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35. The authors wish to thank F. Pfeifer (Darmstadt), M. Teixeira and M. A. Carrondo (both Oeiras) for encouragement and support, T. M. Bandeiras for valuable experimental assistance, and the staff at European Synchrotron Radiation Facility Grenoble (France) and European Molecular Biology Laboratory, Outstation Hamburg (Germany). This work was supported by a grant from the Deutsche Forschungsgemeinschaft (to A.K., Kl885/3-3) and by a Deutscher Akademischer Austausch Dienst (Germany) and Gabinete de Relações Internacionais da Ciência e do Ensino Superior (Ministério da Ciência, Inovação e Ensino Superior, Portugal) collaborative travel grant (to A.K. and C.M.G.). T.U. was awarded a Marie Curie fellowship for the structure determination at Instituto Tecnologia Química e Biológica (Oeiras). The atomic coordinates of the SOR have been deposited in the Protein Data Bank at www.rcsb.org (accession code 2CB2).

A Keystone Mutualism Drives Pattern in a Power Function

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Data that can be described by a power function are ubiquitous in nature. Although there is consensus that such data frequently emerge generally from nonlinear complex systems, a variety of specific mechanisms may be responsible for creating the pattern in particular cases. Here, we report on the distribution of a scale insect (*Coccus viridis*) that is a common agricultural pest. Its distribution in an organic coffee farm in southern Mexico generally follows a power function, but there are subtle deviations from that function. We offer a biological explanation for both adherence to the power functions and associated deviations, along with supporting evidence.

The distribution of clusters of organisms, much like other patterns in nature (*1*, *2*), is frequently characterized by a power function (*3*). For a variety of distinct dynamic scenarios, when cast in a spatial framework, biological interactions of several distinct types are capable of generating spatial pattern characterized by power law scaling (*4*). This pattern is usually interpreted as a signal of self-organization resulting from spatial extension. In most ecological examples, clusters are formed through various biological interactions manifest in a spatial context, such as local depletion of resources (*5*), local disturbance regimes (*6*) or predator-prey interactions (*7*). That clusters form in the first place is an interesting aspect of these theories, but the evidence that the distribution of individuals within those clusters approximates a power law is the most intriguing aspect of self-organization (*2*). Any spatial process that combines a local spread (for example, local production of a prey population) with a regional control (for example, a searching predator that ranges widely) will likely generate clusters (*8*). A similar mechanistic statement is more elusive for the power function nature of those clusters.

For the green coffee scale (*C. viridis*), the formation of clusters is of little interest because each "cluster" is a population of scale insects on a coffee bush. However, the ecology of this organism offers a potential explanation of both the evident power law and subtle deviations from it at high and low population sizes.

The green coffee scale is a common herbivore, frequently noted as a pest in greenhouses and a known pest of coffee (*9*, *10*). Although normally maintained by natural enemies below critical damage thresholds, it can sometimes reach pest status (*11*). It is tended by a variety of ant species in a classic mutualistic form: The homopteron supplies honeydew to the ant, and the ant protects the homopteron from predators (*12*). *Azteca instabilis*, a mutualist of *C. viridis* in southern Mexico (*13*), is a tree-nesting species that occurs in obvious spatial clusters (*14*) in the shade trees of coffee farms. Those coffee bushes that are near a tree occupied by *A. instabilis* are frequently sites of large concentrations of *C. viridis*. At least two species of encyrtid wasps are parasitoids on *C. viridis* and the coccinelid beetle *Azya orbigera* is a voracious predator. Direct observations and experimental results indicate that the *A. instabilis* ants are efficient protectors of the scale insects in the face of these natural enemies (*15*), and casual observations leave little doubt that the ants collect honeydew from the scales.

To investigate the spatial pattern of *C. viridis*, we set up a 45-ha plot on an organic coffee farm in southwestern Mexico (*16*), identified each shade tree therein, and assessed whether or not it contained an *A. instabilis* colony (*13*). Of 10,597 trees located, 276 contained *A. instabilis* colonies. We systematically chose five locations surrounding such a colony and four locations that were clearly outside of the influence of any such colony (*17*). In each of the nine sites, we determined the scale abundance (*17*) on approximately 50 to 100 coffee plants, for a total of 678 coffee plants surveyed.

The frequency distribution of scale insect numbers per tree is shown in Fig. 1. A power function is clearly suggested by the approximately linear nature of the points. However, subtle deviations from the power function at both high and low scale densities are also evident by casual observation. Because of the deviations at both high and low densities, we

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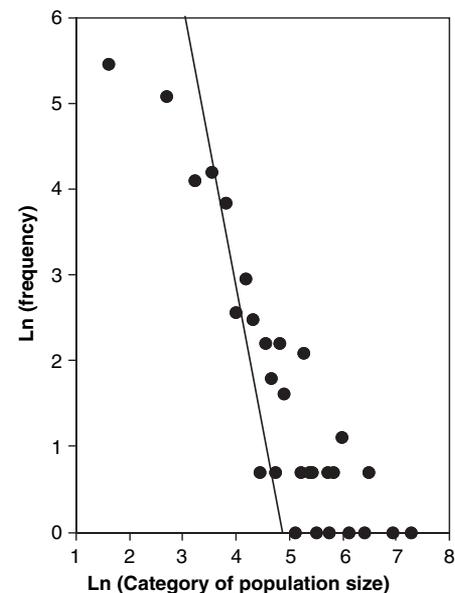
Fig. 1. Log-log plot of population size versus frequency of size of cluster. The line is a regression based on the data points located between 3.5 and 4.5 on the abscissa (*17*). Slope of power function is −2.72.

considered points in the intermediate range (between log category size 3.5 and 4.5) as a basis for casting a regression line (Fig. 1) (*17*).

Underlying biological processes may account for both the power function and its deviation. Assume that each propagule of *C. viridis* encounters coffee bushes randomly. That propagule will begin population growth that is effectively exponential, at least for a time. Thus, if the exponential growth parameter is normally distributed, the limiting distribution of scales ought to be lognormal. Consequently, we expect a lognormal distribution as the neutral base, which translates directly into a power function. Although this is the expectation at the limit, the approach to that power law may be extremely slow, depending on the mean value of the intrinsic rate of natural increase and its variability. Moreover, the system is substantially complicated by its existence in an extended space. When the exponential process, operative independently at the level of each individual coffee bush, is augmented by random additions of individuals resulting from the spatial extension of the system, the approach to the power-law scaling may be significantly accelerated. The general pattern to be expected can be seen in a simple simulation (*18*), as shown in Fig. 2. Notably, as the overall distribution approaches a lognormal (Fig. 2A), the power function emerges (Fig. 2B). Furthermore, it is the apparent disappearance of the effect of space (i.e., when the late arrivals of populations at bushes are swamped by the population growth on those bushes) that represents a critical state, that is, the state of the pure power function without the deviations (e.g., after eight iterations in Fig. 2). That is, once all or almost all bushes are occupied by at least a single scale insect, the overall dynamics rapidly become dominated by

the distributed exponentials with the emerging power law. Before that time, many bushes will have zero or very low occupancies, which maintains an extended tail on the lognormal distribution. Thus, the point of "criticality" is when the random process thought to represent space in this model reaches the critical point of filling all coffee bushes with at least one scale insect. The general idea of criticality and the self-organization that goes along with it (*3*) is thus repeated in this system, although here we are dealing with a second order of critical state, which is to say, the disappearance of the space effects.

Evidence that this dynamic is operative in the system under study is gained from an examination of the frequency distribution of the logs of scale numbers (Fig. 3) compared with the lognormal expected from the underlying biology (local reproduction on a coffee bush), shown by an approximate normal curve superimposed on the data in Fig. 3. It is qualitatively clear from Fig. 3 that there is a strong deviation from the lognormal at the low population size category, much as observed in simulations before the moment of criticality (compare Fig. 3 with Fig. 2A). We thus conclude that the system is near its critical point, in which the random allocation of scales to bushes is almost complete.

However, there is also a less obvious, but equally important deviation from the lognormal distribution at the high end of the spectrum. This is the same deviation that can be seen in the log-log graph presented in Fig. 1. We hypothesize that this high cluster deviation is a consequence of the key mutualism operative in the system. When the coffee bush is near to an ant colony, the inherent limitation on the population, probably due to predation and

parasitism, is reduced, and the local population is released to reach much higher values.

Support for this hypothesis is strong if we eliminate those sampling sites in which an *A. instabilis* colony is resident. Plotting only the antless sites from Fig. 1, we obtain the points displayed as solid circles in Fig. 4, which is evidently a linear function with no obvious deviation at high cluster sizes. We take this power law to be the underlying power law that derives from independent populations growing exponentially and randomly dispersing in space. The key mutualism acts to generate a deviation at high cluster sizes from the basic pattern, given by the dotted line in Fig. 4 (with the same slope as the ant-free distribution but with a higher *y* intercept corresponding to the higher numbers of total scales in the pooled samples).

In sum, the basic power law that *C. viridis* seems to follow is a product of independent populations growing exponentially, giving rise to a basically lognormal distribution, but organized in space such that extremely small populations are common as a consequence of a time delay in the dispersal of individuals to new bushes. The large-cluster deviation from this basic law is caused by the key mutualism between *C. viridis* and *A. instabilis*. Thus, both the power law and the key deviation from the power law are understandable in terms of simple biological processes.

Interpretation of the power law in this particular case is of interest in its own right and represents one of the few cases where it is easy to recognize biological phenomena that can account for the pattern. However, the result may also have practical applications. In the case of a potential pest species, it is always necessary to be able to project the population into the future to determine when control activities may be necessary [the so-called action

Fig. 2. Results of simulations of the simple exponential model coupled with random dispersal (*18*). (**A**) Frequency diagrams of the log of number of scales per bush for three different iterations. (**B**) Log-log plot of frequency versus category of number of scales per bush, showing how the system approaches a classical power function in time.
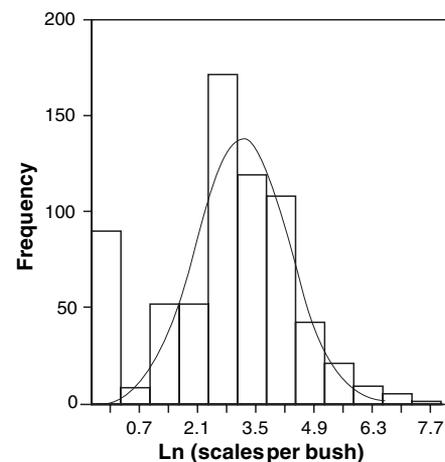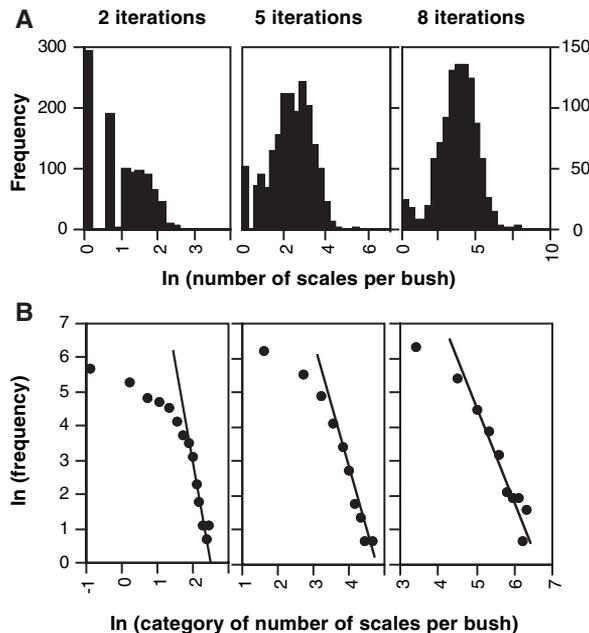
Fig. 3. Frequency diagram of the natural logs of population densities per coffee bush with an approximate normal distribution imposed. The obvious deviation at low cluster sizes is similar to that observed in the simulations (Fig. 2A).
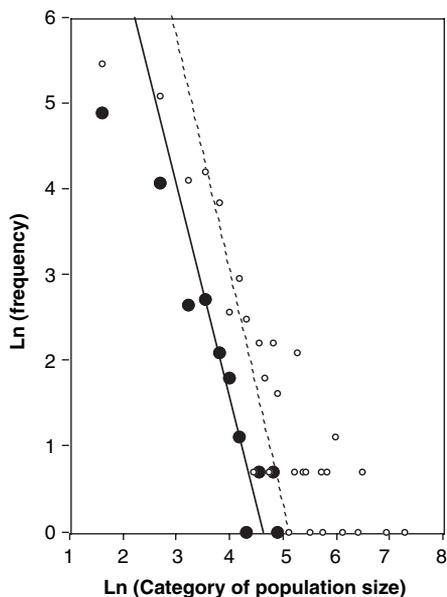
Fig. 4. Log-log plot of population size versus frequency of population sizes for sites away from the influence of an *A. instabilis* colony (solid circles), and all data (small open circles repeat the data of Fig. 1). Slope is −2.48, fitted to the points located between 3.5 and 4.5 on the abscissa (*17*). The evident deviations from the power function at high population densities (small open circles) are not present in this data sample.

threshold (*19*)]. In a spatial context, if all bushes are occupied by scales and density dependence can be ignored, projecting the overall population into the future is a simple matter of applying an exponential function to the total scale abundance. However, if that critical point where all bushes are occupied has not been reached, applying the simple exponential law will necessarily underestimate future population sizes, because the actual spatial dynamic will include newly occupied bushes in the future. Consequently, determining whether the system is at its critical value, at which point the application of the simple exponential would indeed be appropriate, has obvious practical importance. Thus, the degree to which spatial data adhere to a power function can be taken as an indication of the legitimacy of applying an exponential rule to population projections.

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16. The site is located at Finca Irlanda, a 300-ha organic coffee farm in the Soconusco region of Chiapas, Mexico (15° 11′ N, 92° 20′ W). The area receives about 4500 mm of rain annually and is located between elevations of 900 and 1150 m. According to a standard classification, the farm classifies as a commercial polyculture, with almost 100 tree species total.
17. Materials and methods are available as supporting material on *Science* Online.
18. Using 1000 coffee trees as the fixed habitat background, we drew a random number from a Poisson distribution (and truncated it to an integer) and generated the initial population density for each bush. The population density was then iterated as $N(t + 1) = RN(t)$ for one time period, the first generation (where R is the finite rate of increase). We added to the result the number of individuals as determined from another random number generated from a Poisson distribution (and truncated to an integer), and this new number iterated for the second generation.
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Nuclear Receptor Rev-erbα Is a Critical Lithium-Sensitive Component of the Circadian Clock

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Lithium is commonly used to treat bipolar disorder, which is associated with altered circadian rhythm. Lithium is a potent inhibitor of glycogen synthase kinase 3 (GSK3), which regulates circadian rhythm in several organisms. In experiments with cultured cells, we show here that GSK3β phosphorylates and stabilizes the orphan nuclear receptor Rev-erbα, a negative component of the circadian clock. Lithium treatment of cells leads to rapid proteasomal degradation of Rev-erbα and activation of clock gene *Bmal1*. A form of Rev-erbα that is insensitive to lithium interferes with the expression of circadian genes. Control of Rev-erbα protein stability is thus a critical component of the peripheral clock and a biological target of lithium therapy.

Genetic and biochemical analysis reveals that a 24-hour circadian rhythm is present throughout the animal kingdom (*1–3*). In mammals, circadian rhythm is a fundamental regulatory factor for many aspects of behavior and physiology, including sleep-wake cycles, blood pressure, body temperature, and metabolism (*1–3*). Disruption in circadian rhythms leads to increased incidence of many diseases, such as cancer and mental illness (*1*, *3*). Bipolar disorder in particular is associated with disturbed circadian rhythm (*4*).

Cells throughout the body also display 24-hour rhythms (*3*, *5*). These are entrained by signals from a central clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus, which is reset daily by light (*3*). Cellular rhythms are generated and maintained through interconnected transcriptional feedback of clock genes (*3*, *6*). The cycle starts when two bHLH-PAS domain proteins, BMAL1 and CLOCK, heterodimerize to activate a number of clock genes including *Per1*, *Per2*, *Cry1*, and *Cry2*. As a negative feedback loop, PER and CRY accumulate in the cytosol and then translocate into the nucleus. Once inside the nucleus, the PER-CRY complex inhibits its own transcription by binding to BMAL-CLOCK (*3*, *6–8*). An additional negative feedback loop requires the transcription repression function of the orphan nuclear receptor Rev-erbα, which represses the transcription of *Bmal1* during circadian night and is responsible for rhythmic expression of the *Bmal1* gene (*9–11*). *Rev-erbα* itself is activated by BMAL1-CLOCK and thereby represents the link between the positive and negative loops of the circadian clock (*9*).

Posttranslational modifications also play an essential role in resetting the clock (*2*, *3*, *12*).

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