Journal of Developmental Origins of Health and Disease

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Original Article

Cite this article: G-Santoyo I, Ramírez-Carrillo E, Sanchez JD, and López-Corona O. (2023) Potential long consequences from internal and external ecology: loss of gut microbiota antifragility in children from an industrialized population compared with an indigenous rural lifestyle. *Journal of Developmental Origins of Health and Disease* **14**: 469–480. doi: 10.1017/S2040174423000144

Received: 20 August 2022
Revised: 21 April 2023
Accepted: 25 April 2023
First published online: 24 May 2023

Keywords:
Gut microbiota; antifragility; lifestyles; criticality; ecology

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Potential long consequences from internal and external ecology: loss of gut microbiota antifragility in children from an industrialized population compared with an indigenous rural lifestyle

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Abstract

Human health is strongly mediated by the gut microbiota ecosystem, which, in turn, depends not only on its state but also on its dynamics and how it responds to perturbations. Healthy microbiota ecosystems tend to be in criticality and antifragile dynamics corresponding to a maximum complexity configuration, which may be assessed with information and network theory analysis. Under this complex system perspective, we used a new analysis of published data to show that a children's population with an industrialized urban lifestyle from Mexico City exhibits informational and network characteristics similar to parasitized children from a rural indigenous population in the remote mountainous region of Guerrero, México. We propose then, that in this critical age for gut microbiota maturation, the industrialized urban lifestyle could be thought of as an external perturbation to the gut microbiota ecosystem, and we show that it produces a similar loss in criticality/antifragility as the one observed by internal perturbation due to parasitosis by the helminth *A. lumbricoides*. Finally, several general complexity-based guidelines to prevent or restore gut ecosystem antifragility are discussed.

Introduction

The introduction discusses the complexity of the gut microbiota, which is composed of thousands of bacterial species that self-organize to exhibit non-trivial global structures and behaviors. Two main characteristics of complex systems – emergence and self-organization – are described, and it is explained how complexity can be considered a balance between these two factors. The concept of criticality is introduced, which is a scale-invariant dynamical regime that maintains a balance between flexibility and robustness in a system. Criticality is present in all living systems and is associated with maximum inference and computational capabilities. We propose that complexity is a universal payoff function of living systems and may be used in the measurement of both criticality and antifragility. Please see the glossary in the supplementary materials.

The gut microbiota is an ecosystem mainly composed of thousands of bacterial species that, through local interactions with each other, self-organize to exhibit non-trivial global structures and behaviors at larger scales, giving place to properties that may not be understood or predicted from the full knowledge of the species biology alone. These properties are acknowledged in the standard definition of a complex system, and it is well recognized that new mathematical frameworks and scientific methodologies are required for their understanding.[1]

Two of the main characteristics of complex systems are Emergence and Self-organization. *Emergence* is the information that results in a system after being subjected to any process that modifies it. This information is only observable when all elements of the system are included, and it can be mapped and measured by Shannon information (S). On the other hand, *Self-organization* can be considered as the magnitude of change in the system order over time,[2] and it is usually seen as the opposite of emergence since whenever the system increases organization, information diminishes. In that sense, Complexity (C) can be considered as the product of emergence and self-organization, somehow encoding a balance between processes that generate information and randomness with processes that generate order-reducing information.[3]

In terms of dynamics, this translates into a balance between flexibility and robustness[4] that usually evolve into a scale-invariant dynamical regime called criticality. This property is present

in all living systems,[5] where the maximum inference and computational capabilities are achieved.[6]

Criticality is, in consequence, a state that maintains the system in an equable trade-off between flexibility and robustness in a specific scale of observation. Hence, it is expected that the criticality regime would be observed as part of what we consider health in a system. For instance, there is cumulative empirical evidence that in young and healthy individuals, both the heart and brain are in criticality[7-10]; on the opposite side of the coin, under conditions of elderly or chronic diseases (such as obesity or diabetes), there is a loss of criticality mainly by loss of flexibility/emergence.[11] There is also solid evidence that gene regulatory networks of natural organisms are in or close to criticality.[12-15]

Taking into consideration the ecosystems formed by the microbiota, and from a more general network theory perspective, Huitzil and co-workers[4] have proposed that microbiota ecological networks are critical,[16] conferring the system evolvability[17,18] that enhances faster information storage, processing, and transfer.[19,20] This informational capability means that healthy microbiota ecosystems are able to respond to external perturbations.[21] For instance, recent work has shown that greater network complexity is related to higher resilience to perturbation by microbiota communities[22] and that more complex microbial networks are characteristic of the least disturbed (external) ecosystems, as shown in soil microbial networks that reduce their complexity when agriculture intensifies.[23]

On the other hand, microbiota ecosystems (and ecosystems in general) could also and must do much more than merely respond to environmental perturbations; they most certainly have built-in characteristics that enable them to even take advantage of them. Antifragility is maybe the core one of these characteristics[24,25]; which is the exact opposite of fragility (being broken by randomness, perturbations, or time) and is defined by Taleb as the nonlinear locally convex response of a specific payoff function in front to a well-defined perturbation, in terms of type, intensity or frequency (i.e., A formal definition of antifragility as convexity in the payoffs space is found in Taleb & Douady[26] and Taleb.[27]

As we have eco-evolutionary reasons and empirical evidence that strongly support the idea that all living systems tend to criticality in which complexity (balance of *Emergence* and *Self-organization*) and Fisher information (system stability) are maximum, meaning that they have the best computational and inferential capabilities, then any deviation from criticality (depart from maximum complexity) must result in a diminishing of the system capabilities to respond to perturbations. So, one may consider that complexity is a universal payoff function for living systems and may be used in the measurement of criticality and antifragility.[6,28,29]

A gut ecosystem perturbation might come from internal and external factors. For instance, it is known that gut parasites could be a source of internal perturbation, since they produce changes in physiological processes, including hormonal,[30] neurological,[31] and immunological[32] processes, that can even affect the host's behavior; for example, the parasitic wasp *cotesia congregata* induces the host *manduca sexta* to increase the octopamine concentration in its hemolymph, then the frontal ganglion's motor pattern is disrupted by the elevated octopamine concentration, which prevents food intake.[33,34] Evidence points out that, to some extent, not only micro but also macro-organisms in the gut are capable of modifying several physiological axes of the host. In recent work[28] authors found compelling evidence that suggests the presence of the gut parasite *Ascaris lumbricoides* induced perturbations in human gut microbiota network properties, translating to a loss of emergence, a departure from criticality, and ultimately loss of health.

On the other hand, external perturbations may come from different sociocultural practices present in a particular lifestyle and in the ecological conditions in which the individual is living. Both external factors are essential during childhood since, during this period, the human gut microbiota is more sensitive to perturbations, which affects its stability and maturity.[35,36]

Different environments and behaviors have influenced the evolution of the human microbiota throughout human evolutionary history, and it has become an essential line of research in which multiple studies have compared the gut microbiota of industrialized versus non-industrialized (i.e., traditional and rural) human populations.[36,37] As a result, it has been found that gut microbiota might be very vulnerable to industrialization.

For example, cultural strategies to kill or limit exposure to pathogenic microbes, such as broad-spectrum antibiotics and sanitation, or the consumption of ultra-processed foods containing preservatives and additives, could act as selective forces for gut microbiota favoring certain groups but affecting others. Consequently, the gut microbiota of individuals living in industrialized societies is less rich and diverse than that of individuals living in non-industrialized societies. Also, this last lifestyle shares taxa that have been lost or reduced, such as members of the Spirochaetes or Prevotellaceae family.[36,38]

The changes in the micro-ecosystem configuration as a product of industrialization might affect the host´s health due to the subsequent loss of the ecosystem services offered. The gut microbiota intervenes in the maturation and regulation of the immune system, the synthesis of vitamins and hormones, food digestion, protection against pathogens, etc. Hence, the relationship between gut microbiota and several chronic diseases mainly present in industrialized societies has become more evident. The evidence of this relation has been mainly constructed by either evaluating specific species isolated from the rest of the gut microbial ecosystem, or by measuring its composition, structure, and diversity under classical ecological lenses.[39-41] However, these approaches could underestimate ecosystem emergence and self-organization, both important not only to quantify the current health state of the microbiota (and its host) but also, its ability to respond to subsequent perturbations. In that sense, a scenario that includes internal and external sources of perturbations, such as lifestyles or parasites, may set an excellent ecologically valid experiment to determine differences or similarities regarding the criticality/antifragility of gut microbiotas that have been shaped under these conditions.

Furthermore, microbes in the gut ecosystem interact with each other in non-trivial ways including the use of intermediary molecules, metabolites, and/or toxins,[42-47] yet the exact nature of each interaction and more importantly its measurement is usually inaccessible using standard methods. So, as pointed out by Cickovski and co-workers,[48] an alternative method to assess this interaction is to measure bacterial co-occurrence networks, which has been widely applied in exploring the potential interactions among microbes.[23,44,47,49,50] In very general terms, a co-occurrence network is an undirected, weighted network with nodes that represent bacterial taxa present in the community and edges that correspond to how strongly the two taxa tend to co-occur (i.e., co-infect) in the sampled communities.

Therefore, using a novel perspective of complex systems, we evaluate the criticality/antifragility of gut microbiotas from

https://doi.org/10.1017/S2040174423000144 Published online by Cambridge University Press

Figure 1. Locations of Plan de Gatica and El Naranjo, indigenous localities located in the municipality of Ayutla de los Libres and Acatepec (respectively) in the Montaña Alta region of the state of Guerrero, México. Families of these locations were the study subject of this research.

children subjected to an external perturbation promoted by an industrialized lifestyle and an internal perturbation promoted by the presence of the gut parasite *Ascaris Lumbricoides*. In this work we are using the labels "external "and "internal" in relation to (1) the ecological perturbations that come from the ecosystem where the individuals live in form of their diet regimes (as part of a specific lifestyle); and, (2) the ecological perturbations that come from the conditions of the gut microbiome ecosystem inside the individuals. This labeling, used basically to remind the reader that we are working with two different types of ecosystems, should not be interpreted as if we are equating industrialized lifestyle and the presence of parasites.

Methods

Study subjects

We study two populations of children from 5 to 10 years old under two sources of perturbations. The first one, living in a non-industrialized rural indigenous population located in southwest Mexico, was under the influence of an internal source caused by the presence of the gut parasite *A. lumbricoides*. The second one was affected by an external perturbation induced by the contrasting lifestyle lead in an urban population in Mexico City.

The geographical region called "la Montaña Alta" in Guerrero, México, has an essential history of economic marginalization. In particular, the Me'phaa indigenous communities have access to a homogeneous and limited variety of diets and depend on subsistence farming and seasonal foods.[51] Data from the federal office that evaluates poverty and socioeconomic development (i.e., CONEVAL) point out that in 2018, 27.8% of the population in Guerrero was below the threshold of food insecurity; 93% of this population was located in two regions, "montaña alta" and "montaña baja."

We obtained the rural samples from two Mephaa communities; "Plan de Gatica" (17°7′ 49.5552″ N, 99.7′ W, EASL 510 m) and "El Naranjo" (17°9'54.0036" N 98°57', 50.9832" W, EASL 860 m); both communities are part of the geographical region of "the Montaña Alta" in Guerrero (see Fig. 1) and 56 km away from each other.

The 2020 Population and Housing Census conducted by the National Institute of Statistics and Geography shows that the inhabitants of both communities are exclusively indigenous, and are within the regions with the greatest poverty and social vulnerability in Guerrero and the entire country. Thus, the consensus in the municipality that includes the "Plan de Gatica" community has 28.4% of individuals living in extreme poverty (20,998 people). Similarly, 67.75% of the people from "Acatepec," the other municipality that includes the "El Naranjo" community, live in the same poverty conditions.

These indigenous people generally dwell in settlements of fifty to eighty households, each with five to 10 individuals. Most residents only speak "Me'phaa," their native language, and they mainly depend on subsistence farming of legumes such as beans and lentils, with corn being the primary grain grown. In addition to gathering wild edible plants, some fruits and vegetables are grown in garden plots.[52] Hunting and rearing some poultry provide animal protein, but the consumption of this food is primarily on special occasions, such as festivities; hence it is not a regular food in the diet of the "Me'Phaa" people.[52]

In contrast, the samples from the city group comprise children from the southern area of Mexico City (18.102" W 19°12'36.36" W). This urban population is essentially the opposite of the indigenous population mentioned above. The children of urban dwellers lead a Western lifestyle that is comparable to that of upper-middle class families, who routinely consume diets based on ultra-processed foods and animal-products consumption; refined products, such as oils, sugar, salts, and grains; as well as low consumption of whole grains, fiber, and vegetables. Additionally, they have easy access to allopathic medications, such as antibiotics and other medications.

It is important to highlight that the urban population does not present parasites and that previous work[41] suggests that the presence of *Ascaris lumbricoides* in the rural population can cause a perturbation in the gut microbiota network, leading to a loss of emergence and departure from criticality, ultimately resulting in a loss of health. This highlights the importance of studying the interactions between gut microbiota and parasites and their potential impact on human health. The study also demonstrates the usefulness of network analysis techniques in understanding these complex interactions. The practical implications of this research could include the development of new strategies for managing and treating parasitic infections and their associated health effects.

The non-industrialized Rural (R) population in this study consists of 29 children; 18 Non-Parasitized (NP) and 11 Parasitized (P), all of them belong to the Me´phaa population. The Urban (U) population considers 13 children all NP from México City, who practice a clearly industrialized style of life. Parasites were determined following the protocol implemented in Ramírez-Carrillo et al.[41]

The Rural population has a particular set of historical conditions that make it the more contrasting group in terms of lifestyle in regard to typical urbanized areas of Mexico City.[53-55]

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Due to the socioeconomic context of this population, associated with historic poverty and marginalization, they have the lowest income and the lowest access to health services in the country. In terms of biological path dependence, this population has almost no access to allopathic medications that we know and that may have induced important changes in the microbiota ecosystem.[54,56-59] Although allopathic medication is practically absent in these communities[59,60] we selected only participants that had not taken any medications such as antibiotics or anthelmintic treatment during the two years prior to the study.

Finally, Lewis et al.[61] argues that indigenous populations in research on the human microbiome are essential for several reasons. First, indigenous populations often have unique microbiomes due to differences in diet, lifestyle, and environmental exposures, which can provide valuable insights into the factors that shape the human microbiome. Second, indigenous populations have a long history of traditional medicine practices that often involve the use of microbial communities, which can inform new approaches to microbiome-based therapies. Third, the participation of indigenous communities in microbiome research can help to address health disparities and promote health equity by identifying microbiome-based interventions that are effective in diverse populations. Overall, the inclusion of indigenous populations in microbiome research is essential in increasing our understanding of the human microbiome and developing new interventions for improving human health.

Taxonomic bacterial inference

For this work, as explained in more detail by Ramírez-Carrillo and co-workers (2020), gut microbiota taxonomic inference was obtained from fecal samples through High Throughput Sequencing in the Illumina platform. Briefly, each participant provided a fecal sample in a sterilized plastic bottle, which was frozen with liquid nitrogen in subsequent storage at −20°C, until DNA extraction. After extraction, the V4 hypervariable region of the 16S rRNA gene (ribosomal ribonucleic acid) was amplified with the universal bacterial/archaeal primers 515F/806R. Characterization of fecal purified 16S rRNA fragments (20 ng per sample) was sequenced on an IlluminaMiSeq platform and paired-end reads of around 250 bp were generated. These readings were processed in QIIME2, noise was removed with the DADA2 complement to obtain the Amplicon Sequence Variants (ASVs). Through filters and comparisons with databases, tables of abundance and phylogeny of the representative ASVs were made.

ASVs represent the biological sequences of the 16S rRNA gene and distinguish sequence variants that differ by as little as one nucleotide between each sample.[62] Abundance and phylogeny data were analyzed under R environment using phyloseq[63] and ggplot2 packages. 21,000 reads per sample were used as the minimum sequencing effort for Plastidic ASVs filtering. Sequence data is available in the NCBI database with Bioproject number PRJNA593240.[64] All the testing and recruitment procedures of the study were approved (September 25, 2017) by the Research Ethics Committee of the Faculty of Psychology of the National Autonomous University of Mexico (FPSI/CE/01/2016) and were executed in accordance with the ethical principles and guidelines of the Official Mexican Law (NOM -012-SSA3-2012). The persons responsible for the care of participating infants read and signed a written informed consent.

Network modeling and complexity estimation

In this work, we construct a co-occurrence matrix from the ASVs dataset (i.e., bacteria species) using the Cooccur package[65] (https://cran.r-project.org/web/packages/cooccur/cooccur.pdf) in R (74) for the three populations under study.

Although the network theory approach has shown to be most useful in a number of contexts[66-69] and the concept of network complexity is central, there is still a lack of a universally accepted measure of complexity.[70-72] Among many possible measures of network complexity, the entropy-based ones including number of vertices, number of neighbors, and number of neighbors at a given distance have been recognized to be both simple to use and useful.[73] For this, we used the CytoHubb app inside CytoScape,[74] an open-source Network Analysis software, to calculate the average number of neighbors, number of nodes, and Network heterogeneity which as we have commented are related to different aspects of complexity. Additionally, to determine complexity directly we calculate the Shannon information (S), which is a proxy of informational emergence,[3] for each individual of the population Rural-P (R-P), Rural-NP (R-NP), U.

As was pointed out before, this study considered an indigenous community that depends on traditional agriculture and foraging; and an urban community that relies on industrialized food production. The rationale for choosing two communities with contrasting subsistence models is that these dissimilarities were expected to lead to differences in the gut microbiome of the two groups, as diet is a significant determinant of gut microbiome composition. In order to compare the gut microbiome of the two groups, fecal samples were collected from each participant and analyzed using 16S rRNA gene sequencing to identify the bacterial species present in their gut microbiome. The researchers also collected information on the children's diets and lifestyles through surveys and interviews.

Overall, the sample design was devised to test the hypothesis that different subsistence models lead to differences in gut microbiome composition, intending to improve our understanding of how diet and lifestyle factors influence the gut microbiome.

Results

In general terms, the current work describes a study case that analyzes the gut microbiota networks of three populations: U, R-NP, and R-P. The study uses The Graph Edit Distance (GED) analysis, to compare the complete network structures of the three populations. The higher the value of GED, the more dissimilar the networks are.

In particular, Fig. 2 shows the GED analysis score of the gut microbiota ecosystem network for the R-NP group (considered the control group for comparison) and the two under perturbation (R-P and U-NP). The results indicate that U and R-P characteristics affect gut microbiota networks in a similar manner, suggesting that U lifestyle could be thought of as a perturbation that may lead to similar patterns of microbiota dysbiosis.

Fig. 3 shows three standard network metrics related to complexity and discusses them in terms of heterogeneity, highlighting the balance nature of complexity.

Fig. 4 shows complementary network measurement metrics, while Fig. 5 shows the differences in Shannon Information (emergence) for the three populations. Both populations under perturbation, R-P and U, show a statistically lower value of Shannon information (emergence, diversity) than R-NP.

https://doi.org/10.1017/S2040174423000144 Published online by Cambridge University Press

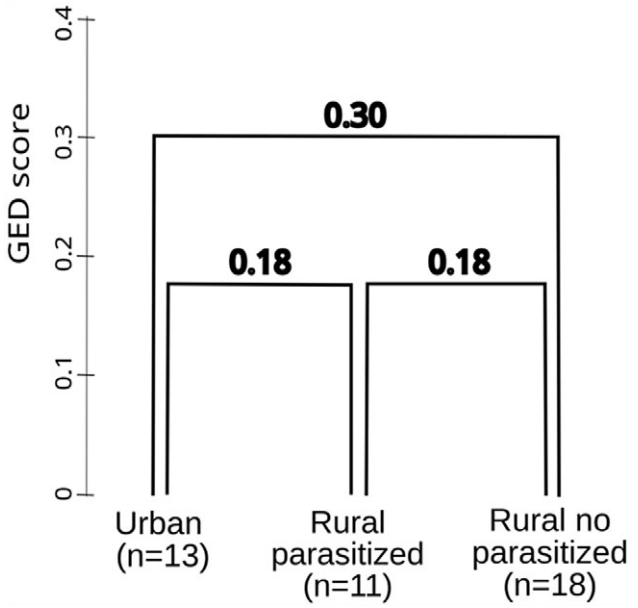

Figure 2. We show the GED analysis score of gut microbiota ecosystem network for the Rural-NP group (considered as the control group for comparison) and the two under perturbation (Rural-P, Urban NP).

Overall, the study suggests that the U lifestyle could lead to similar patterns of microbiota dysbiosis as R-P and that the rural populations exhibit greater complexity in their gut microbiota networks than the urban population.

In more detail, Fig. 2 presents the results of The GED analysis, which compares complete network structures[75] for the three populations, U, R-NP and R-P. The higher the value of GED the more dissimilar the networks are. We see that the interval of GED between U and R-P is given by GED(U, R-P) <GED(U, R-NP) and GED(U, R-P) < GED(R-P, R-NP). So U and R-P characteristics affect gut microbiota networks in a similar manner. As it was previously reported, R-P corresponds to a perturbation that might produce a dysbiosis in gut microbiota, then U lifestyle could be thought of also as a perturbation that may lead also to similar patterns of microbiota dysbiosis.

In Fig. 3 we show three standard network metrics related to complexity. Both rural populations show greater values of the number of nodes and neighbors than urban (industrialized) populations. Between both rural populations, the R-NP exhibits greater values than R-P. We also found that urban microbiota networks are much more heterogeneous than rural ones, being the Parasitized the lowest. In general, systems that are either too heterogeneous or too homogeneous are less complex. Complexity is always manifested in the balance between self-organization (in this context homogeneity as a manifestation of the structuring that comes from order) and emergence (in this context heterogeneity as a manifestation of randomness).

Moreover, both populations under perturbation, R-P and U, show a statistically (Wilcoxon rank sum test one tail, $W = 162$, p-value $= 0.037$) lower value of Shannon information (emergence, diversity) than R-NP, as we can see in Fig. 5.

Discussion and conclusions

In a structural taxonomic approximation of these two children's populations, Sanchez-Quinto et al[76] found that compared with children from Mexico City, the indigenous population showed higher alpha diversity in several indexes, such as Faith's phylogenetic diversity, Shannon diversity, and observed ASVs. In addition, a subsequent beta diversity analysis indicated a clear separation between these two populations. In consequence, only a quarter (23.64%) of the total species (i.e., ASVs) were shared among the indigenous and urban populations (Fig. 6B; SUP); from these, 56 species showed statistically differentiated abundances, most of them overrepresented in the Me'phaa children.

Related to a specific taxonomic structure, Firmicutes, Bacteroidetes, and Actinobacteria Phyla were more prevalent in children from México City than those from the Me'phaa (Supplementary Fig. 6H). Interestingly, several phyla were only found in the indigenous community in very low abundances, such as Deinococcus-Thermus (0.079%), Chloroflexi (0.01%), Elusimicrobia (0.01%), Acidobacteria (0.0071%), and Fibrobacteres (0.004%). (Supplementary Table S1) (Supplementary Fig. 6H).

In consequence, the GM composition and structure were remarkably different. These results are consistent with other studies that have pointed out the impact of lifestyle on GM.[77-82]

Our results agree with Kaplan and co-workers.[83] They found that Hispanic populations who immigrate early in life to the USA have low GM alpha diversity through the Shannon index, contrasting with those who relocate to the USA during adulthood, over 45 years old.

In that sense, our results contribute to the emergent concept of "social microbiome," which suggests that interactions of social and ecological contexts that can take place at various levels of the biological organization may have an impact on the microbial exchange between organisms, and hence, in the states of GM ecosystems health.

We consider that by studying this interplay between lifestyles and GM ecosystems, we are starting to understand how the Holobiont co-evolves in a particular social context, in what we have proposed as a new eco-evolutionary ontological unit, named the ecobionts.

Returning to the discussion of standard analysis versus complex systems perspective, it is proposed that high GM taxonomic diversity is a proxy of GM health, since GM low-abundance great numbers of taxa are essential for the homeostasis and the constant maintenance of certain functions in human GM.[84] Nevertheless, there are some valid critiques.[85,86]

For instance, a recent study on soil microbiome showed that its diversity and functionality can change under global environmental perturbations, but it does not always lead to microbial diversity loss. Furthermore, changes in land covered by agricultural practices increase alpha diversity. This seems to be occurring even during the conversions from highly diverse natural ecosystems to homogeneous agricultural monocultures, which is not a beneficial process for the original ecosystem.

In this sense, the ecosystem's health is not only a function of composition, structure, and function in a particular moment, but it is also a function of how these attributes change over time and, more importantly, how they combine to allow the ecosystem to respond to perturbations, variability and ultimately to persist over time. In terms of how ecosystems respond to perturbations, there is information not contained in the composition and structure of its populations, but that emerges from several species interactions working together as a network. These properties of a biological system justify why a complex systems perspective using network theory is necessary and complements more standard analysis.

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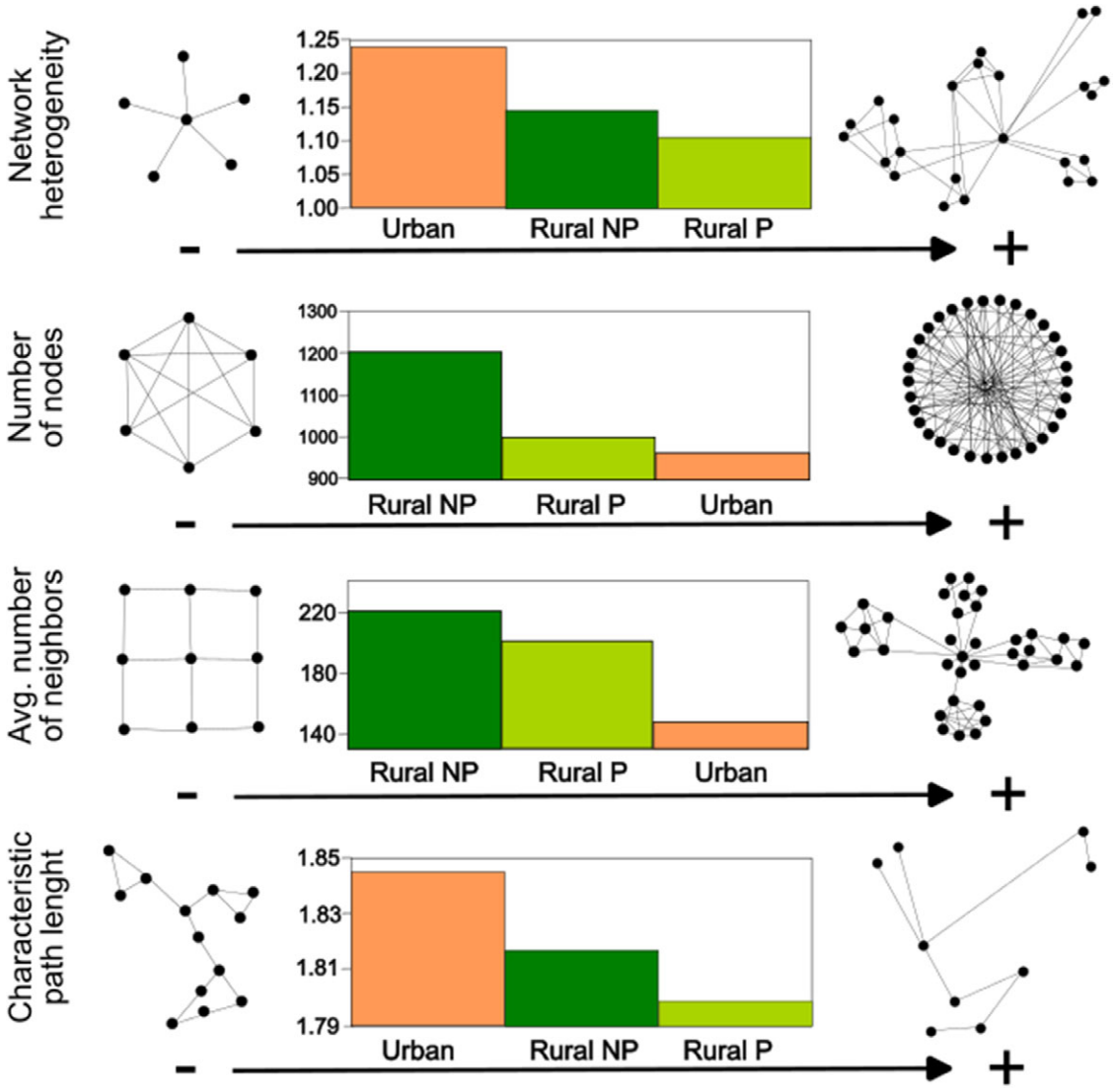

Figure 3. Network metrics usually associated with connectivity for the three populations.

As with diversity in ecology, standard network theory metrics as heterogeneity do not map directly to criticality or antifragility, as has been discussed by López-Corona and co-workers[87] who suggest that maximum antifragility arises at an "optimal" balance between homogeneity and heterogeneity that seems to be non-trivial, context-dependent, and in some cases, dynamic.

In that sense, this work implements the idea of how to use metrics from network theory to assess ecosystem antifragility which we have shown is a more general and rigorous conceptual framework to understand EH.[29] Contrary to standard network metrics usually associated with criticality but in an indirect way, Minimum Spanning Tree has strong theoretical reasons[88-90] as well as empirical evidence associated[91] that prove why it is a valid metric to compare networks in terms of criticality/antifragility, and therefor is a promising metric for future works. For instance, we know that MST reflects global information transmission optimality (a requisite for criticality); it represents an informational backbone that has been diluted to the maximum possible level while maintaining connectivity. Specifically, its role as an informational backbone has been highlighted in recent applications.[87,92,93] Some applications of MST as an informational backbone include children with math difficulties,[94] dyslexic problems,[95] amyotrophic lateral sclerosis disease,[96] understanding sub-networks for the distinction of subject traits,[97] discrimination of motor imagery hand movement,[98] testing cognitive impairment in dementia,[99] and to track some changes in the brain's functional networks following surgery.[90]

In the same line of thought, taking the new ideas about what an ecosystem is from a recent work about planetary antifragility,[100] we consider that the GM is an open thermodynamic system constituted by a community of living organisms in conjunction with the nonliving components of their environment that is in health when through its interactions and evolutionary processes, constrained by the external conditions, self-organize into a criticality dynamic regime, with maximum computational and inferential capabilities that allow it to respond and thrive under uncertainty, stressors, perturbations and ultimately time, achieving maximum antifragility.

Even more, we could hypothesize that human systemic health arises from thermodynamic mechanisms that operate through human anatomy and physiology in its exchange of matter, energy, and information with its surroundings, until reaching an

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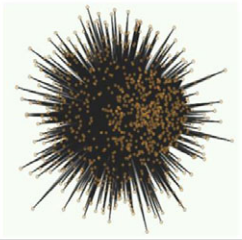
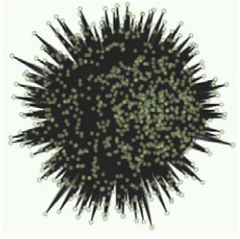
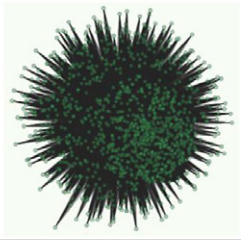
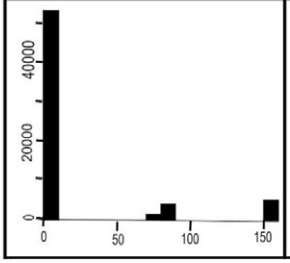
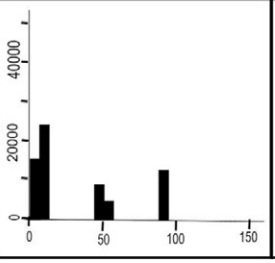
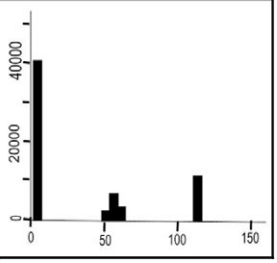
	City	Rural P	Rural NP
Number of nodes	957	1000	1205
Number of edges	70767	100617	132740
Avg. Number of neighbors	147.893	201.234	220.315
Characteristic path length	1.845	1.799	1.817
Cluster coefficient	0.926	0.919	0.921
Network density	0.155	0.201	0.183
Network heterogeneity	1.239	1.104	1.143
Network centralization	0.847	0.8	0.818
Network			
EdgesBetweenness histogram			

Figure 4. Complementary network measurements metrics.

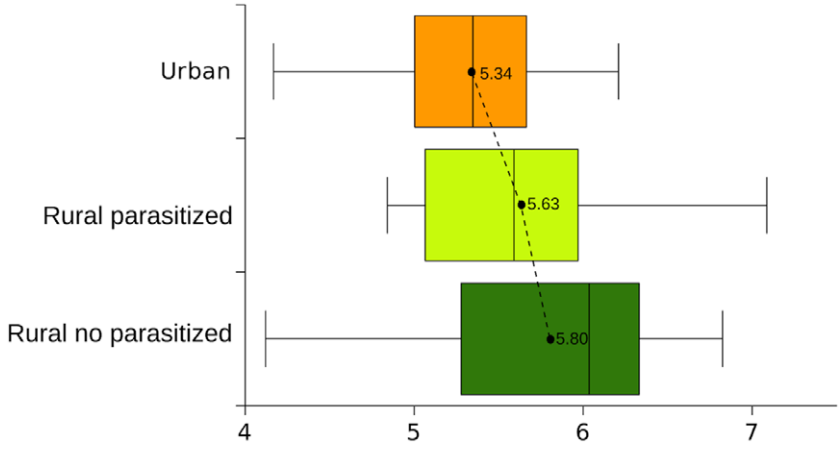


Figure 5. Difference of Shannon Information (emergence) for the three populations ($W = 162$, p-value = 0.037). The box plot shows the median, quartiles, min-max, and point is the mean.

operational scale-invariant configuration in which there is an optimal balance, called Criticality; between order/robustness (self-organization) and random/flexibility (emergence) processes that confer the organism with the best capacities to respond and adapt to the environment, in what is called antifragility.

As suggested by Stuart A. Kauffman and others.[5,101-106] Life on a macroscopic scale displays a large amount of variability but it is much more uniform at the scale of cells, where all living systems share many common structural and functional features. How this macroscopic biodiversity emerges from the microscopic subsystems is explained by the principles of evolution, but even then, one may ask what natural selection chooses. A very promising basic principle to respond to that fundamental question is that evolution should have driven living beings toward critical states since they are favored by maximum computational and inferential capabilities called criticality; and which translate into system capacity to take advantage of environmental variability, randomness, and time, captured in the concept of Antifragility.[6,25]

Traditionally, until recently, the vast majority of studies in gut microbiota focus on the relationship between some bacterial group and a specific pathology, comparing the abundances of species between samples or populations with some disease, versus a control sample; or through the relationship between the presence of certain bacteria and genetic properties of the host. These studies have generated a great deal of useful information by finding possible key relations with certain diseases, but these isolated analyses do not capture the complexity of the bacteria–bacteria interaction and bidirectionality between bacteria-hosts. This

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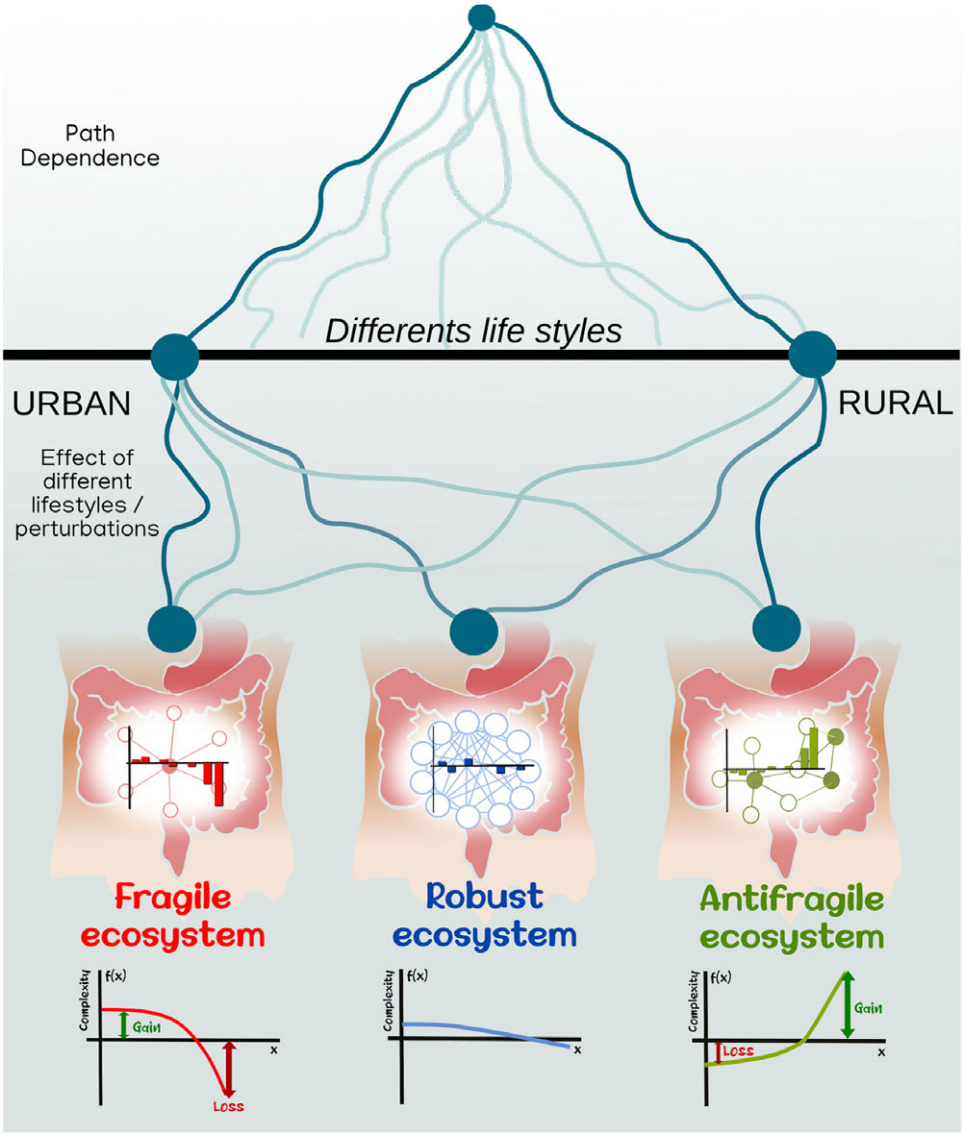

Figure 6. Conceptual figure showing the effect of path dependence on the set of possible future configurations for gut microbiota ecosystem in terms of how it responds to perturbations to complexity as a general payoff function valid for systems under eco-evolutionary processes, and that define three types of configurations: fragility when it responds in a nonlinear concave way; robust if it is essentially insensible to perturbations or antifragile if it responds in a nonlinear convex way.

multi-scale dynamic set of interactions gives place to a very complex cascade of bacterial adaptations until a homeostatic balance is reached between the host and its microbiota. The new technical capabilities and analytical tools have made clear that the use of network theory promises to be a key piece in the future investigation of the complex relationship between the host and its gut microbiota.[4,107,108]

In this context, we have shown that the overall structure of the R-P (internal perturbation) microbiota network is 40% closer to U (external perturbation) than to R-NP (non-perturbed) population. We also found that the number of neighbors and nodes is the highest in the R-NP, followed by the R-P, and the lowest in the U population. These two-network metrics are directly related to the biodiversity in the microbiota ecosystem, and if taken together with the result that the U network is very heterogeneous, the R-P has a very low value of network heterogeneity and the R-NP has a middle value, we infer that the R-NP microbiota network is more complex than that in the perturbed populations. We know that complexity is lost whenever the system network heterogeneity is very high or low. In terms of Shannon information – a standard proxy of total richness and diversity, but also a system emergence[3] – we found that R-NP has a higher value that is statistically different from both R-P and U. As we know that R-P is a condition that might lead to dysbiosis due to the presence of parasites,[42] then the lower value of Shannon Information represents a lower complexity level and hence a loss in criticality/antifragility compared to R-NP. Thus the lower value of Shannon information for U is also a loss of complexity and criticality/antifragility.

Our work offers evidence that external perturbations in the form of U lifestyle may be considered equivalent to internal perturbations such as the presence of parasites; and that both lead to a loss of antifragility in the gut microbiota ecosystems. This result is consistent with recent studies that show that Industrialized populations exhibit a consistent loss of gut microbial diversity and also that they are clearly related to several non-communicable chronic diseases.[109-114]

Our results also adhere to the idea that microbiota in general plays a key role in host evolution and ecology and particularly that the gut microbiota acts as a fast response network coupled with a slow response one, the genome, that confers evolutionary criticality. In this sense, there is accumulated evidence that industrialized lifestyles have rapidly changed the human gut

https://doi.org/10.1017/S2040174423000144 Published online by Cambridge University Press

microbiota ecosystem which translates into high rates of these Noncommunicable diseases.[4,109,115] We now know that some kind of "extinction event" in human gut bacteria might have already happened involving the loss of some species, such as *Ruminococcus callidus*, *Butyrivibrio crossotus*, and *T. succinifaciens*; and the increase in the number of Bacteroides and Prevotella SGBs[116]; the direction and changes of the different functional groups in the gut microbiota ecosystem may still remain far from being fully understood.

Growing evidence suggests that recent lifestyle changes, most notably the high-fat, high-sugar "Western" diet, have affected the genetic makeup and metabolic processes of the human gut microbiome.[117] It is currently believed that such diet-induced changes to the microbial populations in the gut are responsible for the escalating epidemics of chronic illness in the developed world, including obesity[117,118] and inflammatory bowel disease.[119] Under these considerations, there are calls to restore the composition, structure, and functioning of the ancestral gut microbiota ecosystem using the concept of "rewilding" (4). Although there are successful examples of rewilding such as the widely celebrated reintroduction of gray wolves (*Canis lupus*) to Yellowstone National Park; appropriate applications of rewilding remain under debate. For example, Carmody and co-workers[120] have raised questions about how this could be implemented, considering for example that high microbial plasticity may underpin an industrialized gut microbiota that is reasonably well adapted to its environment, even if it is then less well paired with the host. They proposed that there may be some sort of "third body problem" for the human microbiota environment giving place to an unsolvable puzzle for human health. We think that our Ecosystem Antifragility framework[29] and the evidence found here, solve this problem. Taking all into account, using a complex system approach showed that the arrow of health points in the direction of critical/antifragile (more complex) gut microbiota, and that arrow is aligned with non-industrialized lifestyles.

As suggested by Sonnenburg and Sonneburg[36] it seems that to fully understand how gut microbiota modulates human health it is necessary to incorporate an ecological perspective to identify gut microbiota ecosystem services. In this way, assessing the impact of an urban industrialized lifestyle on these services might depend on the specifics of numerous factors and could require isolating and archiving bacterial strains that are sensitive to this kind of external perturbations, and conducting specific studies for them. Nevertheless, this traditional approach to ecology based on ecosystem integrity is limited because it has an underlying model for ecosystem health (EH) as a function of the ecosystem state measured as integrity or EH = f(state). But as we have been arguing, we also need to think of the dynamics and how the system responds to perturbation; so for us, it is clear that we need a much wider model of health given by EH = f(state, dynamics, response to perturbations) than the one is given by EH = f(integrity, criticality, antifragility) in terms of assessment.[29]

Fig. 6 shows a conceptual diagram showing the potential effect of path dependence[77,121] that combined with different lifestyles restrict the space of possible network structures and type of response to perturbation. Due to path dependence including lifestyle, gut microbiota ecosystems may turn fragile if they lose complexity under perturbation; robust if it is essentially insensible to it; or antifragile if it benefits from it as has been observed for example in molecular ecological networks in grassland soil microbial communities.[122]

We consider that this change of framework is not only interesting from the theoretical perspective to understand for example longevity[123] but it has also been shown that using its principles of an antifragility perspective may improve clinical practices in oncological drug administration.[124]

Supplementary material. For supplementary material accompanying this paper visit https://doi.org/10.1017/S2040174423000144

Data Availability Statement. All sequences obtained were uploaded to the NCBI database under the Bioproject number PRJNA593240 with the link: https://www.ncbi.nlm.nih.gov/bioproject/?term=PRJNA593240

Complementary data is available at: https://osf.io/g6ub2/?view_only=d97583bfc8284db0a294e3233e2b96d0

Acknowledgments. We are grateful to Margarita Muciño, and Julio Naranjo from Xuajin Me'Phaa a non-governmental association, for their help in the liaison with the Me'Phaa community, and their help in sample collection and logistics. We also are grateful to Santiago Martinez-Correa for their contribution to DNA amplification. IG-S explicitly acknowledges the UNAM and PASPA-DGAPA program for the financial support granted to carry out his sabbatical stay and the development of this project.

Conflicts of interest. The authors declare no conflict of interest.

Funding. This project was funded by UNAM-PAPIIT [grant numbers IA209416, IA207019], DGAPA postdoctoral Fellowship, CONACYT Ciencia Básica [grant number 241744], CONACyT Investigadores por México Fellowship.

Institutional review board statement. All procedures for testing, experimental protocols, and recruitment were approved by the National Autonomous University of Mexico Committee on Research Ethics (FPSI/CE/01/2016) and run in accordance with the ethical principles and guidelines of the Official Mexican Law (NOM-012-SSA3-2012).

Informed Consent Statement: All adult participants signed a written informed consent, and for the case of participants under 18 years, we obtained specific written informed consent from their parents, or legal guardians according to the normativity of Mexican Law.

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