic attractor'. Multistability arises when there is more than one dynamic attractor in the system. Starting from slightly different initial states, the system may enter different dynamic attractors. Furthermore, an ecosystem may persist indefinitely in any of several contrasting states under the same external conditions. This 'multistability' plays a significant role in several basic biological processes, such as enzymatic activity in gene expression and cell differentiation [24].

Because it is a complex emergent phenomenon not present in the organisms or species making up the ecological community, multistability is best understood through specialized mathematical and computational tools. In community ecology, the primary mathematical model is the Lotka–Volterra family of equations (Equation I):

$$\frac{dx_i}{dt} = \epsilon_i x_i + \sum_{k=1}^{N} \alpha_{ik} x_i x_k; i = 1, \ldots, N \qquad \text{(I)}$$

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[*]Since its inception, the domain of applications of the Lotka–Volterra System (LVS) has been expanded far beyond its initial context. In particular, it has been shown that LVS is well suited for describing complex dynamics in multidimensional systems with arbitrary structure of interactions [35,36], and thus may be regarded as a universal canonical form for describing a wide range of phenomena in complex nonlinear systems [37].
[†]This is because stable equilibrium at a fixed point in a high-dimensional system would have to meet a very large number of constraints of high algebraic order equivalent to simultaneous negativity of real parts of all the Jacobian eigenvalues. The probability that all these requirements may be satisfied is miniscule in nature [23].

Equation I describes the population dynamics of a community of N interacting species; $[x_i]$ is the state vector characterizing abundance of each species, and $\boldsymbol{\alpha}$ is the matrix of interactions among them. Depending on the structure of $\boldsymbol{\alpha}$, the abundance of any species may have positive, negative or neutral effects on the abundance of any another. The Lotka–Volterra equation describes an astounding number of possible scenarios of behavior, including various forms of stability, instability, periodicity and chaos [25,26]. In particular, mathematical analysis has revealed the explicit conditions under which multiple attractors will exist in a high-dimensional Lotka–Volterra system, resulting in multistability [27].

Multistability and other forms of complex behavior in large networks have been the subject of many publications ([28] and references therein). These have included treatments of population dynamics in large ecological communities [29,30]. Several papers have specifically addressed complex dynamics in microbial food webs [31,32]. Although it addresses much simpler artificial systems, theoretical work has developed several approaches to the problem of controlling multistable systems, some of which have been experimentally validated [33,34].

Complex dynamical systems, including ecosystems, where the properties of interest arise through nonlinear interactions and feedbacks among many entities, are notorious for defying intuitive expectations, because intuitions are typically based on assumptions of simple linear causation, which are often violated in complex dynamical systems (Table 1). Managing such systems effectively requires both appropriate mathematical tools and a shift in conceptual viewpoint.

In summary, incorporating the dynamical systems perspective can help to interpret recent findings on the human gut microbiome. Here, we discuss several specific issues where the interpretation of recent biomedical research results on the gut microbiome can be clarified through an appreciation of theoretical ecology and its mathematical tools.

Sources of individual variation

Gut bacterial communities are highly variable among individuals, and apparently vary in ways that are important to health outcomes. Therefore, it is crucial to understand what determines the make-up and characteristics of individual gut microbiomes. The potential causes of individual variation that have received the most consideration can be classified into two categories, involving either local differences in the founding bacterial species that individuals are exposed to, or differing environmental influences (either internal or external to the body) on the microbiome. However, some recent results on individual variation are not easily interpreted as resulting from either of these two categories of explanation. In an analysis combining samples from several different studies, bacterial species composition of individual gut microbiomes reportedly fell into three robust clusters (termed 'enterotypes') that were not specific to countries or continents [15]. Moreover, these enterotypes were not correlated with age, gender, or body mass index [15]. The lack of correlation between enterotypes and geography seems to rule out explanations based on local differences in colonizing bacterial species. This leaves the possibility that differences among, and similarities within, enterotypes are the result of external influences (e.g. age, gender, body mass or nationality) that might be shared among individuals of the same enterotype, but differ among enterotypes. However, these most obvious candidates for such external influences have already been ruled out. This leaves the results difficult to interpret in the standard framework of simple linear causation.

Recognizing gut microbial communities as complex dynamical systems raises other possibilities, and leads to new testable hypotheses. One important property to emerge from theoretical studies of ecosystems as dynamical systems is the potential for multistability (Box 1). As the name implies, a multistable system can stabilize in any of several alternative states. It may also exhibit switch-like behavior in which it can make a sudden jump from one steady state to a drastically different one under gradual change in an external influence, or even spontaneously, through internal stochastic fluctuations. Multistability has long been recognized as a key concept for understanding behaviors of ecological communities, including bacterial communities [17]. Consistently with theoretical models, ecologists have found empirical evidence of multistable behavior in various ecological communities [18,19].

Thus, a third class of explanation for distinct enterotypes is that the human gut microbiome is multistable, with at least three stable states. This hypothesis would obviate the search for explanatory factors external to the intrinsic dynamics of the gut ecosystem. It also generates its own novel and testable empirical predictions, many of which are consistent with otherwise puzzling empirical observations.

Temporal variation within individuals

In the absence of any conspicuously varying external influences, human gut microbiomes show considerable temporal variation, both in the ileum [20] and colon [14]. Depending on the detail and the duration of observation, human gut microbiomes may appear stable, but similar to many others, these ecosystems are fundamentally dynamic, fluctuating such that only their average state is stable [14]. This is consistent with theory-based expectations of asymptotic dynamic stability, as opposed to static equilibrium (Box 1).

Long-term changes in gut microbiomes after transient perturbations

It is typical of complex dynamical systems, such as ecosystems, that perturbation may dislodge the system from its current basin of attraction, causing it to settle into an alternative stable state after the perturbation [18,19]. This type of behavior has been observed after perturbation of human gut microbiomes by a short course of antibiotics [14]. This observation has led to concerns that antibiotic treatment could accidentally cause an unexpected shift to an alternative stable state in a patient's gut ecosystem, with poorly understood health consequences [14].

Individualized responses to perturbation of gut microbiomes

In the standard paradigm of simple causation, a system can not be understood until experiments can be replicated and repeatable results produced. Thus, it is perplexing that different individuals responded differently to the same experimental treatment of perturbing their gut microbiome. A key consequence of multistability is that different instances of the same type of system, such as different individual gut microbiomes, may show very different responses to the same perturbation. Even within the same individual, a repeated treatment sometimes produced a different response each time [14]. This is not an unexpected result in a complex dynamical system, because initial conditions are different with each application of the same treatment. This property further complicates the pitfalls of accidentally causing a shift to an alternative stable state in a patient's gut ecosystem, because it makes such shifts less consistent and predictable.

Concluding remarks

Biologists have often been tasked with the difficult problem of managing complex ecosystem dynamics. Medical professionals have not been in the past, but that is rapidly

changing. Because of the broad health importance of the human gut microbiome, all available conceptual tools must be used to understand and manage it. This is a pressing concern for public health as well as medicine. Beyond the issue of perturbing a single individual's microbiota, extensive antibiotic use, along with other practices (including cesarean sections), may be reducing or eliminating, from whole populations, the presence of mutualistic and beneficial bacterial species that have been part of human physiology throughout human evolution. Major resulting health problems have been suggested that, in most cases, have not yet been rigorously investigated [21].

Coming to terms with complex interspecies interactions within the gut microbiome, and between it and the human host, will require medicine to borrow from other disciplines, both for relevant theory, and for case studies and examples. The fields of ecology and complex dynamical systems may provide rich sources of useful insights. Hopefully, adding to the range of empirically testable hypotheses will speed progress in this emerging field of study.

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Table 1

Standard assumptions for simple (single-entity) linear systems versus complex nonlinear networks

Simple linear systems	Complex nonlinear networks
Deterministic systems are highly predictable	Deterministic systems may show chaotic behavior and extreme sensitivity to initial conditions
Stability reflects static equilibrium	Stability can reflect trapping within a complex dynamical attractor
Shared properties among different instances of the same type of system suggest shared external influences	Shared properties may reflect a system attractor
Differing properties among instances suggest different external influences	Differing properties may reflect system multistability