and development of statistical methods. Briefly, the statistical model is:

$$\frac{N_i(t)}{N_T(t)} = f_i(t) \quad (1)$$

where $N_i(t)$ are the observed counts for genotype i in a sample of size $N_T(t)$ at time t, and $f_i(t)$ is a quadratic function representing the temporal genotype dynamics. We use a Dirichlet-multinomial distribution as the error structure for the observed counts to accommodate possible over-dispersion in the data. Equation (1) was fitted with the statistical library VGAM[28] in the R software environment (R Development Core Team, http://www.R-project.org). The temporal dynamics of selection are calculated from

$$s(t)_i = \frac{\mathrm{d}p(t)_i}{\mathrm{d}t}\frac{1}{p(t)_i(1-p(t)_i)} \quad (2)$$

where $s(t)_i$ is the coefficient of selection for genotype i at time t, and $p(t)_i$ is the estimated relative abundance. Net selection is calculated from equation (2) as:

$$\bar{S}_{n_i} = \frac{\int_{t_1}^{t_2} s_i(t)\mathrm{d}t}{(t_2 - t_1)} \quad (3)$$

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Host immunity and synchronized epidemics of syphilis across the United States

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A central question in population ecology is the role of 'exogenous' environmental factors versus density-dependent 'endogenous' biological factors in driving changes in population numbers[1]. This question is also central to infectious disease epidemiology, where changes in disease incidence due to behavioural or environmental change must be distinguished from the nonlinear dynamics of the parasite population[2]. Repeated epidemics of primary and secondary syphilis infection in the United States over the past 50 yr have previously been attributed to social and behavioural changes[3]. Here, we show that these epidemics represent a rare example of unforced, endogenous oscillations in disease incidence, with an 8–11-yr period that is predicted by the natural dynamics of syphilis infection, to which there is partially protective immunity[4]. This conclusion is supported by the absence of oscillations in gonorrhoea cases, where a protective immune response is absent[5,6]. We further demonstrate increased synchrony of syphilis oscillations across cities over time, providing empirical evidence for an increasingly connected sexual network in the United States.

Syphilis and gonorrhoea are endemic sexually transmitted diseases in the United States. After the introduction of widespread screening and treatment by the Surgeon General Thomas Parran after the Second World War, reported cases of primary and secondary syphilis dropped to an all-time low in 1955 before they rose again and began to oscillate with an approximately 10-year cycle (Fig. 1a). The introduction of treatment for gonorrhoea also resulted in a decline in incidence during the 1950s, but, unlike syphilis, periodic oscillations did not ensue (Fig. 1b). Oscillations in the incidence of syphilis have been attributed to social and behavioural changes[3]. For example, the epidemic in the 1970s is attributed to the sexual revolution and gay liberation movement, the epidemic in the 1980s to poverty, urbanization and crack-cocaine-related prostitution. Here we re-examine this idea by gathering and analysing data on syphilis and gonorrhoea cases reported to the US Centers for Disease Control and Prevention between 1941 and 2002 for 68 cities across the United States. These data provide a rare opportunity to examine the relative roles of endogenous and exogenous factors in driving infectious disease dynamics, with the availability of both syphilis and gonorrhoea case reports allowing a comparative approach to testing hypotheses.

We tested the time series of primary and secondary syphilis and gonorrhoea case reports from individual cities for significant periodicity by calculating smoothed periodograms using standard spectral analysis techniques[7]. We focus on the period 1960–93, beginning with the initial resurgence of infection after the introduction of treatment and ending before declines due to the HIV epidemic, and thus avoid complications that can arise from non-stationarity in the epidemic period (in which case wavelet approaches may be more appropriate[8]). The analysis confirms the oscillatory nature of endemic syphilis previously noted from national case numbers (Fig. 1c). The resolution of the period estimate is restricted by the number of years of observations, but the average spectrum for these cities peaks at about 8–10 yr and a significant periodicity is found between 8.25 and 11 yr for 21 of the 47 cities with complete reporting during 1960–93 ($P < 0.05$).

Analysis of gonorrhoea case reports from the same cities reveals flat spectra, indicating an absence of any periodicity in the data over the scale of interest (Fig. 1d) (weak seasonality has been demonstrated for gonorrhoea, but not syphilis, dynamics possibly due to a small increase in rates of sexual partner change during the summer[9]). The contrasting patterns seen for syphilis and gonorrhoea time series and their spectra are illustrated for the largest and smallest cities with complete data from the northeast and south of the United States in Fig. 2a.

Primary and secondary syphilis and gonorrhoea both have a relatively short duration of infection (<6 months)[10,11] and similar transmission probabilities and case detection and treatment protocols[12,13]. This predicts a close relationship between levels of unsafe sex and disease incidence[14], and indeed these diseases typically infect similar 'core' groups[15]. If social and behavioural changes are responsible for the oscillations observed for primary and secondary syphilis infections, then similar oscillations should be observed for gonorrhoea. Their absence leads us to an alternative explanation based on a key biological difference between syphilis and gonorrhoea infections.

In both treated and untreated syphilis partial immunity to reinfection occurs, either due to acquired immune memory or continued presence of antigens respectively[4]. The presence of immunity has important effects on the dynamics of infectious diseases. When the period of infectiousness is short compared with immunity, fluctuations in incidence occur over a timescale determined by the supply of susceptible individuals[16]. This can be illustrated by a simple SIRS compartmental model with 'susceptible', 'infected' and 'recovered' (immune) states followed by the loss of immunity and a return to the susceptible state. The stochastic version of this model shows sustained oscillations in incidence, with a period that is a function of the natural history of the infection and the rate at which susceptible individuals enter the population, but independent of population size (see Methods). These oscillations persist even if a significant fraction of infected individuals do not develop protective immunity (see Supplementary Fig. 1).

For parameters consistent with the natural history of syphilis, the SIRS model predicts both the period and amplitude of oscillations in incidence seen for US cities (Fig. 2b). The basic reproductive number (R_0) of an infection can be defined as the average number of secondary infections caused by a single infectious individual in a completely susceptible population, and is a key parameter determining disease invasion, spread and persistence. A range of values for R_0, typically less than about 3, are consistent with the observed 8–11-yr oscillations when realistic rates of treatment and entry to the susceptible population are specified (Fig. 2c). A small R_0 for syphilis in the United States is also indicated by the slow increase in the number of cases observed during syphilis outbreaks and estimates based on transmission probabilities and rates of sexual partner change[10].

The close consistency of both period and amplitude of oscillations in syphilis incidence in the model and data suggests that it is the endogenous nonlinear dynamics of syphilis after the introduction of treatment that are largely responsible for the oscillations in incidence rather than exogenous forcing by repeated social and behavioural change. This conclusion is supported by comparison with gonorrhoea, which does not lead to any protective immunity, as revealed by repeat infections with the same serovars seen for both STD clinic patients[5] and inoculated human male volunteers[6]. Gonorrhoea dynamics can therefore be described by an SIS model of incidence, where the recovered state is absent, and which does not predict oscillations in incidence. Oscillations are only possible when a period of immunity (or death) removes individuals from the population of susceptibles. The gradual rise and fall in gonorrhoea incidence since 1960 is therefore perhaps more likely to reflect the underlying dynamics of unsafe sexual behaviour in the United States (although case numbers may also be affected by the effort put into case detection and reporting).

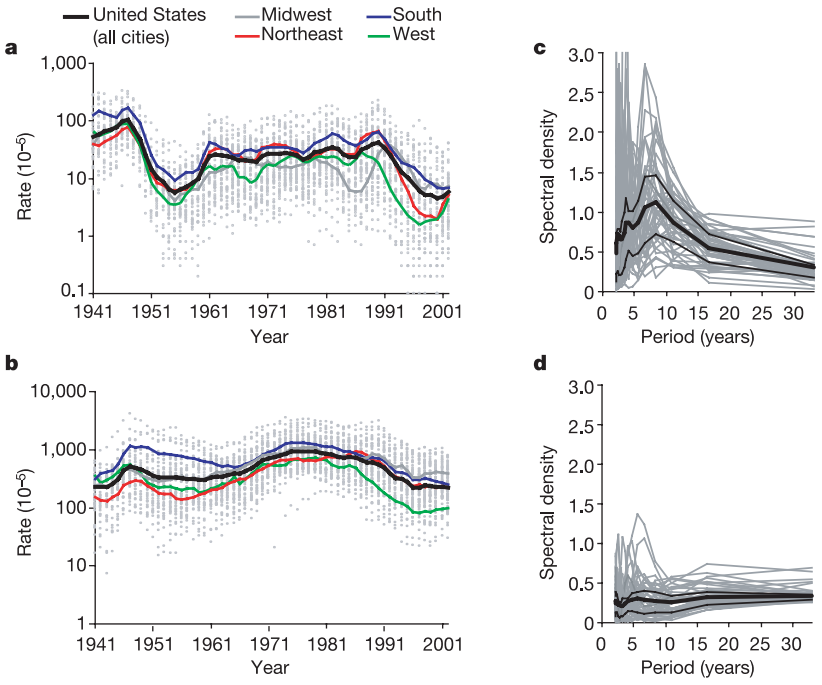

Figure 1 Syphilis and gonorrhoea cases in the United States. **a**, **b**, Case reports for primary and secondary syphilis (**a**) and gonorrhoea (**b**) plotted against time as grey points for each of the 68 major cities of the United States. Cases are plotted as a rate per 100,000 of the city population on a $\log_{10}$ scale and regional and national totals are shown as lines. **c**, **d**, The spectra of the differenced data for syphilis (**c**) and gonorrhoea (**d**) are shown for 47 cities with complete reporting over the period 1960–93. The average spectrum is shown by the thick black line and inter-quartile range by the thin black lines.

The reported cases of syphilis come from a network of cities, which are connected by travel and sexual contact between individuals from different cities. This broader sexual network may also be important for the dynamics of syphilis. Behaviour and treatment patterns are likely to vary between cities, resulting in different R_0 values and different intrinsic periods for oscillations in incidence. However, coupling through contact between individuals from different populations can synchronize both the period and phase of oscillations in disease incidence[17].

We demonstrate the importance of coupling for primary and secondary syphilis dynamics by calculating the correlation in incident cases reported for the different cities. Shortly after the introduction of treatment the average correlation between cities is low, but during the latter half of the twentieth century it shows a large increase (Fig. 3a). Peaks in correlation typically occur during epidemics, as the disease sweeps through the susceptible population in different cities. Over time these peaks have increased in size, with an average correlation coefficient over the period 1980–96 of 0.24 compared with 0.04 during 1960–79. This suggests an increasingly connected sexual network across the United States and is certainly consistent with the well documented increases in passenger travel over the last few decades[18].

The pattern of increase in correlation of incidence during epidemics is well captured by a simple metapopulation version of the stochastic SIRS model, where a fraction ε of sexual contacts are 'global' rather than local (Fig. 3b). In this model oscillations in incidence synchronized in phase and frequency emerge as the level of coupling increases. Synchronization is balanced by stochastic drift in the phase of the oscillations in different cities and local extinction followed by re-introduction of infection. For a reasonable number of populations, increased coupling is found to increase the average correlation of incidence in the metapopulation at all levels of coupling (Fig. 3c). This contrasts with the threshold effects observed for deterministic models[17].

Cross-correlation is significantly lower among the ten smallest cities compared with the ten largest cities ($P < 0.001$), even after accounting for sampling error, as expected if random drift in phase and local extinction are important for the dynamics of the disease. However, populations at risk of infection in these smaller cities may also be less strongly coupled to other cities. This has been demonstrated for several directly transmitted infections, including HIV, which have spread predominantly through the size hierarchy of cities[19,20]. In general the extent of coupling required to synchronize disease dynamics in different populations will depend on the exact nature of the connections between populations[21,22].

Syphilis incidence in the United States is concentrated among African Americans from lower socioeconomic groups in the south and among men who report sex with other men[23]. The epidemiological linkage of these groups predicts endogenous oscillations in incidence, which are coupled in phase and frequency as for the metapopulation. More generally, SIR infection dynamics in structured populations described by an explicit contact network show periodic oscillations for all but the lowest level of network disorder[24]. Social and behavioural changes among these groups will, of

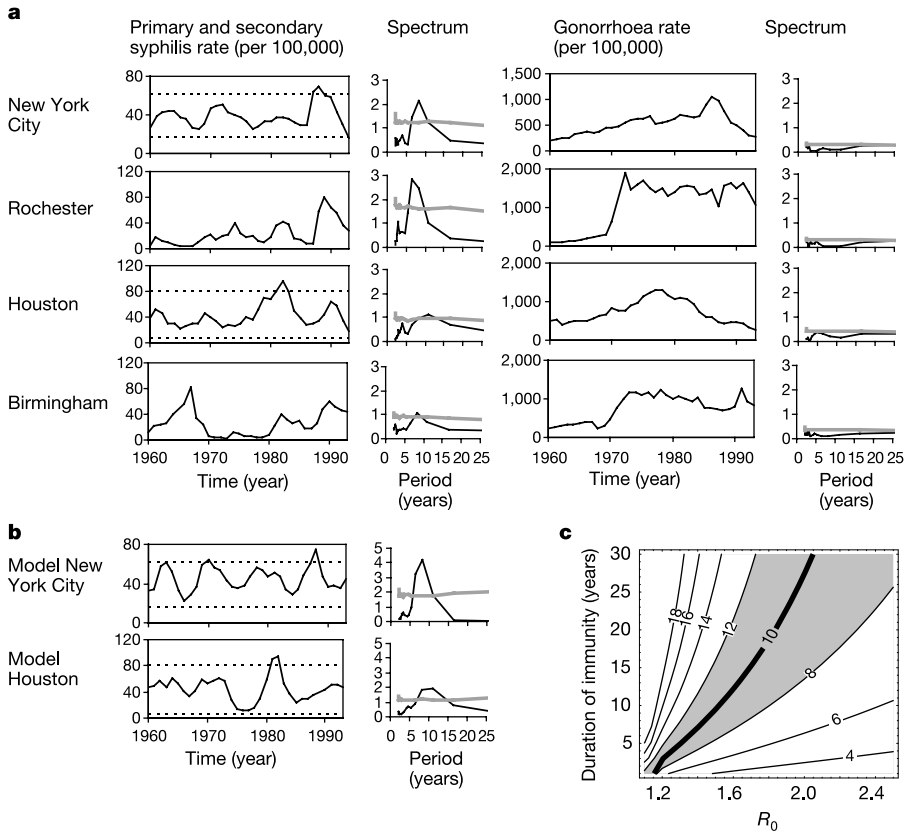

Figure 2 Oscillations in syphilis incidence due to immunity. **a**, Time series of syphilis and gonorrhoea case reports together with their spectra for the largest and smallest cities in the northeast (New York City, Rochester) and south (Houston, Birmingham). **b**, Stochastic realizations of a SIRS model with R_0, population size N and the duration of immunity estimated for New York City and Houston, respectively. The estimated amplitude (± 2 s.d., dashed lines) and period (spectral density, black lines) of these oscillations in incidence is the same for the model and data. Significant periodicity may be assessed by comparing the spectral density with the 95th percentile of the spectra of the randomized data (grey line). **c**, The period of the oscillations for different R_0 values and duration of immunity, in the case that syphilis infection lasts 2 months on average before treatment and individuals are sexually active for an average of 30 yr.

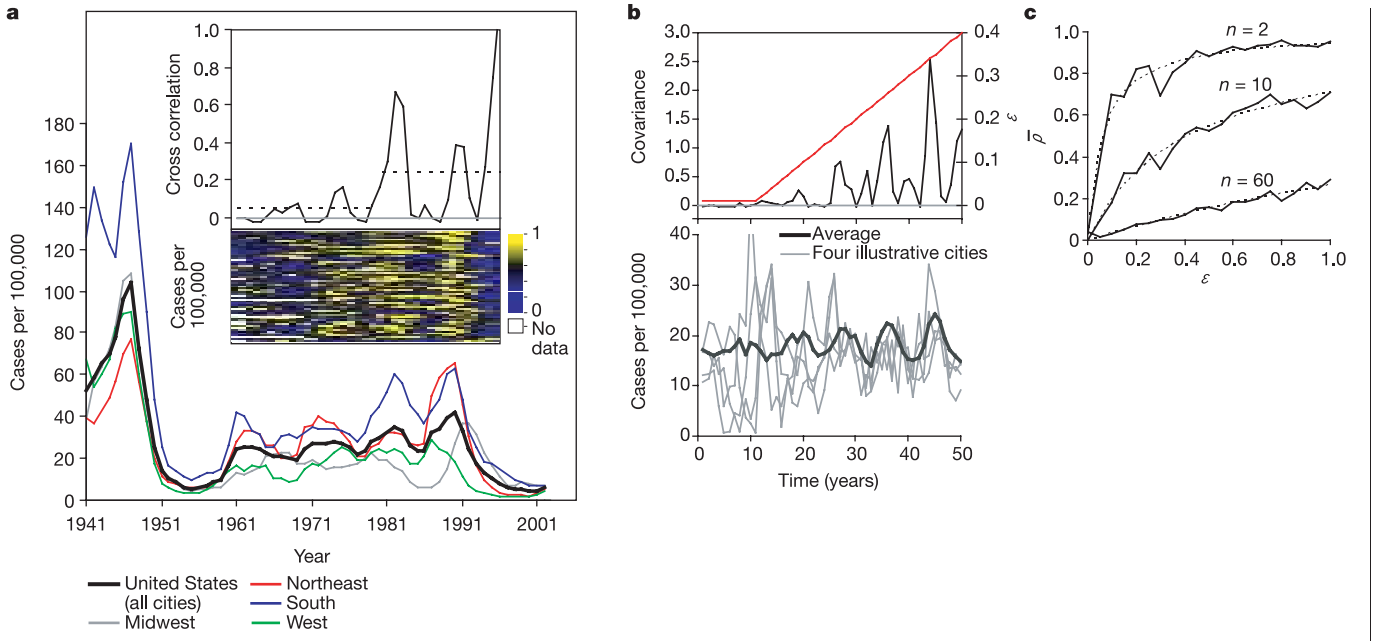

Figure 3 The metapopulation dynamics of syphilis. **a**, Primary and secondary syphilis case reports per 100,000 population by region and for 59 cities as a colour intensity plot (inset) for the period 1960–96 together with the average cross correlation. Reported rates in the intensity plot are scaled between 0 and 1 after transforming by $\log_{10}(1 + \text{rate})$, and cities are arranged in descending order of population size (from top to bottom). Vertical bands corresponding to synchronized epidemics begin to emerge to the right of the plot. Correlation of case reports between cities given by standardized covariance (solid line) is shown for each year, and the average correlation coefficient ($\bar{\rho}$) (dashed line) for the periods 1960–79 and 1980–96. **b**, Stochastic realization of a metapopulation SIRS model with 60 populations showing the standardized covariance (black line) over time as coupling (ε; red line) increases linearly from 0.01 to 0.4. **c**, Average correlation ($\bar{\rho}$; solid line) between n populations for numerical simulations of the stochastic metapopulation SIRS model at different levels of coupling. The relationship is well approximated by $\bar{\rho} \approx \varepsilon/(\xi + \varepsilon)$ (dashed line) where ξ is a parameter that can be estimated directly from the simulations (compare with moment closure approximation for the two-population case[21]).

course, affect the incidence of syphilis, even if they are not responsible for the large amplitude oscillations in case reports. In particular, the epidemic in the late 1980s was uniquely associated with a significant increase in the fraction of infections among women, probably the result of an increase in crack-cocaine-related prostitution[3], and the decline of both syphilis and gonorrhoea throughout the 1990s a result of mortality and behaviour change due to the HIV epidemic[25]. In general, deviations from an oscillatory pattern may be driven by changes in behaviour, surveillance systems or random local extinction of infection and phase drift. Disentangling these factors remains a formidable challenge.

Here, we have demonstrated large amplitude oscillations in syphilis incidence, absent for gonorrhoea, which can be explained by the endogenous dynamics of syphilis where there is a partially protective host immune response. This important role of host immunity driving endogenous disease dynamics highlights the need to carefully interpret data from routine surveillance and intervention studies, where changes in incidence may not always be attributable to changes in behaviour or the environment. In particular, recent synchronized increases in syphilis incidence across the United States have sparked concern that there is growing complacency about the risks of HIV and returns to unsafe sexual behaviour, particularly among men who report sex with other men[26,27]. Our analyses, however, suggest that these synchronized increases may largely reflect natural dynamics after a period of build up of non-immune individuals, a conclusion supported by the lack of any correlated increases in gonorrhoea case reports. □

Methods

Data

We compiled reported cases and rates of primary and secondary syphilis and gonorrhoea infection for the period 1941–2002 for 68 major cities (population size >200,000) of the United States, from data collected by the Centers for Disease Control and Prevention.

Spectral analysis

Long-term trends in the mean reported rate for each city were removed before spectral analysis by subtracting a best-fit straight line and the series normalized to zero mean and unit variance. Periodograms representing Fourier transforms of the differenced data ($\nabla c_t = c_t - c_{t-1}$ where c_t is the observed case report rate at time t) were calculated and smoothed using a standard Daniell window of width 3 yr[7]. Differencing removes any long-term changes in the mean rate (non-stationarity) remaining after the linear transformation, resulting in a suppressed spectral density for low frequency 'noise' (see Supplementary Methods).

Tests for significant periodicity in each city spectrum were based on the spectra of 1,000 random permutations of the differenced data for each city. Randomization removes any periodicity and is equivalent to the hypothesis of random noise in the differenced data.

Cross-correlation

Correlation of the rate of primary and secondary syphilis infection between 59 cities was estimated using the average of Pearson's correlation coefficient ($\bar{\rho}$) between each city pair (nine cities with 25 or less years of reporting were removed from the analysis). To examine temporal trends in cross-correlation we simply plot the annual components of the average covariance, standardized by dividing by the variance across cities at each point in time to avoid spurious trends in cross-correlation that may result from changes in the variance. Unlike the average correlation, the standardized covariance does not have a natural scale between −1 and 1, and for both measures there is no simple statistical test for significance owing to the non-independence of the correlation coefficients[28]. We therefore make comparisons of $\bar{\rho}$ with the same measure of correlation in the metapopulation SIRS model (Fig. 3c).

The spread of disease through the size hierarchy of US cities confounds the use of spatial correlograms[28] (see Supplementary Methods). Instead we compare the number of significant pairwise correlations in incident cases during 1960–96 in the ten largest and ten smallest cities. Significance was assessed after bootstrapping the case report data from the ten largest cities with additional sampling error described by the binomial distribution where the number of reported cases equalled that for the smallest cities (see Supplementary Methods).

The model

We extend the classic SIRS model of infection[29] to allow for a network of connected populations (metapopulation). In this simple model, infection is followed by recovery (with rate ν) to an immune class with the possibility of subsequent loss of immunity (with rate γ) to return to the susceptible class. We denote the population size and number of infected individuals in population i by N_i and Y_i respectively, and prevalence by $y_i = Y_i/N_i$. The population size is equivalent to those at risk of infection, which in the case of syphilis can be considered analogous to the core group of sexually active individuals[14].

We do not explicitly consider heterogeneity in sexual activity, although the results are robust to consideration of contact networks and stratification of the population (see Supplementary Methods).

The hazard of infection for susceptible individuals in the ith population is

$$\lambda_i = (1-\varepsilon)\beta_i y_i + \varepsilon\beta_i \bar{y} \quad (1)$$

where ε is the fraction of contacts that are global, β_i the transmission parameter for population i, and $\bar{y}$ is the prevalence among global contacts, which is simply the average prevalence over the n populations of the metapopulation weighted by the transmission parameter β_i to ensure numbers of contacts between populations balance ($\bar{y} = \sum_n Y_i\beta_i / \sum_n N_i\beta_i$). This type of representation of coupling between populations has been shown to be a good approximation to more explicit mechanistic models of migration, where individuals spend periods outside their 'home' city[21,22].

The stochastic version of this model can give sustained oscillations in prevalence and incidence due to continued perturbation of the system by random events[16]. In the case that $\varepsilon = 0$, prevalence in each population oscillates with period

$$T = 2\pi / \sqrt{s(\gamma+\mu) - 0.25(\gamma+\mu+qs)^2} \quad (2)$$

where μ is the birth/death rate, $q = (\gamma+\mu)/(\gamma+\mu+\nu)$, $s = (\nu+\mu)(R_0-1)$ and R_0 the basic reproductive number given by $R_0 = \beta/(\nu+\mu)$. We omit the subscript i for notational clarity. Although seasonality has not been shown to be important for syphilis[9], we note that for parameters consistent with syphilis natural history the period predicted by equation (2) does not change with the inclusion of seasonal forcing, which merely acts to ensure that the period is an integer number of years. The amplitude of oscillations is given by the variance in the number of infected individuals, which can be estimated through a diffusion approximation for reasonably large N as $\sigma_Y^2 = N(R_0-1)/R_0^2$ (ref. 29). These oscillations can also occur in the SIR model and persist in both models even when a significant fraction of individuals do not develop immunity (see Supplementary Fig. 1). As the metapopulation becomes increasingly coupled ($\varepsilon \to 1$), these oscillations become synchronized in phase and frequency, until in the fully coupled system synchronized oscillations occur with period approximated by equation (2) with a basic reproductive number given by $\bar{R}_0 + \sigma_{R_0}^2/\bar{R}_0$, where $\bar{R}_0$ is the mean and $\sigma_{R_0}^2$ the variance of the reproductive number for each population.

The model parameters γ, R_0 and N for New York City and Houston in Fig. 2b were estimated from the period, amplitude and mean of the oscillations in case reports, by making the simplifying assumption that the number of reported cases $C \approx fY\nu$, where f is the fraction of incident infections that are reported. For this illustration we assume that the other model parameters are fixed ($f = 0.5$, $\nu = 9$ in New York City and 6 in Houston, and $\mu = 0.03$).

The impact of different levels of coupling (ε) on cross-correlation of incidence (Fig. 3b, c) was examined numerically for a metapopulation where R_0 varies across cities according to a lognormal distribution (a few cities have high R_0), with mean 2 and variance 0.5 (although the results are closely consistent for different values of the variance, including zero). The distribution of N was assumed to follow a power law, in agreement with the decennial census estimates of the US city sizes in 1970 (ref. 30), but only a small fraction (1–5%) of the total population is assumed to be at risk of infection. The average cross-correlation $\bar{\rho}$ shown in Fig. 3c is for 5,000-yr simulations. All other model parameters are fixed ($\nu = 6$, $\mu = 0.03$, $\gamma = 0.05$).

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How the Venus flytrap snaps

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The rapid closure of the Venus flytrap (*Dionaea muscipula*) leaf in about 100 ms is one of the fastest movements in the plant kingdom. This led Darwin to describe the plant as "one of the most wonderful in the world"[1]. The trap closure is initiated by the mechanical stimulation of trigger hairs. Previous studies[2–7] have focused on the biochemical response of the trigger hairs to stimuli and quantified the propagation of action potentials in the leaves. Here we complement these studies by considering the post-stimulation mechanical aspects of Venus flytrap closure. Using high-speed video imaging, non-invasive microscopy techniques and a simple theoretical model, we show that the fast closure of the trap results from a snap-buckling instability, the onset of which is controlled actively by the plant. Our study identifies an ingenious solution to scaling up movements in non-