

NETWORKS

The importance of being modular

An experiment proves the value of modularity in complex systems under perturbation

By **Marta Sales-Pardo**

In the 1970s, ecologists began to speculate that modular systems—which are organized into blocks or modules—can better contain perturbations and are therefore more resilient against external damage (1). This simple concept can be applied to any networked system, be it an ecosystem, cellular metabolism, traffic flows, human disease contagion, a power grid, or an economy (2, 3). However, experimental evidence has been lacking (4). On page 199 of this issue, Gilarranz *et al.* (5) provide empirical evidence showing that modular networked systems do indeed have an advantage over nonmodular systems when faced with external perturbations.

The authors designed an elegant metapopulation experiment with the arthropod *Folsomia candida*. In the experiment, habitat patches (nodes) were connected in a modular fashion; specimens could freely move between patches. Initially, the au-

thors inoculated all patches with the same number of specimens. Once the whole system had reached a stable population, they continuously removed specimens from one of the nodes for a sustained period of time. The results show that modular systems can contain the spread of such a perturbation more effectively than a nonmodular system would, so that only the populations of nodes within the same module as the perturbed node is affected (see the figure).

Gilarranz *et al.* also show that the capacity to contain perturbations comes with a cost. The more modular the system, the larger the overall population in the presence of even strong perturbations, but that is not the case in the absence of a perturbation. In the latter case, the overall population levels are higher in nonmodular systems. These results not only align with theoretical expectations, they also help explain the large-scale organization of complex systems.

To further put this result in historical context, we should cast our minds back more than 10 years. At that time, the definition of module in a networked system was still a loose concept, especially for large systems (6).

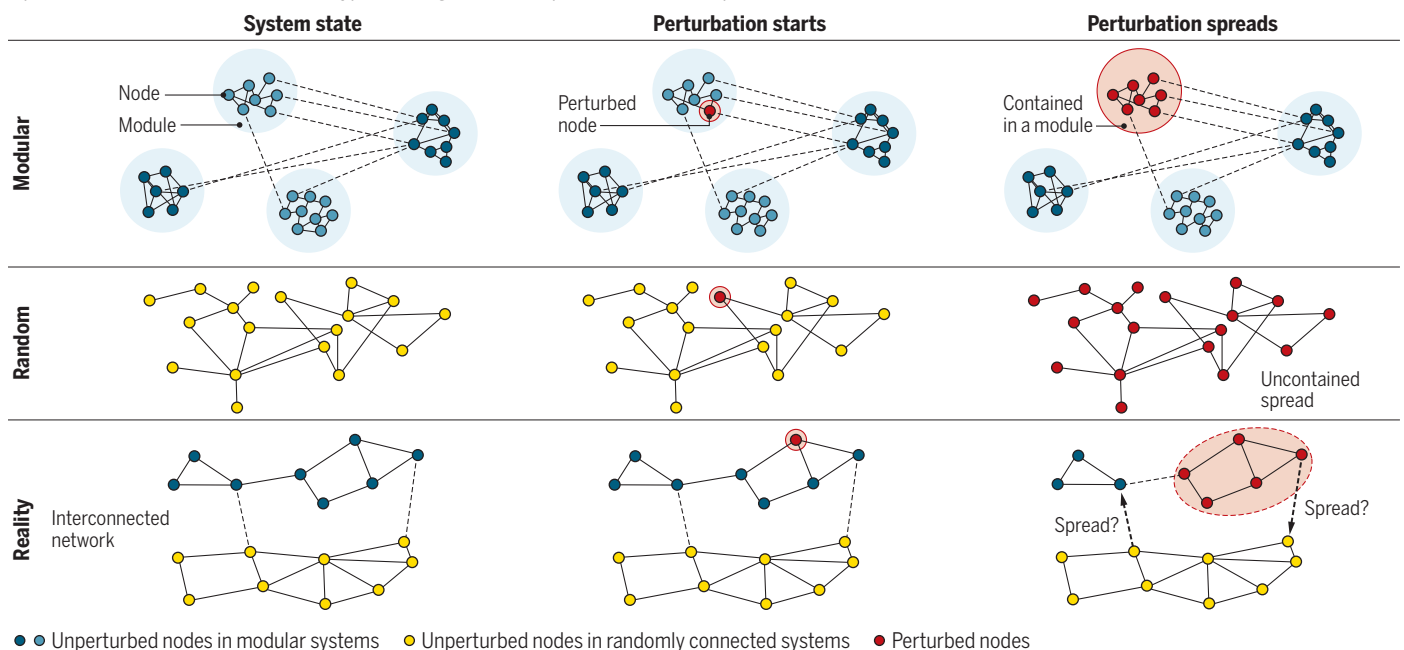
Based on commonalities in the systems-level organization of large networked systems, network scientists proposed to define a module as a set of nodes that are densely connected among themselves but loosely connected to other parts of the network (7, 8). This is the definition that Gilarranz *et al.* use. The modularity of a network then quantifies how well-defined these densely connected groups of nodes are within the network.

Using this definition of modules, scientists soon found that the vast majority of large-scale networked systems in any context—including social, biological, ecological, and engineering systems—have a strong modular component (9, 10). The question arose why this was the case. In engineered systems, modularity is arguably a useful design principle because modular systems are easy to fix and update (11). However, the justification for the modularity of natural networked systems mostly hinged on the aforementioned theoretical stability considerations. The results reported by Gilarranz *et al.* show that the need to contain perturbations can plausibly explain the modularity of at least some natural systems.

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How to contain perturbations

In modular systems, perturbations can be contained in one module, whereas they spread throughout randomly connected systems. Real systems could be represented as a combination of the two types, making it difficult to predict the effects of perturbations.



We should not, however, disregard Gilaranz *et al.*'s other findings. As the authors show, modularity does not necessarily result in the best outcome in all situations. The empirical system that the authors analyzed provides a very good proxy for other networked systems in which nodes receive, produce, and exchange flows. Consider, for instance, people exchanging information through on-line platforms. A strong modular component can result in the appearance of bottlenecks, thus preventing the efficient spread of information through the network. This might be remedied by introducing long-range shortcuts into the system, but these modifications would not be smart strategies for containing the spread of malicious information.

A more complex networked system is the interbank payment network, which has been in the spotlight since the 2008 financial crisis. It has been argued that the interconnectedness of economies, markets, information flow, and disruptive events such as natural disasters, the refugee crisis in Europe, or Brexit makes the financial system extremely vulnerable, increasing the risk of small perturbations resulting in severe consequences (3, 12–14). The question that the scientific community is trying to answer in this context is how a local perturbation became so amplified and what strategies might prevent further worldwide crises (14, 15).

It may be possible to use principles of natural design to reshape the organization of the financial system and mitigate these risks (3, 14, 15). However, it remains to be explored how the concept of modularity can be exported to interconnected networked systems. Connecting modular networked systems does not ensure modularity on a global scale. Additionally, the nature of the connections between networked systems will likely play a critical role in their capacity to contain perturbations. Hopefully, the study of natural systems will soon provide us with clues about how to design robust interconnected networked systems. ■

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IMMUNOLOGY

Immunology taught by rats

A rodent model of hepatitis C virus infection should guide therapeutics and vaccines

By Paul Klenerman and Eleanor J. Barnes

Immunology may be best taught by viruses (1), and possibly by humans (2), but the rats of New York City surprisingly also have plenty to offer. A survey published in 2014 of the pathogens carried by rats trapped in houses and parks in Manhattan identified a huge burden of infectious agents in these animals, including several novel viruses (3). Among these are Norway rat hepaciviruses (NrHVs), which belong to the same family as hepatitis C virus (HCV). NrHVs were found in rat livers, raising the possibility of establishing a small animal model of human HCV infection. On page 204 of this issue, Billerbeck *et al.* (4) fulfill this prediction.

HCV is a major human pathogen and part of a viral family that has recently expanded to include viruses in horses, dogs, and deer mice (5). It causes persistent liver inflammation and, with time, leads to cirrhosis and possibly liver cancer. For many years, treatments were based on the cytokine interferon- α (which boosts host antiviral responses), but this had many side effects and cured only 50 to 70% of patients. The advent of a range of new oral combined-drug regimens [targeting HCV protease, nonstructural protein 5A (NS5A), and polymerase] has transformed the field, with a cure for HCV achievable in more than 95% of patients in many different groups (6).

Despite this remarkable achievement in therapy, there are many unanswered questions about HCV. These include the role of the host immune response in controlling the infection and the potential for vaccination. After infection, about 25% of individuals clear HCV through innate and adaptive immunity, notably CD4⁺ T cell and CD8⁺ T cell responses. In most patients, however, the virus persists long term, evading and subverting these responses. Because the early stages of HCV infection are often clinically silent and the main site of immunological activity—the liver—is not readily accessible, the early innate and adaptive responses associated with controlling HCV have not been well defined. Hence, the development of a

small animal model could help address both the fundamental features of a hepatotropic virus and vaccine strategies that are based on priming effective host immunity.

Billerbeck *et al.* set out to establish whether they could infect immunocompromised and immunocompetent mouse strains with NrHV. Mice lacking type I interferon signaling and adaptive immunity readily became persistently infected. Immunocompetent animals cleared the virus over a few weeks; the length of time depended on the animal's age and whether the virus adapted to the mouse through serial passage. The mutations that facilitated adaptation were mainly in the viral envelope glycoproteins, suggesting that viral entry into host cells or antibody binding to the virus had become modified.

“...NrHV may have something particular to teach us about viral hepatitis...for successful control of infection...”

Having established the mouse model of NrHV infection, Billerbeck *et al.* explored the immune factors controlling the virus. The authors identified specific T cells that infiltrated the liver following acute infection and found roles for CD4⁺ T cells and CD8⁺ T cells that appeared similar to those observed during human HCV infection and in response to vaccination of chimpanzees (7, 8). Interestingly, even transient early depletion of CD4⁺ T helper cells in the mouse model of NrHV infection resulted in viral persistence over several months, associated with immune exhaustion. This places the T helper cell response at the center of immune control, in agreement with human genetic and experimental data (e.g., ex vivo T cell proliferation and cytokine responses) (9).

The impact of transient CD4⁺ T cell depletion is also reminiscent of observations from the well-established lymphocytic choriomeningitis virus (LCMV) mouse model of viral persistence. A specific LCMV strain (clone 13) can slowly be cleared from the blood and liver of an infected mouse over many weeks, but short-term loss of CD4⁺ T helper cells can

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