Chapter 7

Criticality in epidemiology

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For a long time criticality has been considered in epidemiological models. We review the body of theory developed over the last twenty five years for the simplest models. It is at first glance difficult to imagine that an epidemiological system operates at a very fine tuned critical state as opposed to any other parameter region. However, the advent of self-organized criticality has given hints in how to interpret large fluctuations observed in many natural systems including epidemiological systems. We show some scenarios where criticality has been observed (e.g., measles under vaccination) and where evolution towards a critical state can explain fluctuations (e.g., meningococcal disease.)

7.1. Introduction

The simplest classical models in epidemiology describe the transition of susceptible hosts, S, to infected hosts, I, with a pathogen and the subsequent transition either to become a susceptible host again or recover from the infection to a permanently immune host R. In the first case we speak about an SIS-model, in the second about an SIR-model.[1] Often further transitions are described, e.g. from a non-permanent recovered back to a

susceptible host (sometimes called SIRS-model to distinguish from the SIR without exit from R), or when including an exposed class (E), describing an already infected but not yet infective host, and transitions into and out of E (SEIR-model). The SEIR-model has been studied extensively to describe measles epidemics before the introduction of vaccination.[2–6] Also the consideration of a non-constant population size leads to additional transitions for birth into the susceptible class, and death from every class. We will initially consider the simplest models SIS and SIR, since they already show rich dynamic behavior, which is only marginally altered by most of the above described extensions.

The founding papers on criticality in simple epidemiological models are written by Grassberger and de la Torre[7] in 1979 for a simplified SIS-model, a time discrete stochastic automaton in 1 dimension, and by Grassberger[8] in 1983 on the SIR-model, again a time discrete stochastic automaton, this time in 2 dimensions. Some historic remarks on the context in which the articles appear might be in place here. Criticality in statistical physics of equilibrium thermodynamic systems has been studied for a long time,[9] however, the theoretical understanding of scaling and universality of exponents appearing in the power laws of many quantities near and at criticality only came with the application of renormalization theory originated in quantum field theory. Rapidly, applications to time dependent quantities of the equilibrium systems appeared, as well as applications to other phenomena, for example autocatalytic processes. Grassberger and de la Torre looked at such an autocatalytic process, the so-called Schlögel's first model, with the aim of comparing the critical behavior with results from a field theory for Reggeon particles. The model they looked at in detail is also that of an SIS epidemic, and they explicitly make the connection to epidemiology, as well as pointing out the analogy to simple birth-death processes. The universality class is called Directed Percolation (DP). Quickly after Grassberger investigated the general epidemic process, a version of the SIR system, and found that it belongs to the universality class of bond percolation, now also called Dynamic Percolation (DyP) to emphasize the dynamical aspect of the underlying processes. The fascination among physicists about these two quite general universality classes is ongoing.

Criticality occurs at the boundary between two regions in which the dynamics behavior of a system differs qualitatively. Only the finding of self-organized criticality[10,11] (SOC) could explain why fingerprints of criticality often appear in nature without fine tuning of a parameter. The parameter leading to criticality becomes a dynamic variable, for example

the slope of a sandpile, and evolves until the system becomes critical, in the sandpile paradigm the avalanches show a wide distribution of sizes having the shape of a power law.[12] An essential ingredient to a self-organized critical system, like a sand pile, is the slow excitation of the system, the toppling of sand onto the pile, which increases tension in the sandpile, until one more excitation causes a small, medium sized or eventually catastrophic event. Long after the physicists fascination for the topic there are the first attempts to investigate data showing criticality in epidemiology. Island host populations subject to rare events of importation of disease[13] results in a scenario which is reminiscent to forest fires, which in turn show self-organized criticality.[12] For a detailed analysis see Rhodes, Jensen, Anderson.[14]

An even simpler scenario of a critical state and the consequent appearance of huge fluctuations could be the following: a system parameter which shows at some value a critical transition could be externally slowly changing, hence driving the system into and through the critical region. Such a scenario is exactly happening in a near-completely vaccinated population, hence the system is subcritical, but vaccination for some reason decreases slowly, eventually reaching and passing the so-called vaccination threshold, below which huge epidemics can appear in the now less vaccinated population. This scenario is actually present in measles in the UK where the population has been vaccinated well since the end of the nineteen sixties. But because of unfounded fears that the vaccines have side effects the vaccination level has decreased in recent years, such that the system approaches the vaccination threshold.[15] The distribution of outbreaks following an imported first case, the so-called index case, shows an approach to a power law behavior during the last years, whereas before during the well vaccinated phase it was far away from such power law behavior. See Jansen, Stollenwerk.[16]

Another scenario in epidemiology is that of accidental pathogens. Childhood diseases which are highly contagious but also show symptoms quickly after infection have been the epidemiological examples where modeling has been most fruitful. The infection results in disease cases, I, which are also the infectious hosts. As opposed to such paradigmatic childhood diseases some pathogens result mostly in asymptomatic infection and only rarely cause disease. Most known micro-organisms live in their hosts as a commensal, and do not cause any harm. An interesting case is the meningococcus (*Neisseria meningitidis*) causing meningitis and septicaemia, which is carried by large fraction of the human population, but rarely causes disease.

However, if it causes disease, the consequences for the host are dramatic, and if not treated can lead to the death of the host within a few days after infection. This is not in the interest of the bacteria, since the killing of the host reduces transmission. The pathogenicity is an accident for the bacterium causing it.

A stochastic model with competing strains[17,19] shows that strains which do not cause disease dominate the infection in the host population, while highly pathogenic strains die out quickly. However, a nearly harmless strain causing disease rarely will persist for a long time in the population alongside the completely harmless strain, showing critical fluctuations in the limit of vanishing pathogenicity.[17] Considering a model with a large variety of pathogenicities, resulting from mutations in strains trying to escape the host's immune system, shows that the system evolves to a state where only these nearly harmless pathogens remain in the system for long times to cause disease cases in significant numbers.[18] Hence, the system evolves towards critical behavior. The case study of meningitis where the difference between harmless infection and disease is large is a very good system to study the effects of accidental pathogens.[20] It is to be expected that the mechanism is much wider spread but then more difficult even to analyse with real world data. The critical fluctuations on their own make the example of meningitis difficult to analyse.

7.2. Simple epidemic models showing criticality

As the simplest epidemic model with interesting behavior we present the SIS epidemic. In this model the susceptible hosts become infected when meeting already infected with rate β, and recover with rate α back into the susceptible class.

7.2.1. *The SIS epidemic*

The SIS epidemic characterized by the reaction scheme

$$\begin{aligned} S + I &\xrightarrow{\beta} I + I \\ I &\xrightarrow{\alpha} S \end{aligned}$$

is a stochastic process with non-linear transition rates in the master equation

$$\frac{d}{dt}p(I,t) = \frac{\beta}{N}(I-1)(N-(I-1))p(I-1,t) + \alpha(I+1)p(I+1,t) - \left(\frac{\beta}{N}I(N-I)+\alpha I\right)p(I,t) \quad . \tag{7.1}$$

Since we assume constant population size N, we have $S = N - I$. For the dynamics of the mean value $\langle I\rangle := \sum_{I=0}^{N} Ip(I)$ we obtain by inserting the master equation Eq. (7.1)

$$\frac{d}{dt}\ \langle I\rangle = (\beta-\alpha)\langle I\rangle - \frac{\beta}{N}\langle I^2\rangle \tag{7.2}$$

where now the second moment $\langle I^2\rangle := \sum_{I=1}^{N} I^2 \cdot p(I,t)$ enters the right hand side of the equation. So we do not obtain a closed system for the mean $\langle I\rangle$. However, as will be described in more detail in the following sections, an approximation, called mean field approximation, can help to close the system. Here it consists of

$$\langle I^2\rangle \approx \langle I\rangle^2 \tag{7.3}$$

meaning that the variance is neglected, $var := \langle I^2\rangle - \langle I\rangle^2 \approx 0$. So now we obtain a closed ordinary differential equation (ODE)

$$\frac{d}{dt}\ \langle I\rangle = \frac{\beta}{N}\langle I\rangle(N-\langle I\rangle) - \alpha\langle I\rangle \quad . \tag{7.4}$$

Considering the density $x := \langle I\rangle/N$ instead of the absolute numbers $\langle I\rangle$ we find the simple quadratic ODE

$$\frac{dx}{dt} = \beta x(1-x) - \alpha x \quad . \tag{7.5}$$

In this form it will appear again later as a result in Section 7.2.3.

7.2.2. *Solution of the SIS system shows criticality*

Now we examine Eq. (7.5) and its solution more closely, particularly its dependence on the parameter values and initial conditions. The stationary point x^* ist given by the condition that the rate of change becomes zero

$$0 = \beta x^*(1-x^*) - \alpha x^* \tag{7.6}$$

obtaining for the quadratic form in general two stationary states

$$x_1^* = 0 \qquad , \qquad x_2^* = 1 - \frac{\alpha}{\beta} \quad . \tag{7.7}$$

The time solution of the ODE Eq. (7.5) can be obtained by separation of variables and integration which gives as result

$$x(t) = \frac{\left(1 - \frac{\alpha}{\beta}\right)}{\left(1 - e^{-(\beta-\alpha)t}\right) + \frac{1}{x_0}\left(1 - \frac{\alpha}{\beta}\right) e^{-(\beta-\alpha)t}} \tag{7.8}$$

with initial condition x_0 at starting time $t_0 = 0$. The stable fixed points x^* (given by x_1^* if $\beta < \alpha$ and x_2^* if $\beta > \alpha$) are approached exponentially fast in time

$$x(t) - x^* \sim e^{-|\beta-\alpha|t}. \tag{7.9}$$

However, for $\beta \to \alpha$ we have a problem with the time solution. First, we see that for $\beta \to \alpha$ the second stationary point falls together with the first

$$x_2^* = 1 - \frac{\alpha}{\beta} \qquad \to \qquad x_2^* = 0 = x_1^* \tag{7.10}$$

and for β smaller than α it would become negative. A stability analysis reveals that at $\beta = \alpha$ the two solutions change stability. Below the threshold x_1^* is stable, above it x_2^* becomes stable. In that sense the point $\beta = \alpha$ marks a critical point, or β takes the critical value β_c, where in this model $\beta_c = \alpha$. (This will not be true any more in spatial models, where β_c is in general larger than α.) Also for $\beta \to \alpha = \beta_c$, the critical value of β, the time solution shows remarkable behavior

$$x(t) = \frac{\left(1 - \frac{\alpha}{\beta}\right)}{1 - e^{-(\beta-\alpha)t}} \qquad \to \frac{0}{0} \tag{7.11}$$

which we can however analyse in this model directly by solving the ODE at the critical point $\beta = \beta_c$, obtaining the ODE at criticality

$$\frac{dx}{dt} = \beta x(1-x) - \alpha x = \alpha x(1-x) - \alpha x = -\alpha x^2 \tag{7.12}$$

Now this ODE $dx/dt = -\alpha x^2$ can be solved directly and gives the following result

$$\begin{aligned} x(t) &= \frac{1}{\frac{1}{x_0} + \alpha \cdot t} \\ &\sim t^{-1} \end{aligned} \tag{7.13}$$

which has a power law behavior in its time dependence, as opposed to the exponential behavior in other parameter regions. The exponent -1 will

turn out to be a mean field critical exponent of a whole class of stochastic systems, the directed percolation universality class. Such power law behavior is a general sign of systems at and around critical states.

7.2.3. *The spatial SIS epidemic*

Also the spatial version of the SIS system has been investigated extensively. A site i can either have an infected individual $I_i := 1$ or be a susceptible $S_i := 1$, hence $I_i = 0$ (in general $S_i := 1 - I_i$). The transition rate corresponding to a change in the state of site i from I_i to $1 - I_i$ is given by w_{1-I_i,I_i}.

The master equation for the spatial SIS-system for N lattice points describes the change in the probability $p(I_1, ..., I_N, t)$ that the system is in state $(I_1, ..., I_N)$ at time t:

$$\begin{aligned}\frac{d}{dt}p(I_1,...,I_N,t) = &\sum_{i=1}^{N} w_{I_i,1-I_i}\ \ p(I_1,...,1-I_i,...,I_N,t) \\ &- \sum_{i=1}^{N} w_{1-I_i,I_i}\ \ p(I_1,...,I_i,...,I_N,t)\end{aligned} \tag{7.14}$$

for $I_i \in \{0, 1\}$ and transition rate

$$w_{I_i,1-I_i} = b\left(\sum_{j=1}^{N} J_{ij}I_j\right)\cdot I_i + a\cdot(1-I_i) \quad , \tag{7.15}$$

and

$$w_{1-I_i,I_i} = b\left(\sum_{j=1}^{N} J_{ij}I_j\right)\cdot (1-I_i) + a\cdot I_i \quad , \tag{7.16}$$

with b infection rate and a recovery rate. Here $J = (J_{ij})$ is the adjacency matrix containing 0 for no connection and 1 for a connection between sites i and j. Hence $J_{ij} = J_{ji} \in \{0, 1\}$ for $i \neq j$ and $J_{ii} = 0$. So a state is now defined by $I_1, ..., I_N$, and the probability of each state has to be considered to describe the spatial system accurately.

The way the model is formulated allows an economic calculation, but the formulation may at first site seem somewhat cryptic. Looking at one site i, the transition rate b gives the probability per time to get infected by a neighboring site j. The number of infected sites being neighbors to site i

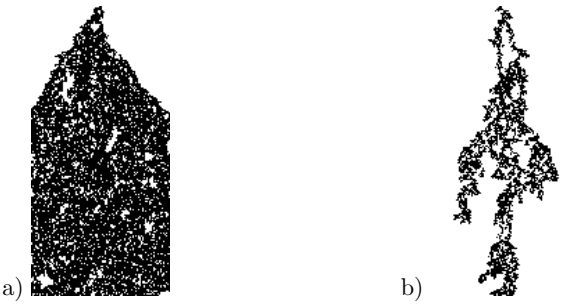


Fig. 7.1. One dimensional SIS epidemic with $N = 100$ individuals. Parameters: $b = 1$ fixed, and a varied, a) $a = 0.3$, low death rate gives a high incidence, b) $a = 0.62$. Space goes horizontally, time from top to bottom.

is given by $\sum_{j=1}^{N} J_{ij} I_j$, so that the force of infection to site i is given by $b \cdot \left(\sum_{j=1}^{N} J_{ij} I_j\right)$. For a site to become infected it needs to be susceptible first. Hence, the transition rate $w_{1,0} = b \cdot \left(\sum_{j=1}^{N} J_{ij} I_j\right)$ describes the transition into the infected state. Once infected, the site can lose the infection through recovery, hence $w_{0,1} = a$ describes the transition away from the infected state. We can, likewise, formulate the transition rates as leading to and from the susceptible state ($w_{0,1}$ and $w_{1,0}$, respectively). This formulation follows the master equation approach for a spatial system as for example used by Glauber[21] for a spin system.

We first show some simulations of the spatial birth and death process in Fig 7.1. For low death rates or high birth rates we see that the system approaches the stationary state quickly and then shows noisy fluctuations around that state.

However, for an increasing recovery rate (or, respectively, a decreasing infection rate), the stationary state is lower, but also is approached more slowly. Especially, for a low stationary state we observe huge fluctuations around that stationary state, also with much longer autocorrelation, (Fig. 7.2). For even higher recovery rates, we observe a further increase in fluctuations with longer autocorrelation, eventually leading to the extinction of the process. For very high recovery rates (or respectively low infection rates), the process tends to die out quickly, after some initial fluctuations.

We now want to describe the stochastic system by easily accessible global quantities, such as the dynamics of the total number of infected,

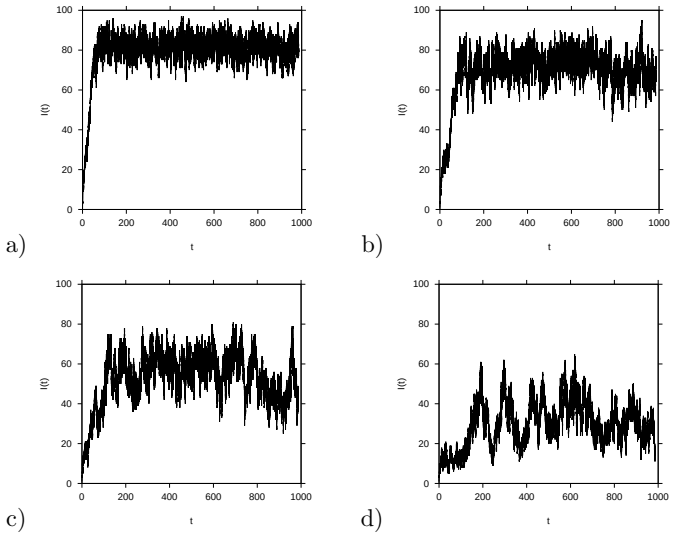


Fig. 7.2. One dimensional SIS epidemic with $N = 100$ individuals. Parameters: $b = 1$ fixed, and a varied, a) $a = 0.3$, low death rate gives a high incidence, b) $a = 0.4$, c) $a = 0.5$, d) $a = 0.6$. High death rate gives not only smaller mean incidence, but also larger variance.

or the number of clusters of certain shapes.

7.2.4. *Dynamics for the spatial mean*

Since the dynamics of the total number of infected depends on the number of neighboring pairs due to the non-linearity in the transition rates, e.g. $w_{1-I_i,I_i} \sim I_i \cdot I_j$, we need to examine clusters of sites. The methods we use here are in analogy with the methods used for the non-spatial master equations.

We consider statistics for the number of clusters with certain shapes, starting with the number of single sites that are infected. For the total number of infected sites we have $[I] := \sum_{i=1}^{N} I_i$ and respectively $[S] := \sum_{i=1}^{N} (1 - I_i)$. For pairs we have $[II] := \sum_{i=1}^{N} \sum_{j=1}^{N} J_{ij}\ I_i \cdot I_j$ and triples $[III] := \sum_{i=1}^{N} \sum_{j=1}^{N} \sum_{k=1}^{N} J_{ij} J_{jk} \cdot I_i I_j I_k$ or triangles $[\Delta] := \sum_{i=1}^{N} \sum_{j=1}^{N} \sum_{k=1}^{N} J_{ij} J_{jk} J_{ki} \cdot I_i I_j I_k$ and so on. These spatial averages, e.g $[I] := \sum_{i=1}^{N} I_i$, depend on the ensemble $(I_1, ..., I_N)$ which changes with

time. Hence we define the ensemble average, e.g.

$$\langle I\rangle(t) := \sum_{I_1=0}^{1} ... \sum_{I_N=0}^{1} [I]\; p(I_1, ..., I_N, t)$$

or more generally for any function $f = f(I_1, ..., I_N)$ of the state variables we define the ensemble average as

$$\langle f\rangle(t) := \sum_{I_1=0}^{1} ... \sum_{I_N=0}^{1} f(I_1, ..., I_N)\; p(I_1, ..., I_N, t) \quad . \tag{7.17}$$

The ensemble average $\langle f\rangle(t)$ describes the expected value of $f(t)$ over repeated realizations of the stochastic process. Then the time evolution of the ensemble average is determined by

$$\frac{d}{dt}\langle f\rangle(t) := \sum_{I_1=0}^{1} ... \sum_{I_N=0}^{1} f(I_1, ..., I_N)\; \frac{d}{dt} p(I_1, ..., I_N, t) \tag{7.18}$$

where the master equation is to be inserted again giving terms of the form $\langle f\rangle$ and other expressions $\langle g(I_1, ..., I_N)\rangle$. Hence, for the total number of pairs we have

$$\langle II\rangle(t) = \sum_{i=1}^{N}\sum_{j=1}^{N} J_{ij}\langle I_i I_j\rangle \tag{7.19}$$

and with $\langle S_i I_j\rangle = \langle (1 - I_i) I_j\rangle$

$$\langle SI\rangle(t) = \sum_{i=1}^{N}\sum_{j=1}^{N} J_{ij}\langle S_i I_j\rangle = \sum_{i=1}^{N}\langle I_i\rangle \left(\sum_{j=1}^{N} J_{ij}\right) - \sum_{i=1}^{N}\sum_{j=1}^{N} J_{ij}\langle I_i I_j\rangle \tag{7.20}$$

with

$$\sum_{i=1}^{N}\langle I_i\rangle \left(\sum_{j=1}^{N} J_{ij}\right) = Q \cdot \sum_{i=1}^{N}\langle I_i\rangle = Q \cdot \langle I\rangle \tag{7.21}$$

for $Q_i := \sum_{j=1}^{N} J_{ij}$ the number of neighbors to site i or degree. Here we assume the Q_i to be constant $Q_i = Q$ for all lattice sites i, since we are mainly interested in regular lattices (and have to assume even periodic boundary conditions). For irregular or random lattices the index i has to be kept for Q_i, which introduces a considerable amount of hidden complexity in the analysis. Generally, terms of the form

$$\langle II\rangle_\nu := \sum_{i=1}^{N}\sum_{j=1}^{N} J_{ij}^{\nu} \cdot I_i I_j \tag{7.22}$$

will appear with any ν^{th} power of the adjacency matrix, e.g. $J^2_{ij} = \sum_{k=1}^N J_{ik}J_{kj}$, and respectively

$$\langle III\rangle_{\mu,\nu} := \sum_{i=1}^{N}\sum_{j=1}^{N}\sum_{k=1}^{N} J^{\mu}_{ij}J^{\nu}_{jk}\cdot I_iI_jI_k \tag{7.23}$$

and so on.

7.2.5. *Moment Equations*

For the ensemble mean total number of infected sites $\langle I\rangle := \sum_{i=1}^N \langle I_i\rangle$ we obtain the dynamics

$$\begin{aligned}\frac{d}{dt}\langle I\rangle &= \sum_{i=1}^{N}\frac{d}{dt}\langle I_i\rangle \\ &= \sum_{i=1}^{N}\left(-a\langle I_i\rangle + b\sum_{j=1}^{N} J_{ij}(\langle I_j\rangle - \langle I_iI_j\rangle)\right)\end{aligned} \tag{7.24}$$

as a result of straightforward but tedious calculations have entered up to here.[24] Then in detail

$$\frac{d}{dt}\langle I\rangle = -a\underbrace{\sum_{i=1}^{N}\langle I_i\rangle}_{=\langle I\rangle} + b\underbrace{\sum_{j=1}^{N}\langle I_j\rangle\underbrace{\sum_{i=1}^{N}J_{ij}}_{=Q_j=Q}}_{=Q\langle I\rangle} - b\underbrace{\sum_{i=1}^{N}\sum_{j=1}^{N}J_{ij}\langle I_iI_j\rangle}_{=\langle II\rangle_1}$$

$$= -a\langle I\rangle + bQ\langle I\rangle - b\langle II\rangle_1$$

such that

$$\begin{aligned}\frac{d}{dt}\langle I\rangle &= b\left(Q\langle I\rangle - \langle II\rangle_1\right) - a\langle I\rangle \\ &= b\langle SI\rangle_1 - a\langle I\rangle\end{aligned} \tag{7.25}$$

with $\langle SI\rangle_1 := \sum_{i=1}^N\sum_{j=1}^N J_{ij}\langle S_iI_j\rangle = Q\langle I\rangle - \langle II\rangle_1$. To obtain the dynamics for the total number of pairs

$$\frac{d}{dt}\langle II\rangle_1 = \sum_{i=1}^{N}\sum_{j=1}^{N}J_{ij}\frac{d}{dt}\langle I_iI_j\rangle \tag{7.26}$$

we first have to calculate $\frac{d}{dt}\langle I_i I_j\rangle$ from the rules given above and substitute the master equation. A detailed calculation yields

$$\begin{aligned}\frac{d}{dt}\,\langle II\rangle_1 &= 2b\left(\langle II\rangle_2 - \langle III\rangle_{1,1}\right) - 2a\langle II\rangle_1 \\ &= 2b\langle ISI\rangle_{1,1} - 2a\langle II\rangle_1 \end{aligned} \tag{7.27}$$

with $\langle ISI\rangle_{1,1} := \sum_{i=1}^{N}\sum_{j=1}^{N}\sum_{k=1}^{N} J_{ij}J_{jk}\langle I_i(1-I_j)I_k\rangle$. Again the ODE for the nearest neighbors pair $\langle II\rangle_1$ involves higher moment terms like $\langle II\rangle_2$ and $\langle III\rangle_{1,1}$.

We now try to approximate the higher moments in terms of lower ones in order to close the ODE system. The quality of the approximation will depend on the actual parameters of the birth-death process, i.e. a and b. We investigate the mean field approximation, expressing $\langle II\rangle_1$ in terms of $\langle I\rangle$. Other schemes to approximate higher moments, like the pair approximation can be found in the literature.[22,23]

7.2.6. *Mean field behavior*

In mean field approximation, the interaction term which gives the exact number of inhabited neighbors is replaced by the average number of infected individuals in the full system, acting like a mean field on the actually considered site. Hence we set

$$\sum_{j=1}^{N} J_{kj}I_j \approx \sum_{j=1}^{N} J_{kj}\,\frac{\langle I\rangle}{N} = \frac{Q}{N}\cdot\langle I\rangle \tag{7.28}$$

where the last line of Eq. (7.28) only holds again for regular lattices. We get for $\langle II\rangle_1$ in Eq. (7.24)

$$\begin{aligned}\langle II\rangle_1 &= \langle\sum_{i=1}^{N}\sum_{j=1}^{N} J_{ij}I_iI_j\rangle = \langle\sum_{i=1}^{N} I_i\sum_{j=1}^{N} J_{ij}I_j\rangle \\ &\approx \langle\sum_{i=1}^{N} I_i\,\frac{Q}{N}\cdot\langle I\rangle\rangle = \frac{Q}{N}\cdot\langle I\rangle\cdot\langle\sum_{i=1}^{N} I_i\,\rangle \\ &= \frac{Q}{N}\cdot\langle I\rangle^2 \quad .\end{aligned} \tag{7.29}$$

Hence, we obtain the dynamics for the total mean of individuals in the mean field approximation:

$$\begin{aligned}\frac{d}{dt}\langle I\rangle &= b\left(Q\langle I\rangle - \frac{Q}{N}\langle I\rangle^2\right) - a\langle I\rangle \\ &= b\frac{Q}{N}\ (N-\langle I\rangle)\langle I\rangle - a\langle I\rangle \quad . \end{aligned} \tag{7.30}$$

For homogeneous mixing, i.e. the number of neighbors equals roughly the total population size $Q \approx N$, we obtain the logistic equation for the total number of infected sites

$$\frac{d}{dt}\langle I\rangle = b\ \langle I\rangle(N-\langle I\rangle) - a\langle I\rangle \tag{7.31}$$

or for the proportion $\frac{\langle I\rangle}{N} =: x \in [0,1]$

$$\frac{d}{dt}\frac{\langle I\rangle}{N} = Nb\ \frac{\langle I\rangle}{N}\left(1-\frac{\langle I\rangle}{N}\right) - a\frac{\langle I\rangle}{N} \tag{7.32}$$

hence

$$\frac{dx}{dt} = Nb\ x\cdot(1-x) - a\cdot x \quad . \tag{7.33}$$

This is the logistic equation (see section 7.2) with $a = \alpha$ and $Nb = \beta$. See Fig. 7.3 for the time solution for $\langle I\rangle$ for a population size of $N = 100$ on a double logarithmic plot. In this plot the straight line is clearly visible for the critical value β_c, indicating the power law with exponent -1. The spatial system has been investigated in respect to criticality by Grassberger and de la Torre.[7]

We have seen criticality in a simple epidemic model where a parameter has to be adjusted to or near to its critical value. In applications we have such a situation for example when the epidemic system crosses slowly through the critical region, as in the example of measles under vaccination.[15,16] However, in self-organized criticality (SOC) the system evolves on its own to a critical state showing power law behavior. As a paradigmatic system for SOC in epidemiology, in the next section we will describe a theory of accidental pathogens and applied it to meningococcal disease.

7.3. Accidental pathogens: the meningococcus

7.3.1. *Accidental Pathogens*

A classical example of different scientific disciplines working together fruitfully from the beginning of 20th century is the explanation of chemical

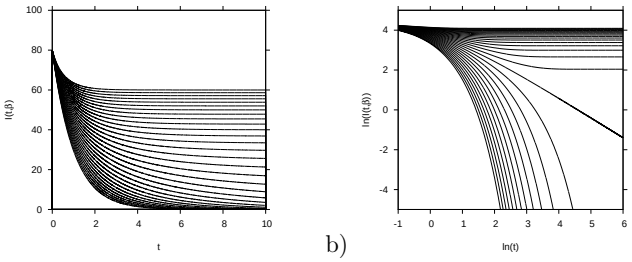


Fig. 7.3. a) Starting with $I(t_0) = 80$ infected individuals, we plot 31 trajectories varying β between $\beta = 0$ and $\beta = 2.5$ of the SIS epidemic ODE up to $t_{max} = 10$. The parameter α is fixed to $\alpha := 1$. b) We now change t_{max} up to $t_{max} = 500$ and plot $I(t)$ for various parameter values β on a double-logarithmic scale. For small β-values the solutions $I(t)$ decreases fast, exponentially fast. For large β-values the solutions converge quickly onto the final stationary value, observed as constant here. Only for $\beta = \alpha$ the curve becomes a straight line in the double-logarithmic plot, indication the power law at criticality.

reactions by physical atomic models. More recently, evolutionary biology and epidemiology, accompanied by statistical physics of critical phenomena, present a new picture to explain unpredicted outbreaks of a severe disease as we will show in a case study on meningococcal infection. This case study will also provide a new mechanism to understand the epidemiology of this particular example, meningococcal disease. It will also serve as a test bed for general principles discussed in evolutionary biology, namely that minor effects at the individual level can cause more harm at population level than a major individual effect which is subject to strong negative selection.

Meningococcal disease is caused by the bacterium *Neisseria meningitidis* (also known as the meningococcus.) The epidemiology of the disease in the developed world is characterized by outbreaks of variable size and duration. The occurrence of these outbreaks has long puzzled epidemiologists. The meningococcus differs from most other pathogens in that transmits almost exclusively through hosts which carry the bacterium, but do not show any symptoms and do not fall ill. Transmission is mainly through close social contact (e.g sharing accommodation). Disease caused by the bacterium is a rare occurrence, however, if it happens the resulting *septicaemia*, or meningitis *meningitis* can be life threatening. Because illness is very severe, ill people rarely transmit the bacterium, and causing disease harms not only the human host, but also the bacterium. Therefore causing disease can be seen as accidental for the pathogen.

The epidemiology of accidental pathogens is difficult to study: for nor-

mal diseases it suffices to keep track of the number of individuals that fall ill, to monitor the size of the pathogen population. Carriers of accidental pathogens, such as the meningococcus, are asymptomatic and therefore not easy to identify. This does not the pathogen population is not present: it has been estimated that 5-10% of the human population normally carries the meningococcus, and that in same age classes in certain environments (e.g adolescents such as army recruits or students who often share accommodation) this can go up to 40%. The number of cases of meningococcal disease, in contrast, is small, in the order of 1-10 per 100,000 per year; the pathogenicity of the meningococcus is actually very small.[26]

The small pathogenicity can cause huge critical fluctuations at the population level, a mechanism most clearly visible in meningococcal disease, but possibly underlying many other epidemiological systems, not only of bacterial infections but also viral infections. Whereas bacteria have their own metabolism and are able to reproduce with little effect on their host, viruses have to hijack host cells in order to do so. For example in polio infection most of the time the viruses live in the host's gut undetected and only when entering nerve cells they cause severe disease. As epidemiology is one of the best data sources of biological interactions, especially notifiable diseases, and micro-organisms in a hostile environment like the pathogen-host interaction are the fastest mutating biological systems, this is the ideal set-up for evolutionary biology to be tested quantitatively.

On the technical side, the critical fluctuations that are so crucial in understanding major epidemic outbreaks were originally investigated in physical systems much larger than the human population. Though finger prints of a critical state can be obtained near criticality, it becomes increasingly difficult to investigate critical quantities the closer to criticality the system is. So we can only hope to find these finger prints, but not really attempt to measure accurately for example critical exponents. It has to be mentioned that we are in a so-called non-equilibrium critical system, a birth-death process effectively, whereas the most powerful characterization of criticality is obtained in equilibrium systems, like the famous Ising model for magnetic phase transitions. However, as the system under investigation evolves on its own towards a critical state, we can expect that the system is most of the time reasonably close to criticality in order to detect the large fluctuations reliably in empirical data.

7.3.2. *Modeling Infection with Accidental Pathogens*

Classically, epidemics are modelled dividing the host population into susceptible S, infected I and sometimes recovered R, where the infected are asymptomatic.

Meningoccocci mostly live as commensals in the nasopharynx of the hosts as an unnoticed, completely harmless infection. We will denote the harmlessly infected hosts by I. Rarely, meningococci cross the nasal wall into the blood stream and cause septicaemia or meningitis. In the model ill hosts are labeled X and ill hosts are removed from normal social interaction such hosts do not transmit. The resulting SIRX-model would allow a transition from harmlessly infected to diseased hosts with a small rate ε. It is only the number of diseased cases X which is recorded in empirical data of meningococcal disease. We will investigate the quantitative outcome of this SIRX-model with respect to the statistics of the disease cases, X, below, but can already say here that the Poisson process-like behavior of the SIRX-model does not account for the basic epidemiological findings that meningococcal disease often appears in clusters with pronounced phases of silence between outbreaks.

Only when we include another finding of the biology of the meningococcus in the modeling of its epidemiology can such clustered outbreaks be obtained. Namely, it is necessary to take into account that the bacteria are are highly mutating easily mutate and evade the hosts' immune system during harmless carriage.[27] The different mutants of the bacterium have different likelihoods accidentally harming their host by causing severe disease. Hence in the simplest modeling set-up where we found clustered outbreaks[17] we distinguished between harmless infection never causing disease, the I class, and potentially harmful infection with a different mutant strain of the bacteria, the Y class, from which with a small rate ε, the pathogenicity, disease cases X are created. For pathogenicity close to its critical value of zero we found huge fluctuations, to be expected from the theory of critical phenomena in physics of condensed matter[9,28] and in biology of critical birth and death processes[7,8] (for a general audience introduction see Warden[29]). These fluctuations are giving rise to clustered outbreaks in disease cases X in our SIRYX-model.[17]

7.3.3. *The meningococcal disease model: SIRYX*

We include demographic stochasticity in the description of the epidemic. As such, for the basic SIRYX-model we consider the dynamics of the proba-

bility $p(S, I, R, Y, X, t)$ of the system to have S susceptible, I asymptomatically infected with harmless strain, R recovered, Y asymptomatically infected with potentially harmful strain and X with symptomatic infected, all at time t, which is governed by a master equation[30,31] (see also in a recent application to a plant epidemic model[32,33]). For state vectors $\underline{n}$, here for the SIRYX-model $\underline{n} = (S, I, R, Y, X)$, the master equation reads

$$\frac{dp(\underline{n})}{dt} = \sum_{\underline{\tilde{n}} \neq \underline{n}} w_{\underline{n},\underline{\tilde{n}}} \; p(\underline{\tilde{n}}) - \sum_{\underline{\tilde{n}} \neq \underline{n}} w_{\underline{\tilde{n}},\underline{n}} \; p(\underline{n}) \tag{7.34}$$

a more complicated master equation than used for the SIS-system in Eq. (7.1). For the SIRYX-system the transition probabilities $w_{\underline{\tilde{n}},\underline{n}}$ are then given (omitting unchanged indices in $\underline{\tilde{n}}$, with respect to $\underline{n}$) by

$$\begin{aligned}
w_{(R-1,S+1),(R,S)} &= \alpha \cdot R && , && R &\xrightarrow{\alpha} S \\
w_{(S-1,I+1),(S,I)} &= (\beta - \mu) \cdot \tfrac{I}{N} \, S && , && S + I &\xrightarrow{\beta-\mu} I + I \\
w_{(S-1,Y+1),(S,Y)} &= \mu \cdot \tfrac{I}{N} \, S && , && &\xrightarrow{\mu} Y + I \\
w_{(I-1,R+1),(I,R)} &= \gamma \cdot I && , && I &\xrightarrow{\gamma} R \\
w_{(S-1,Y+1),(S,Y)} &= (\beta - \nu - \varepsilon) \cdot \tfrac{Y}{N} \, S && , && S + Y &\xrightarrow{\beta-\nu-\varepsilon} Y + Y \\
w_{(S-1,I+1),(S,I)} &= \nu \cdot \tfrac{Y}{N} \, S && , && &\xrightarrow{\nu} I + Y \\
w_{(S-1,X+1),(S,X)} &= \varepsilon \cdot \tfrac{Y}{N} \, S && , && &\xrightarrow{\varepsilon} X + Y \\
w_{(Y-1,R+1),(Y,R)} &= \gamma \cdot Y && , && Y &\xrightarrow{\gamma} R \\
w_{(X-1,S+1),(X,S)} &= \varphi \cdot X && , && X &\xrightarrow{\varphi} S
\end{aligned} \tag{7.35}$$

along with the respective reaction schemes. From $w_{\underline{\tilde{n}},\underline{n}}$ the rates $w_{\underline{n},\underline{\tilde{n}}}$ follow immediately. This defines the master equation for the full SIRYX-system.

For the accidental pathogen specific system, the following considerations are needed: In order to describe the behavior of pathogenic strains added to the basic SIR-system we include a new class Y of individuals infected with a potentially pathogenic strain. We will assume that such strains arise by e.g. point mutations or recombination through a mutation process with a rate μ in the scheme $S + I \xrightarrow{\mu} Y + I$. For symmetry we also allow the mutants to back-mutate with rate ν, hence $S + Y \xrightarrow{\nu} I + Y$.

The major point here in introducing the mutant is that the mutant has the same basic epidemiological parameters α, β and γ as the original strain and only differs in its additional transition to pathogenicity with rate ε. These mutants cause disease with rate ε, which will turn out to be small later on, hence the reaction scheme is $S + Y \xrightarrow{\varepsilon} X + Y$. This sends susceptible hosts into an X class, which contains all hosts who develop disease. These are the cases which are detectable as opposed to hosts in

classes Y and I that are asymptomatic carriers who cannot be detected easily. The mutation transition $S + I \xrightarrow{\mu} Y + I$ fixes the master equation transition rate $w_{(S-1,I,R,Y+1,X),(S,I,R,Y,X)} = \mu \cdot (I/N) \cdot S$. In order to denote the total contact rate with the parameter β, we keep the balancing relation

$$w_{(S-1,I+1,R,Y,X),(S,I,R,Y,X)} + w_{(S-1,I,R,Y+1,X),(S,I,R,Y,X)} = \beta \cdot \frac{I}{N} \cdot S \quad (7.36)$$

and obtain for the ordinary infection of normal carriage the transition rate $w_{(S-1,I+1,R,Y,X),(S,I,R,Y,X)} = (\beta - \mu) \cdot (I/N) \cdot S$. The total rate of transmission for a susceptible host through either normal carriage I or mutant carriage Y, by β obeys the balancing equation

$$\sum_{\underline{\tilde{m}} \neq \underline{m}} w_{(S-1,\underline{\tilde{m}}),(S,\underline{m})} = \beta \, \frac{I+Y}{N} \cdot S \quad (7.37)$$

for $\underline{m} = (I, R, Y, X)$. With the above mentioned transitions this fixes the master equation rate $w_{(S-1,I,R,Y+1,X),(S,I,R,Y,X)} = (\beta - \nu - \varepsilon) \cdot (Y/N) \cdot S$. The system shows qualitatively the behavior demonstrated in Fig. 7.4 with the stochastic simulations performed with the Gillespie algorithm.[34–36]

7.3.4. *Divergent fluctuations for vanishing pathogenicity: Power law*

For pathogenicity ε larger than the mutation rate μ a potentially harmful lineage normally does not attain high densities compared to the total population size. Therefore, we can consider the full system as being composed of a dominating SIR-system which is not really affected by the rare Y and X cases, calling it the SIR-heat bath, and our system of interest, namely the Y cases and their resulting pathogenic cases X, is considered to live in the SIR-heat bath. The SIR-heat bath is independent of X and Y and controls the number of susceptible individuals available for infection, S.

Taking into account Eq. (7.38) for the stationary values of the SIR-system

$$S^* = N\frac{\gamma}{\beta} \quad , \quad I^* = N\left(1 - \frac{\gamma}{\beta}\right)\left(\frac{\alpha}{\alpha+\gamma}\right) \quad , \quad R^* = N - S^* - I^* \quad (7.38)$$

we obtain for the transition rates (compare Eq. (7.35)) of the remaining

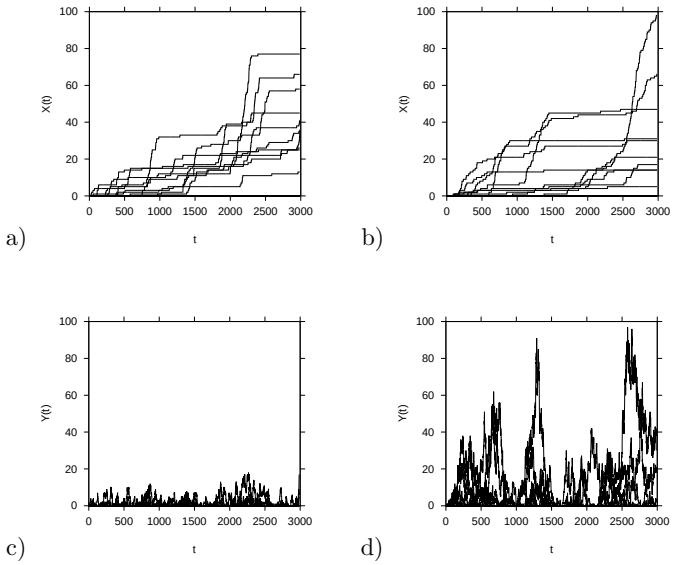


Fig. 7.4. For the SIRYX-model we show simulations of 10 runs for two different values of pathogenicity ε. In a) and c) ε is ten times smaller than in b) and d). The cumulative number of diseased cases X is shown in a) and b). Paradoxically, the cumulative number of diseased cases does not also decrease by a factor of ten, but fluctuates more wildly, sometimes leading to even higher numbers of diseased. The paradox is explained by inspecting the numbers of hosts carrying the potentially harmful bacteria ($Y(t)$) in c) and d) where it can be seen that the number of carriers differs by a factor ten, due to their smaller disadvantage compared to harmless carriage.

YX-system

$$\begin{aligned}
w_{(S^*,Y+1),(S^*,Y)} &= \mu \cdot \tfrac{S^*}{N}\, I^* && =: c \\
w_{(S^*,Y+1),(S^*,Y)} &= (\beta - \nu - \varepsilon) \cdot \tfrac{S^*}{N}\, Y && =: b \cdot Y \\
w_{(S^*,X+1),(S^*,X)} &= \varepsilon \cdot \tfrac{S^*}{N}\, Y && =: g \cdot Y \\
w_{(Y-1,R^*),(Y,R^*)} &= \gamma \cdot Y && =: a \cdot Y \\
w_{(X-1,S^*),(X,S^*)} &= \varphi \cdot X \quad . &&
\end{aligned} \tag{7.39}$$

All terms not involving Y or X vanish from the master equation, since the gain and loss terms cancel each other out for such transitions. If we neglect the recovery of the disease cases to susceptibility, as is reasonable for meningitis, hence $\varphi = 0$, we are only left with Y-dependent transition rates.

In a simplified model, where the SIR-subsystem is assumed to be stationary (due to its fast dynamics), we can show analytically the divergence of the variance and a power law behavior for the size of the epidemics $p(X)$ as soon as the pathogenicity approaches zero. Hence the counter-intuitively large number of disease cases in some realizations of the process can be understood as large scale fluctuations in a critical system with order parameter ε towards zero.

The master equation for YX in stationary SIR results in a birth-death process

$$\begin{aligned}\frac{d}{dt}p(Y,X,t) = &(b\cdot(Y-1)+c)\,p(Y-1,X,t) \\ &+a\cdot(Y+1)\,p(Y+1,X,t)+g\cdot Y\,p(Y,X-1,t) \\ &-(bY+aY+gY+c)\,p(Y,X,t) \quad .\end{aligned} \tag{7.40}$$

For the size distribution of the epidemic we obtain power law behavior

$$p_\varepsilon(X) := \lim_{t\to\infty} p(Y=0,X,t) \sim X^{-\frac{3}{2}} \quad . \tag{7.41}$$

for $\varepsilon \to 0$ and large X (see Stollenwerk, Jansen[17]). The exponent $-3/2$ is the mean field critical exponent of the branching process.[12,37,38] The result Eq. (7.41) was obtained by approximations to a solution with the hypergeometric function

$$p_\varepsilon(X) = \sqrt{\varepsilon}\cdot\frac{2^{-(X+1)}}{\sqrt{\beta}}\cdot\ {}_2F_1\left(\frac{3-X}{2},\frac{2-X}{2};2;1-\frac{\varepsilon}{\beta}\right). \tag{7.42}$$

Such behavior near criticality is also observed in the full SIRYX-system in simulations where the pathogenicity ε is small, i.e. in the range of the mutation rate μ. In spatial versions of this model it is expected that the critical exponents are those of directed percolation (private communication, H.K. Jansen, Düsseldorf, see also Janssen[39]). Further information can be found in Guinea, Stollenwerk, Jansen[40] and in Stollenwerk, Jansen.[24]

7.3.5. *Evolution towards Criticality*

The epidemiological system with accidental pathogens is driven by evolution towards the critical threshold of small pathogenicity and, hence, to large critical fluctuations.[18] The mechanism is simply the disadvantage of the more harmful strains against their less harmful opponents as they remove their hosts from the system, preventing them from spreading the respective harmful mutants further. Only strains with a small pathogenicity can survive for a possible very long long period of time. So one arrives at the

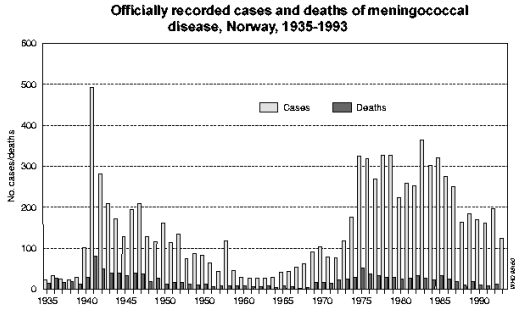


Fig. 7.5. Yearly cases of menigoccocal disease for Norway, notification data, as obtained from the web page of the World Health Organization (WHO), http://www.who.int/emc, document WHO/EMC/BAC/98.3. Decade long outbreaks are visible.

seemingly paradoxical situation that, by reducing the pathogenicity by a factor of ten, one can actually often observe higher numbers of disease cases X (see Fig. 7.4, a)). The paradox is resolved by inspecting the number of mutant infected hosts, Y, which increases by reducing the pathogenicity (see Fig. 7.4, b). This qualitative explanation of why the mildly harmful mutants are dominating the epidemiology of accidental pathogens has been proved quantitatively in Stollenwerk, Jansen.[18]

7.4. Empiric Data Show Fast Epidemic Response and Long Lasting Fluctuations

A first inspection of empirical data on outbreak patterns of meningococcal disease is puzzling. On the one hand, in long time series for a country like Norway one observes decade long outbreaks (see Fig. 7.5), suggesting that basic epidemiological parameters like inverse infection and recovery rate are of the order of several months to one year.

On the other hand, in weekly data from England and Wales a strong seasonal pattern in meningococcal disease notifications is clearly visible, with in addition very strong outbreaks around Christmas and the change of year (see Fig. 7.6). A similar pattern is visible for the 9 regions in which England and Wales are divided. A strong seasonality is present, sometimes accompanied by high Christmas peaks, the regions being of similar

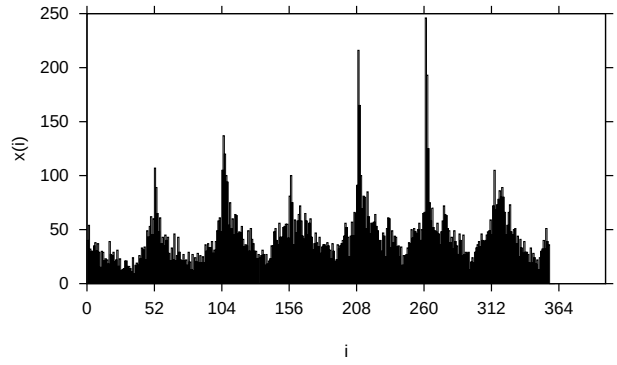


Fig. 7.6. England and Wales weekly data of notified cases of meningococcal disease. A strong seasonality is visible. Time is given in weeks, starting at 1^{st} of January, 1995.

population size as Norway, around 5 million inhabitants.

Assuming a seasonal forcing of the contact rate, possibly based on seasonality in climate, in the underlying population this leaves only a time scale of quick adjustment of the infection process for parameters like inverse infection and recovery rate etc. in the range of a few weeks. On top of that, the Christmas peak, a strong increase of cases in the 52nd week of the calendar year and higher incidents rates also in the two following weeks, the first and second week in January, even suggests a shorter time scale of days to a few weeks.

A possible explanation for the one hand fast response of the epidemic system to seasonality and on the other hand decade long outbreaks could simply be different strains acting on different time scales, and in different countries. Microbiological studies revealed a diversity of lineages to be present, some of which could cause disease.[27,41] On the basis of these data we cannot rule out this explanation but, surprisingly, a very simple model, such as the SIRYX-model described above, can capture both the quick response to seasonal forcing. Due to its closeness to a critical threshold can this model can produce huge long term fluctuations on the time scale of decades when compared to the given time scale of a year given by seasonality. On the contrary, the simpler SIRX-model, being forced seasonally, only can give rise to fluctuations predicted by a Poisson process, with a variance in the range of the mean, but not showing the much larger and time-correlated critical fluctuations of the SIRYX-model.

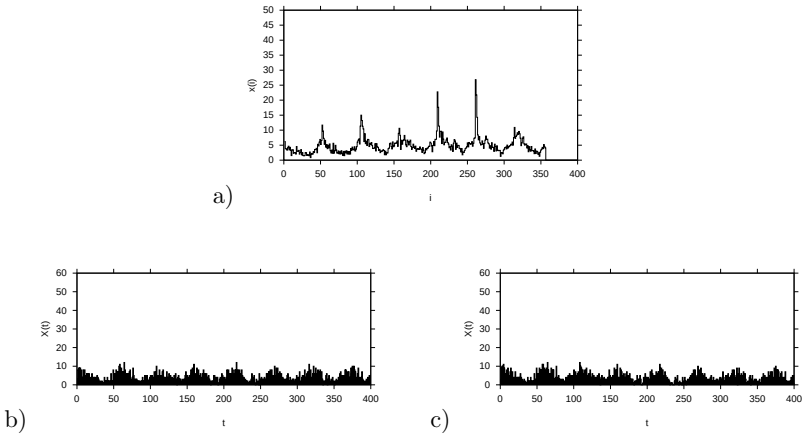


Fig. 7.7. Comparison between a) data from England and Wales and simulations with b) the SIRX-model and c) the SIRYX-model. In a) the weighted mean over 9 regions of England and Wales is shown for the 7 years of weekly data. b) shows a simulation of the simple SIRX, parameters adjusted to qualitatively match the data in a), for a comparable amount of time. c) shows a simulation of the multi-mutant SIRYX-model, taking the same basic parameters of the SIRX-model and further adjustments of the additional parameters into account to match the data. Population size is $N = 5$ million, roughly the size of a typical region in England and Wales. Both models resemble the data farely well in its seasonality and noise level, not attempting to also model the Christmas peak. Little difference is visible between the models.

Interestingly, whereas any distinction between the SIRX and the SIRYX-model would be very difficult on the basis of the short term weekly data from England and Wales, the distinction is quite easy for long term simulations exploiting the critical fluctuations.

7.4.1. *Modeling fast epidemic response finds long lasting fluctuations*

To model the seasonal data from England and Wales, we first observe data from the 9 regions, in which England and Wales is divided. By taking the mean, weighted with the total number of cases in each region over the observation period, we can reduce the effect of the pronounced Christmas peak, which we will not further consider.

In a second step we adjust the parameters of the simple SIRX-model, respectively the multi-mutant SIRYX-model, to the seasonality and the

noise level of the weighted mean data set. Starting from the stationary state solution for the SIRYX-model with constant time independent contact rate we obtained good visual agreement between model and data using a parameter set with fixed ratio of susceptible, infected and recovered. This fixes the ratio of the basic epidemic parameters α, β and γ of the SIR-subsystem and fixes the mutation rate μ and the pathogenicity ε to roughly obtain the noise level of the observed data. Finally, we fixed the absolute value of γ to the time scale given by the data's seasonality, especially the slight shift, i.e. fast response, to seasonal forcing in the contact rate. This left us with an upper limit of inverse recovery $\gamma^{-1} = 4$ *weeks*, giving a minimum of disease cases X about 7 weeks after midsummer, as observed in the data. Uncertainty about the value of the contact rate could change this picture in the range of plus or minus two weeks, but would not result in a response in the range of months or years, needed to smooth out the seasonality.

The SIRX-model uses the same basic epidemic parameters α, β and γ as the SIRYX-model. No mutation rate is needed here, since we only have one strain of pathogens in this model, and an adjusted pathogenicity accounts for the lack of mutants Y in this model. As shown in Fig. 7.7 there are hardly any differences visible between the SIRX-model and the SIRYX-model on this time scale, both describing the mean regional data in England and Wales quite well in terms of seasonality and noise level.

We have to look at a different time scale in order to see any profound difference between the SIRX and the SIRYX model. Therefore, we performed a comparative study, binning the number of disease cases not into weeks but years (keeping the weekly time scale to compare the longer time duration of the simulations) and increasing the simulated time to roughly 1200 weeks (corresponding to 23 years), three times longer than the previous simulations and the empirical data.

The result is shown in Fig. 7.8. In a) the SIRX-model for a population size of 5 million people shows some fluctuations from year to year, whereas the SIRYX-model in b) for the same system size sometimes shows much larger variability, but sometimes not. For example between week 400 and 800 it would be quite difficult to distinguish the two realizations shown here. For ten times larger population size, corresponding to the size of England and Wales, the differences between SIRX-model in c) and SIRYX-model in d) is even less pronounced over the entire simulation time. So again any testing between the models would face severe difficulties, the more since our data sets from England and Wales are much shorter than the simulation

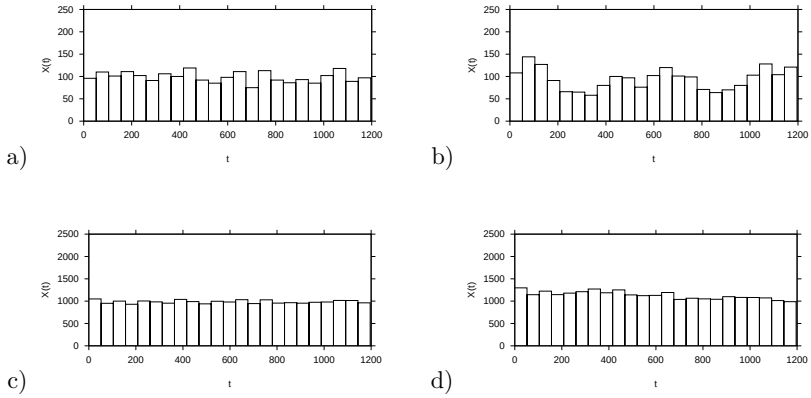


Fig. 7.8. Simulation of weekly cases, now binned into years for a) the SIRX-model and b) the SIRYX-model, for population size 5 *million*, c) and d) simulations of the above mentioned models now for population size 50 *million*. See text for further description.

times used here for the models. Hence only longer term data could help in this situation.

On the other hand, this set of simulations gives us a crucial hint from the theory of critical phenomena how to proceed further in our analysis in so far as comparing the Fig. 7.8 b) and d), the close to critical SIRYX-model shows some time-autocorrelation in its fluctuations which also increases in length with system size. This is predicted by the theory of critical phenomena.[9,28] Namely, at criticality the autocorrelation time diverges and close to criticality the autocorrelation time increases as a power law. Renormalization theory should guarantee that pictures of the system look similar when changing system size and running time accordingly. This is the so called scaling of system size and time.

Under the circumstances of Fig. 7.8 again a rigorous test would be difficult, since in short time series some autocorrelation in realizations of completely uncorrelated fluctuations often ocurs. For example in the simulation of the SIRX-system in Fig. 7.8 a) one easily finds three subsequent years showing decreasing numbers of diseased cases. The situation is similar in Fig. 7.8 c). However, the autocorrelation functions for the data of Fig. 7.8 point into the same direction. Hence, we performed even longer time simulations, expecting more pronounced fluctuations as time passes.

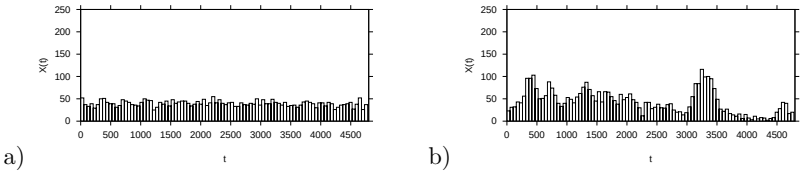


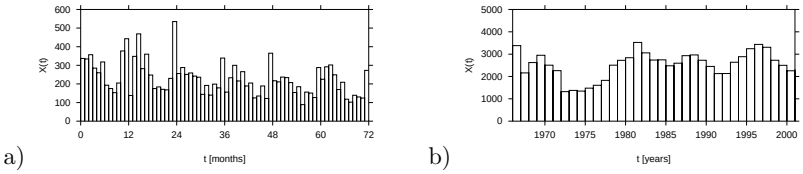
Fig. 7.9. Smaller population size $N = 1\,000\,000$, $4\times$ longer time series than in Fig 7.8. Nearly Poissonian variance over mean ration is observed for SIRX in a), it is 0.95. On the contrary for SIRYX in b) it is 16.72.

Since such simulations are time consuming for large system sizes already at short time simulations we perform longer simulations with just 1 *million* population size.

The results for four times longer simulations as in the previous Fig. 7.8 are shown in Fig. 7.9, comparing the SIRX-model in a) and the SIRYX-model in b). Though again for short periods, as between week 1500 and 2000, there would be little difference between the models, the overall picture is distinguishing very well between the models. Whereas the SIRX-model in a) just shows minor fluctuations over the whole period of simulation, comparable essentially to a Poisson process, the SIRYX-model in b) shows large fluctuations and very surprisingly a huge epidemic between weeks 3000 and 3500 lasting around 12 years. This purely stochastic event could in real life easily be mistaken for an exogenously forced event, or a drastic change in parameters, which it is obviously not here.

This pattern is confirmed by data from other countries. Data from the USA show on the one hand some some seasonality (Fig. 7.10 a), monthly data for 6 years), which is not as clear as the British weekly data but still well visible, and on the other hand huge decade long fluctuations correlated over many years (Fig. 7.10 b), yearly data for 36 years), again not that pronounced as in the Norwegian data, but still clearly observable.

We have concentrated here on modeling the fast dynamics of meningococcal disease data with strong seasonality, as visible in highly time resolved data from England and Wales. In addition, long term fluctuations were found as seen in the Norwegian long term data, without putting any new information into our model. In the case of data from the USA both aspects are much weaker, hence not an ideal starting point for the analysis performed above, but still visible to a level that looks promising for future



a) b)

Fig. 7.10. a) Monthly data from the USA, 1996 to 2001, shows signs of seasonality. b) Yearly data from the USA, 1966 to 2001 have mean $\mu = 2519.7$ and standard deviation $\sigma = 581.9$, hence the variance over mean ratio is $\frac{\sigma^2}{\mu} = 134.4$, indicating strong deviations from the Poissonian behavior.

analysis along the first inspections shown here.

Eventually, fine tuning of single parameters might be possible along the lines of earlier parameter estimation techniques with master equation simulations.[32,33] To achieve this, the simulation time of the models has to be decreased significantly by approximations along the lines sketched in Stollenwerk, Jansen,[17] namely approximating the SIR-part of the system deterministically.

Our results suggest that decade long fluctuations in incidence are not induced by the seasonality in the contact rate, but the closeness to criticality. We checked this by simulations without seasonality, keeping the parameters otherwise as before, and still found huge decade long fluctuations in disease level. We think this has wide implications for public health: critical fluctuations as observed here can lead to long outbreaks of disease without any causal change in external factors. Instead they are due to stochastic fluctuations in hardly detectable levels of asymptomatically carried bacteria which only rarely cause disease.

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