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Meningitis, pathogenicity near criticality: the epidemiology of meningococcal disease as a model for accidental pathogens

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Abstract

We formulate and analyse a model for infectious diseases transmitted by asymptomatic carriers finding, that if harmless and pathogenic strains of the infected agent compete, frequent outbreaks of the pathogenic strains can occur. A counterintuitively high number of clustered outbreaks at low pathogenicity in our model compares well with observations in diseases with severe and often fatal results for the host, as for example in meningitis. These clustered outbreaks can be described by the typical scaling behaviour around criticality.

The epidemic model is a susceptible-infected-recovered system (SIR) for the harmless infective agent, acting as a background to a mutant strain Y which occasionally creates severely affected hosts X. The full system of SIRYX is described in the master equation framework, confirming limiting assumptions about a reduced YX-system with the SIR-system in stationarity. In this limiting case we can analytically show convergence to power law scaling typical for critical states, as well as the divergence of the variance of outbreaks near criticality.

These large fluctuations of outbreaks of accidental pathogens as mutants of otherwise harmless commensal organisms is the challenging new feature of our model for future epidemiology of diseases like meningococcal disease.

Keywords: *Neisseria meningitidis*; Septicaemia; Asymptomatic carriage; Population structure; Branching Process; Power law; Master equation

1. Introduction

A bacterial infection with *Neisseria meningitidis*, named in 1879 after its discoverer Albert Neisser, can cause meningitis and septicaemia. This happens when the bacteria, which normally live in the host's epithelium without causing harm, cross the barrier into the blood stream and replicate quickly with lethal or damaging consequences for the host (Cartwright, 1995). Once the protective barrier is crossed, meningococcal disease develops within a few hours. This disease is an example of the more general class of pathogens which replicate and transmit in their host without usually causing disease. Symptomatic disease develops only occasionally and with disastrous effects for host and pathogen.

Hence not the infection with such bacteria itself, often called natural carriage, and in the case of *Neisseria meningitidis* affecting up to 25% of the host population at one given time, causes disease but a second transition into a diseased state (Coen et al., 2000). Such pathogens have been called accidental pathogens (Maiden, 2000). We denote the hosts carrying the harmless strain as I, whereas we call the diseased cases X, those hosts infected with the pathogenic bacteria having crossed the epithelium–blood barrier. Pathogenicity, which is propensity of the bacteria causing disease, differs in different strains of the pathogen. Still, this transition between normal carriage and disease can be highly dependent on the type of mutant bacteria present in the host. Although the genome sequence of *Neisseria* bacteria is in principle known (Parkhill et al., 2000), there is a huge variability in certain regions of the genome, observed e.g. in recent carriage studies (M. Maiden, private comm.).

Therefore, we investigate a model in standard SIR formulation for the natural harmless infection process,

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and introduce as additional term a mutant type of bacteria, sending the affected host into a Y class. Only these Y hosts can give rise to a transition to the diseased X class with a certain transition rate ε, but otherwise have the same characteristics as the original bacteria in hosts of the harmless variant responsible for the I class.

The mechanism described here qualitatively, will be specified in detail in our SIRYX model in Sections 2 and 3 using the stochastic master equation formalism in order to capture the effects of population fluctuations. It is found that these fluctuations play the key role in understanding the epidemics for only rarely accidental mutants, hence small pathogenicity ε. For large ε the mutants have such a high disadvantage against the normal carriage strain, that they disappear quickly after appearing as mutants, not being able to cause high numbers of meningitis cases X. Therefore, a selection process will drive the whole pool of bacterial strains to small values of the pathogenicity ε.

In the limit for pathogenicity ε going to zero we find the typical behaviour of critical states known from statistical physics of phase transitions (see for example Cardy, 1996; Landau and Binder, 2000), namely that near critical points, here at $\varepsilon = 0$, the fluctuations diverge. In simulations we observe that although in most runs the epidemic dies out quickly, a substantial proportion of runs show huge numbers of disease cases appearing over longer and longer durations of the epidemics, the smaller the pathogenicity ε is.

The criticality of our model for $\varepsilon \to 0$ gives rise to divergence of the variance of Y. In Section 4, we show this analytically in a simplified model for the YX-system under stationarity assumption of the basic SIR-subsystem. The validity of this assumption is shown by quantitative comparison with the full SIRYX-model.

Finally, in a further simplification of our model, a drifting random walk, we can explicitly calculate the total size of the epidemics, the number of cases X, in its probabililty $p_\varepsilon(X)$ depending on the pathogenicity parameter ε (see Section 5). In the limit of $\varepsilon \to 0$ and large X we find that this probability obeys a power law, typical for critical behaviour. X scales with power $-3/2$, which is the mean field exponent for branching processes. Hence, our model seems to fall into a universality class of such processes (Harris, 1989). This is shown in Section 6.

In the discussion we will mention the connection of our model (in a forthcoming spatial version) with the universality class of directed percolation, which was introduced in simulations by Grassberger and de la Torre (1979) and in a theoretical analysis by Janssen (1981). Directed percolation is since a topic of major interest, see recently e.g. Brunel et al. (2000) and Cardy and Täuber (1998), which makes our basic SIRYX-model a starting point for further studies in this direction.

2. Epidemiological model

Normal harmless carriage of the infectious agent, *Neisseria meningitidis* in case of meningococcal disease, in a host population of susceptible, infected and temporally resistant hosts can be modelled by a classical SIR-model (Anderson and May, 1991). We consider our model to describe the fast spread of the epidemics as opposed to the slower variation of the host population due to birth and natural death, and assume a constant population of size N.

The basic SIR-model is constructed as follows: With a rate α a resistant host becomes susceptible, or as a reaction scheme $R \xrightarrow{\alpha} S$. Then, susceptible meet infected with a transition rate β and proportional to the number of infected (divided by N to make the model scale invariant with population size, since we obtain a quadratic term in the variables, as opposed to the linear term in the previous transition). As a reaction scheme we have $S + I \xrightarrow{\beta} I + I$. Finally, infected hosts can recover and become temporally resistant with rate γ, hence $I \xrightarrow{\gamma} R$.[1]

The corresponding deterministic ordinary differential equation (ODE) system reads:

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= \alpha R - \beta \frac{I}{N} S, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta \frac{I}{N} S - \gamma I, \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - \alpha R \end{aligned} \tag{1}$$

and describes merely the dynamic of the mean values for the total number of susceptibles, infected and recovered under the assumptions of mean field behaviour and homogeneous mixing, hence mean values of products can be replaced by products of means in the nonlinear contact term $(\beta/N)\ IS$.

For the diseases described by this model the infected individuals are the hosts which do not suffer at all from the infection, not even notice it. This is different from ordinary models of infectious diseases. In order to describe the invasion process of the infected with a mutant strain, hence a class of hosts called Y, into the population of S, I and R, we have to include demographic stochasticity into the description of the epidemic. As such, for the basic SIR-model we consider the dynamics of the probability $p(S, I, R, t)$ of the system to have S susceptibles, I infecteds and R recovered at time t, which is governed by a master equation (Gardiner, 1985; van Kampen, 1992, and in a recent

[1] We could call this basic SIR-model also SIRS-model, since transitions from R to S are allowed, but stick to SIR, since later in the full SIRYX-model parallel transitions prohibit a simple way of labelling. Hence, here SIR just means that we have three classes of hosts, S, I and R to deal with, as opposed to five classes in the full model.

application to a plant epidemic model Stollenwerk and Briggs, 2000). For state vectors $\underline{n}$, here for the SIR-model $\underline{n} = (S, I, R)$, the master equation reads:

$$\frac{\mathrm{d}p(\underline{n})}{\mathrm{d}t} = \sum_{\tilde{\underline{n}} \neq \underline{n}} w_{\underline{n},\tilde{\underline{n}}}\, p(\tilde{\underline{n}}) - \sum_{\tilde{\underline{n}} \neq \underline{n}} w_{\tilde{\underline{n}},\underline{n}}\, p(\underline{n}) \tag{2}$$

with transition probabilities corresponding to the ones described above for the ODE-system. Here the rates $w_{\tilde{\underline{n}},\underline{n}}$ are

$$\begin{aligned} w_{(S+1,I,R-1),(S,I,R)} &= \alpha R, \\ w_{(S-1,I+1,R),(S,I,R)} &= \beta \frac{I}{N} S, \\ w_{(S,I-1,R+1),(S,I,R)} &= \gamma I \end{aligned} \tag{3}$$

from which the rates $w_{\underline{n},\tilde{\underline{n}}}$ follow immediately as

$$\begin{aligned} w_{(S,I,R),(S-1,I,R+1)} &= \alpha(R+1), \\ w_{(S,I,R),(S+1,I-1,R)} &= \beta \frac{I-1}{N}(S+1), \\ w_{(S,I,R),(S,I+1,R-1)} &= \gamma(I+1). \end{aligned} \tag{4}$$

To describe the behaviour of pathogenic strains 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 backmutate 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 that develop symptomatic disease. These are the cases which are detectable, as opposed to hosts in classes Y and I who are asymptomatic carriers, which cannot be detected easily.

The state vector in the extended model is now $\underline{n} = (S, I, R, Y, X)$. The mutation transition $S + I \xrightarrow{\mu} Y + I$ fixes the master equation transition rate $w_{(S-1,I,R,Y+1,X),(S,I,R,Y,X)} = \mu(I/N)S$. In order to denote the total contact rate still with the parameter β, we keep the balancing relation

$$\begin{aligned} &w_{(S-1,I+1,R,Y,X),(S,I,R,Y,X)} \\ &\quad + w_{(S-1,I,R,Y+1,X),(S,I,R,Y,X)} \\ &\quad = \beta \frac{I}{N} S \end{aligned} \tag{5}$$

and obtain for the ordinary infection of normal carriage the transition rate $w_{(S-1,I+1,R,Y,X),(S,I,R,Y,X)} = (\beta - \mu)(I/N)S$. Continuing, to denote the total rate of contacts a susceptible host can make with any infected, either normal carriage I or mutant carriage Y, by β, we have the following balancing equation

$$\sum_{\tilde{\underline{m}} \neq \underline{m}} w_{(S-1,\tilde{\underline{m}}),(S,\underline{m})} = \beta \frac{I+Y}{N} S \tag{6}$$

for $\underline{m} = (I, R, Y, X)$. With the above-mentioned transitions this fixes the master equation rate $w_{(S-1,I,R,Y+1,X),(S,I,R,Y,X)} = (\beta - \nu - \varepsilon)(Y/N)S$.

For completeness, we denoted by the recovery rate from severe meningitis and septicaemia, i.e. $X \xrightarrow{\varphi} S$. In the case of meningitis and septicaemia in many cases the disease is lethal, hence $\varphi = 0$. With medication the sufferers often survive, but are hospitalized for a long time and then suffer from resulting impairments. So, for the theoretical analysis we will still keep $\varphi = 0$, which might be changed when analysing more realistic situations or recent data.

For the SIRYX-system the transition probabilities $w_{\tilde{\underline{n}},\underline{n}}$ are then given (omitting unchanged indices in $\tilde{\underline{n}}$, with respect to $\underline{n}$) by

$$\begin{aligned} w_{(R-1,S+1),(R,S)} &= \alpha R && , \quad R && \xrightarrow{\alpha} && S, \\ w_{(S-1,I+1),(S,I)} &= (\beta - \mu)\frac{I}{N} S && , \quad S + I && \xrightarrow{\beta-\mu} && I + I, \\ w_{(S-1,Y+1),(S,Y)} &= \mu \frac{I}{N} S && , && \xrightarrow{\mu} && Y + I, \\ w_{(I-1,R+1),(I,R)} &= \gamma I && , \quad I && \xrightarrow{\gamma} && R, \\ w_{(S-1,Y+1),(S,Y)} &= (\beta - \nu - \varepsilon)\frac{Y}{N} S && , \quad S + Y && \xrightarrow{\beta-\nu-\varepsilon} && Y + Y, \\ w_{(S-1,I+1),(S,I)} &= \nu \frac{Y}{N} S && , && \xrightarrow{\nu} && I + Y, \\ w_{(S-1,X+1),(S,X)} &= \varepsilon \frac{Y}{N} S && , && \xrightarrow{\varepsilon} && X + Y, \\ w_{(Y-1,R+1),(Y,R)} &= \gamma Y && , \quad Y && \xrightarrow{\gamma} && R, \\ w_{(X-1,S+1),(X,S)} &= \varphi X && , \quad X && \xrightarrow{\varphi}, && S \end{aligned} \tag{7}$$

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

3. The invasion dynamics of mutant strains

Before we proceed with further theoretical analysis of the model we now demonstrate basic properties of our SIRYX-model in simulation of the master equation, using the Gillespie algorithm, also known as minimal process algorithm (Gillespie, 1976). This is the Monte Carlo method, in which after an event, i.e. a transition from state $\underline{n}$ to another state $\tilde{\underline{n}}$, the exponential waiting time is calculated as a random

variable from the sum of all transition rates, after which the next transition is chosen randomly from all now possible transitions, according to their relative transition rates.

To investigate the dynamics of the infection with mutants, class Y, in relation to the normal carriage I with harmless strains, we first fix the basic SIR-subsystem's parameters to the values $\alpha := 0.1$, $\beta := 0.2$ and $\gamma := 0.1$.

The endemic equilibrium of the SIR-system is given by

$$S^* = N\frac{\gamma}{\beta}, \quad I^* = N\frac{\alpha}{\beta}\left(\frac{\beta-\gamma}{\alpha+\gamma}\right), \quad R^* = N - S^* - I^* \quad (8)$$

as can be seen from Eqs. (1) setting the left-hand side of each subequation to zero. As for the parameters used, we find in equilibrium a normal level of carriage of harmless infection of about 25% in our total population of size N. This is in agreement with reported levels of carriage for *Neisseria meningitidis*. Average duration of carriage is in the order of 10 months, hence we choose $\gamma = 0.1$. We assume the duration of immunity to be the same as the duration of carriage. In equilibrium this results in the ratio of $S^* : I^* : R^* = 2 : 1 : 1$. However, the qualitative results are not affected by these first guesses of parameter values, but rather by the order of magnitude.

In Fig. 1(a) we show 10 simulated runs of the epidemic for a total population of $N = 1000$, with initially $I_0 = 100$ infected, no mutants, and $S_0 = N - I_0$ and $R_0 = 0$ individuals. The upper 10 trajectories show the normal carriage of infected individuals I developing in time from the initial 100 to about 250 individuals plus some variations due to the population noise from the stochastic master equation simulation. This demonstrates the rapid dynamics to the SIR-equilibrium value of 25% normal carriage. In the same way, the equilibrium values for S and R are reached as quickly. The time window 1000 (of arbitrary scale, or if we accept 10 months as recovery and resistance periods, time would be given in months) is chosen here to show the transient to equilibrium as well as the fluctuations in equilibrium.

Fig. 1(b) shows the course of time of the mutants appearing due to the mutation with rate $\mu := 0.0001$ and normal course of infection with α, β and γ as given above. The backmutation rate ν is set to equal the mutation rate μ. The axis of ordinate in Fig. 1(b) is given in larger scale than in Fig. 1(a) to show clearly the appearance and disappearance of the mutants' carriage due to the disadvantage of transitions into the X class with rate $\varepsilon := 0.005$. The mutants relative to the normal level of carriage is shown in Fig. 1(a) with the 10 trajectories near the bottom.

Next we show a simulation with $\varepsilon = 0$, see Fig. 2. Now the mutants can replace the normal strain, since it has no disadvantage due to extra transitions into the X class. This happened in two out of 10 runs in the time window observed. In Fig. 2(b) the two runs, in which they are taking over, the mutants settle at the equilibrium value of 25% carriage (with additional variations due to population noise). This replacement mechanism describes a kind of genetic drift in the bacteria population.

Hence, for vanishing or small ε, that means in the same order of magnitude as the mutation rate or smaller, mutants can substitute the dominant harmless strain. On the other hand, for large ε the mutants will always have a severe disadvantage because of additional transitions into the X class of diseased cases, which are lost entirely from the epidemic cycle. Such strains with large pathogenicity ε will play no role in the pool of strains in the system, as they will be selected against quickly.

An interesting behaviour is observed when the pathogenicity ε is too large for the hyperinvasive strain to take over but small enough to create large outbreaks of mutant infecteds Y before becoming extinct again. In

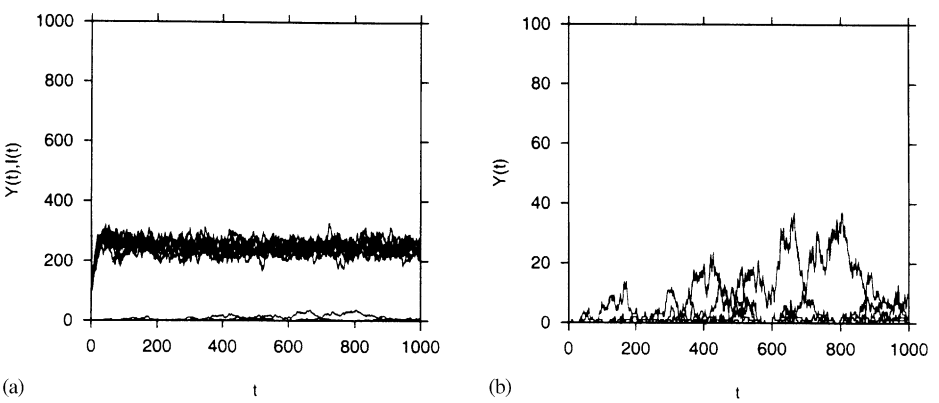

Fig. 1. (a) Infected I from an SIR-model in stationarity and a low level of mutants Y, (b) the mutant strain Y temporarily coexists but cannot replace the normal strain. An ensemble of 10 epidemics is shown in its time evolution. Basic parameters are given in the text, and $\varepsilon = 0.005$, $\mu = 0.0001$.

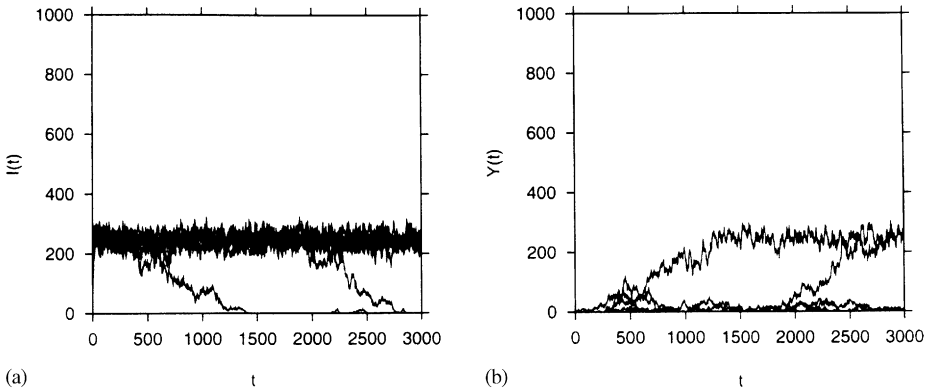

Fig. 2. (a) Infecteds I decrease in two out of 10 runs to very low levels or extinction, when $\varepsilon = 0$. (b) The mutant strain Y replaces the strain carried by I hosts in two of these runs going to the equilibrium value of carriage of 25%.

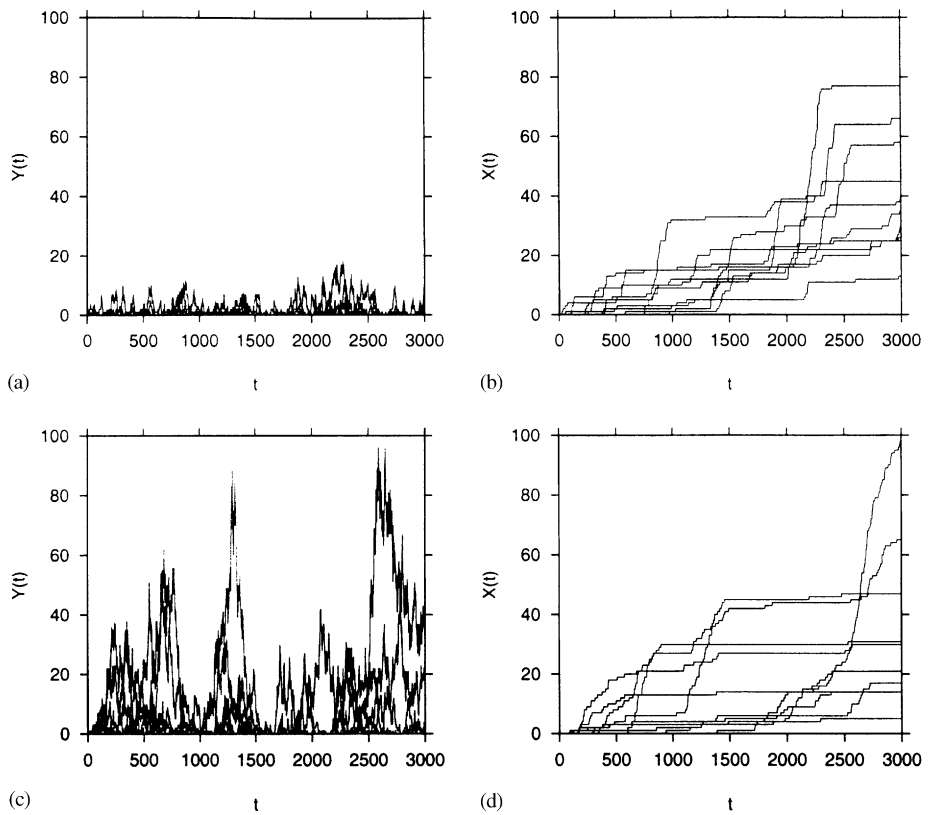

Fig. 3. (a) Time series of 10 runs showing the mutant carriage Y for pathogenicity $\varepsilon = 0.05$. (b) Number of seriously diseased cases X for pathogenicity $\varepsilon = 0.05$. (c) and (d) as (a) and (b) with pathogenicity 10 times smaller, hence $\varepsilon = 0.005$. Although the pathogenicity ε is of the factor 10 smaller, the damage in the number of seriously diseased cases X remains high and even varies more than for larger ε.

Fig. 3 we show two simulations in this ε-region, first $\varepsilon = 0.05$, Fig. 3(a) and (b), then a 10 times smaller ε, Fig. 3(c) and (d). For high pathogenicity ε we find relatively low levels of mutants Y, in Fig. 3(a) less than 20 cases, and at the end of the simulation between roughly 15 and 80 hospital cases X, Fig. 3(b). For smaller pathogenicity ε, Fig. 3(c), we find much larger fluctuations in the number of mutants Y with peaks of more than 80 mutant infected hosts. Though the probability rate to cause disease ε is 10 times smaller than in the previous simulation we find at the end of this simulation similar numbers of disease cases X, Fig. 3(d). We observed larger fluctuations and sometimes much more outbreaks of diseased cases though the probability to create disease is smaller.

This counterintuitive result can be understood by considering the dynamics of the hyperinvasive lineage in detail. We will do so by analysing a simplified version of our SIRYX-model analytically.

4. Divergent fluctuations for vanishing pathogenicity

For pathogenicity ε larger than the mutation rate μ the hyperinvasive lineage normally does not attain very 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, considered to live in the SIR-heat bath.

Taking Eqs. (8) for the stationary values of the SIR-system into account we obtain for the transition rates (compare Eqs. (7)) of the remaining YX-system

$$\begin{aligned} w_{(S^*,Y+1),(S^*,Y)} &= \mu \frac{S^*}{N} I^* =: c, \\ w_{(S^*,Y+1),(S^*,Y)} &= (\beta - \nu - \varepsilon) \frac{S^*}{N} Y =: bY, \\ w_{(S^*,X+1),(S^*,X)} &= \varepsilon \frac{S^*}{N} Y =: gY, \\ w_{(Y-1,R^*),(Y,R^*)} &= \gamma Y =: aY, \\ w_{(X-1,S^*),(X,S^*)} &= \varphi X. \end{aligned} \tag{9}$$

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

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t} p(Y,X,t) = {} & (b(Y-1)+c)p(Y-1,X,t) \\ & + a(Y+1)\, p(Y+1,X,t) \\ & + gY\, p(Y,X-1,t) \\ & - (bY + aY + gY + c)\, p(Y,X,t). \end{aligned} \tag{10}$$

This gives for the marginal distribution $p(Y,t) := \sum_{X=0}^{\infty} p(Y,X,t)$ the master equation for a simple birth–death process with birth rate $b := (\beta - \nu - \varepsilon)S^*/N$, death rate $a := \gamma$ and a migration rate $c := \mu(S^*/N)I^*$. In the definition of the marginal distribution we take the upper limit of the summation to infinity, since we assume numbers of X and Y cases to be well below the stationary values of the SIR-system, i.e. they will not be affected by any finite upper boundary. The validity of this assumption we will check later with simulations of the full SIRYX-system.

Hence we have

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t} p(Y,t) = {} & (b(Y-1)+c)p(Y-1,t) \\ & + a(Y+1)p(Y+1,t) \\ & - (bY + aY + c)p(Y,t) \end{aligned} \tag{11}$$

for $Y \in \mathbb{N}$ and as boundary equation, i.e. for $Y = 0$

$$\frac{\mathrm{d}}{\mathrm{d}t} p(Y=0,t) = ap(Y=1,t) - cp(Y=0,t). \tag{12}$$

For the ensemble mean $\langle Y \rangle := \sum_{Y=0}^{\infty} Yp(Y,t)$ we obtain, using the above master equation,

$$\frac{\mathrm{d}}{\mathrm{d}t} \langle Y \rangle = (b-a)\langle Y \rangle + c. \tag{13}$$

And for the variance, being defined as $Var(t) := \langle Y^2 \rangle - \langle Y \rangle^2$, we obtain

$$\begin{aligned} & \frac{\mathrm{d}}{\mathrm{d}t} \underbrace{(\langle Y^2 \rangle - \langle Y \rangle^2)}_{=:Var(t)} \\ & \quad = 2(b-a)(\langle Y^2 \rangle - \langle Y \rangle^2) + (b+a)\langle Y \rangle + c. \end{aligned} \tag{14}$$

We can simplify further by neglecting the mutation and backmutation terms, hence $c = 0$, and $\nu = 0$ in the definition for b, and solve the two ODEs for mean $Y(t) := \langle Y \rangle$ and variance $Var(t)$, noticing that

$$b - a = (\beta - \varepsilon)\frac{S^*}{N} - \gamma = -\varepsilon \frac{S^*}{N} \tag{15}$$

is proportional to ε. We set $g := \varepsilon \frac{S^*}{N}$. The ODEs then read

$$\begin{aligned} \dot{Y}(t) &= -gY(t), \\ \dot{Var}(t) &= -2g\, Var(t) + (2\gamma - g)Y(t) \end{aligned} \tag{16}$$

under suitable initial conditions $Y(t=0) = 1$, $Var(t=0) = 0$.

The solutions are

$$\begin{aligned} Y(t) &= \mathrm{e}^{-g(t-t_0)}, \\ Var(t) &= \frac{(2\gamma - g)}{g} \mathrm{e}^{-g(t-t_0)}(1 - \mathrm{e}^{-g(t-t_0)}). \end{aligned} \tag{17}$$

The solution for $Var(t)$ is essentially a single humped curve going towards zero for large times t. However, for decreasing ε the hump becomes not only larger, but it takes longer and longer to reach the decreasing end of the curve. A formal analysis (using l'Hôpital's rule) shows for the limit $\varepsilon \to \infty$ that $Var(t) \sim t$, hence diverging linear in time t for all fixed times t.

In Fig. 4 the curve $Var(t)$ is shown for three values of ε. The smallest value for ε gives the highest curve for $Var(t)$, which already nearly appears as a straight line for the times shown. The divergence of the variance is the signature of behaviour near a critical point. The critical point in this case is found for $\varepsilon = 0$.

These results were based on the analysis of a simplified stochastic system in which the dynamics of the YX-subsystem was studied in an otherwise unaffected SIR-system. We finally test the quality of our assumptions by running the full SIRYX-system starting with one mutant Y and no mutation. In Fig. 5 we show the results of a simulation of 10 000 runs for $\varepsilon = 0.01$ of the full SIRYX-system. We start with exactly one

mutant infected Y at each run. This is at the lower boundary for ε since the heat-bath assumption is about to be violated, as Fig. 5(a) shows. Some trajectories for the infected go well below the stationary mean of 250 cases plus population noise. Fig. 5(b) shows the result for the mutant infected Y. In most cases the epidemic dies out quickly, only few survive for more than 1000 time steps. In Fig. 5(c), we compare the mean of realizations $\bar{Y}(t) := \sum_{i=1}^{n} Y_i(t)$ of the $n = 10\,000$ realizations of the full SIRYX-system (with values $Y_i(t)$ each) and its standard deviation (drawn fluctuating lines) with theoretical ensemble mean $\langle Y \rangle$ and standard deviation of the birth–death process (dotted lines) of Eq. (11). The theoretical standard deviation is simply the root of $Var(t)$ in Eq. (17). They are in good agreement with each other except for the large fluctuations in the tails caused by relatively few simulations that reached that far in time. Fig. 5(d) shows the scaling of the epidemics of disease cases X in a log-log plot. This figure suggests that the frequency distribution is described by a power law. Such scaling will be investigated analytically for the simplified birth–death process in more detail in the following sections.

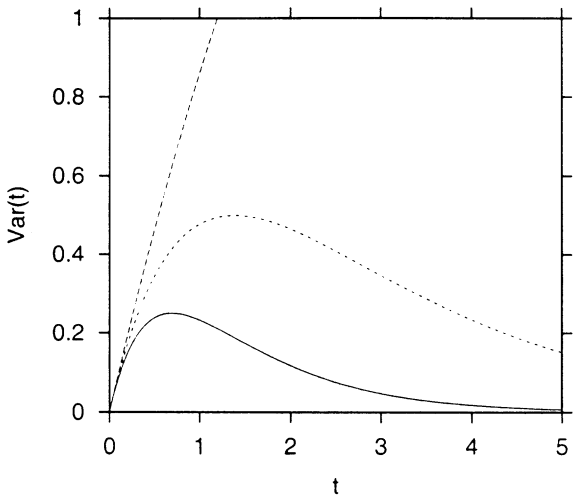

Fig. 4. The time course of the variance $Var(t)$ of the fluctuations in the number of mutants Y, as calculated in Eq. (17), is for decreasing ε-values increasing towards a straight line.

5. Distribution of total number of cases

To find the probability distribution of the number of cases following the introduction of a single Y mutant

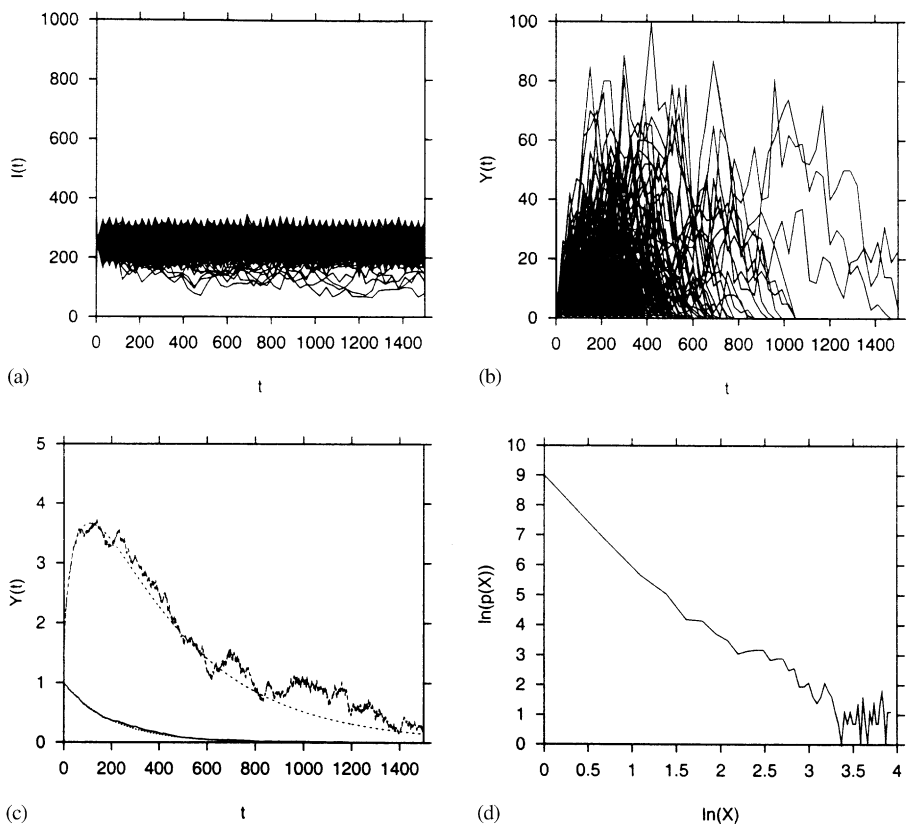

Fig. 5. The single epidemics statistics for $\varepsilon = 0.01$, including the log-log plot of the final distribution of the size of the epidemics, i.e. the number of X. The negative slope is about 2.33, hence still far away from the analytically obtained value for ε going to zero. A total of 10 000 realizations of the epidemics have been used.

carrying host, we consider the master equation for the variables Y and X, still assuming stationarity of the underlying *SIR*-system, i.e. the distribution $p(Y,X,t)$ for $Y=0$, starting with one mutant Y. $p(Y=0,X,t)$ gives the distribution of meningitis cases X when the epidemic has died out, meaning $Y=0$.

To obtain $p(Y=0,X,t)$ we do not necessarily have to consider the exponential waiting times between events, but only the number of events until the mutants vanish. Hence we consider the following time evolution equation (time discrete Markov process) for events like creation of new mutants from already existing, recovery from mutants and creation of actual meningitis cases from mutant infected:

$$\begin{aligned} &p(Y,X,\tau+1)\\ &\quad=\tilde{b}p(Y-1,X,\tau)+\tilde{a}p(Y+1,X,\tau)\\ &\qquad+\tilde{g}p(Y,X-1,\tau) \end{aligned} \tag{18}$$

for discrete times steps τ at which events happen and the parameters

$$\begin{aligned} &\tilde{a}=\frac{a}{a+b+g}=\frac{1}{2},\quad \tilde{b}=\frac{b}{a+b+g}=\frac{1}{2}-\tilde{g},\\ &\tilde{g}=\frac{g}{a+b+g}=\frac{\varepsilon}{2\beta}. \end{aligned} \tag{19}$$

The final values, e.g. $\tilde{a}=1/2$, are obtained by using $g=a-b$ from its definition, see Eq. (15), and with $\tilde{g}$ being small and proportional to ε and $\tilde{b}$ only slightly smaller than $\tilde{a}$.

With boundary equation for the absorbing state $Y=0$:

$$\begin{aligned} &p(Y=0,X,\tau+1)\\ &\quad=\tilde{a}p(Y+1=1,X,\tau)+p(Y=0,X,\tau), \end{aligned} \tag{20}$$

and for $Y=1$:

$$\begin{aligned} p(Y=1,X,\tau+1)&=\tilde{a}p(Y+1=2,X,\tau)\\ &\quad+\tilde{g}p(Y=1,X-1,\tau), \end{aligned} \tag{21}$$

and the initial condition

$$p(Y,X,\tau=0)=\delta_{Y,1}\delta_{X,0} \tag{22}$$

the dynamic is completely defined. Here we used the Kronecker δ, meaning $\delta_{m,n}=1$ for $m=n$, else zero.

The solution (see Appendix A) of the distribution of the size of the epidemic, after the last host Y carrying the mutant strain has vanished, is given by

$$p(Y=0,X,\tau)=\tilde{g}^X\tilde{a}\sum_{\omega=0}^{\omega_{max}}\kappa_{X,\omega}(\tilde{a}\tilde{b})^\omega \tag{23}$$

which is essentially a polynomial in the transition probabilities $\tilde{a}\tilde{b}$, reflecting the random walk in the birth–death process for creating Y cases, and X times the transition $\tilde{g}$ creating disease cases X and one additional transition $\tilde{a}$ to the absorbing state $Y=0$. The coefficients $\kappa_{\tilde{\gamma},\omega}$ are calculated in Appendix A as

$$\kappa_{\tilde{\gamma},\omega}=C_\omega\binom{2\mu+X}{X} \tag{24}$$

with the Catalan numbers $C_\omega:=\frac{1}{\omega+1}\binom{2\omega}{\omega}$ and ω_{max} given by

$$\begin{aligned} \omega_{max}&=\frac{1}{2}\left(\tau-(X+1)-\left\{\begin{matrix}1\\0\end{matrix}\right\}\right)\\ &=:\left\lfloor\frac{1}{2}(\tau-(X+1))\right\rfloor, \end{aligned} \tag{25}$$

where $\omega_{max}=\omega_{max}(\tau,X)$ is a function of time τ and size of the epidemics X. The expression $\left\{\begin{matrix}1\\0\end{matrix}\right\}$ means, that either 0 or 1 has to be chosen to obtain integer ω, giving the same result as the floor symbol in the rightmost expression. From Appendix A also the more general solution for $p(Y,X,\tau)$ for any Y can be derived.

6. Scaling

To obtain the size of the epidemic in the limit of time τ going to infinity and large sizes of the epidemic we analyze further the size distribution

$$\begin{aligned} p(X)&:=\lim_{\tau\to\infty}p(Y=0,X,\tau)\\ &=\lim_{\tau\to\infty}\tilde{g}^X\tilde{a}\sum_{\omega=0}^{\omega_{max}(\tau)}\kappa_{X,\omega}(\tilde{a}\tilde{b})^\omega \end{aligned} \tag{26}$$

with ω_{max} also state X dependent.

For time going to infinity, when the epidemic has almost surely died out, we obtain

$$\lim_{\tau\to\infty}\omega_{max}(\tau)=\infty. \tag{27}$$

Hence we have

$$p(X)=\tilde{g}^X\tilde{a}\sum_{\omega=0}^{\infty}\kappa_{X,\mu}(\tilde{a}\tilde{b})^\omega. \tag{28}$$

It can be shown (see Appendix B) that this is equal to

$$p(X)=\tilde{g}^X\tilde{a}_2F_1\left(\frac{X+1}{2},\frac{X+2}{2};2;4\tilde{a}\tilde{b}\right), \tag{29}$$

where the hypergeometric function is given by

$$\begin{aligned} &{}_2F_1(u,v;w;x)\\ &\quad=\frac{\Gamma(w)}{\Gamma(u)\Gamma(v)}\sum_{v=0}^{\infty}\frac{\Gamma(u+v)\Gamma(v+v)}{\Gamma(w+v)}\frac{x^v}{v!}. \end{aligned} \tag{30}$$

Using the definitions for $\tilde{a}$, $\tilde{b}$ and $\tilde{g}$ we obtain for the argument of the hypergeometric function

$$4\tilde{a}\tilde{b}=1-2\tilde{g}=1-\frac{\varepsilon}{\beta}=1-\eta \tag{31}$$

and define $\eta := \varepsilon/\beta$ being small when ε is small. Using known properties of the hypergeometric functions we finally obtain the solution (see Appendix B)

$$p_\eta(X) = \sqrt{\eta} 2^{-(X+1)} \times_2 F_1\left(\frac{3-X}{2}, \frac{2-X}{2}; 2; 1-\eta\right). \quad (32)$$

as a function of the parameter η which is proportional to ε, hence becomes small for small pathogenicity rates.

For η to zero, $p_\eta(X)$ vanishes for $X \geqslant 1$ whereas $p_\eta(X=0)$ goes to 1, hence taking all probability. To better understand the limiting behaviour we now consider another quantity, the conditional probability $p_\eta(X|X \geqslant 1)$ given that there is at least one disease case X.

It turns out (see Appendix B) that

$$p_\eta(X=0) = \frac{1}{1+\sqrt{\eta}}. \quad (33)$$

Hence for $X \geqslant 1$

$$p_\eta(X|X \geqslant 1) := \frac{p_\eta(X)}{1-p_\eta(X=0)} = (1+\sqrt{\eta}) 2^{-(X+1)}, \times_2 F_1\left(\frac{3-X}{2}, \frac{2-X}{2}; 2; 1-\eta\right). \quad (34)$$

In the limit η to zero we find

$$p_\eta(X|X \geqslant 1) \to \frac{\Gamma(X-\frac{1}{2})}{2\sqrt{\pi}\Gamma(1+X)} \quad (35)$$

(see Eq. (B.20) in Appendix B and for large X see Eq. (B.21) in Appendix B),

$$p_\eta(X|X \geqslant 1) \sim \frac{1}{2\sqrt{\pi}} X^{-3/2}. \quad (36)$$

In the same way we find

$$p_\eta(X) \sim \frac{1}{2\sqrt{\pi}} \eta^{1/2} X^{-3/2}. \quad (37)$$

for time $\tau \to \infty$, parameter $\eta \to 0$ and large number of disease cases X.

Hence in total we find the following scaling laws for the distribution of the epidemics:

$$p_\eta(X) \sim \eta^{1/2}. \quad (38)$$

and

$$p_\eta(X) \sim X^{-3/2}. \quad (39)$$

with critical exponents (of mean field type) $\frac{1}{2}$ and $-\frac{3}{2}$ near the critical value $\varepsilon = 0$, or equivalently $\eta = 0$. And for the conditional probability $p_\eta(X|X \geqslant 1)$ we simply get

$$p_\eta(X|X \geqslant 1) \sim X^{-3/2} \quad (40)$$

independent of any parameter dependence for η. The exponent $-\frac{3}{2}$ is exactly the one for critical branching processes (Harris, 1989; De Los Rios, 2001), for which it is proven by asymptotics of characteristic functions. In total we have obtained power law behaviour for the total size distribution for our simplified YX-model in the limit of vanishing or small pathogenicity.

7. Discussion

Criticality is established in our SIRYX-model in simulations as well as in analytical calculations of a simplified birth–death process obtaining critical exponents. As a result we found large outbreaks of disease cases due to huge variance in hosts carrying a mutant strain prone to accidental pathogenicity. With this scenario observations of clustered epidemics in meningitis and septicaemia can be analysed in a completely new way, stimulating future research on actual outbreak data. In such data analysis parameter estimation is possible from master equation simulations analogous to the ones shown here along the lines of earlier work (Stollenwerk and Briggs, 2000).

Also, the mechanisms we describe in the present article can be used to analyse a wider class of mainly commensal organisms which only accidentally become pathogens to their own disadvantage. Then it is to be expected that the criticality we observe in our model will play a crucial role in understanding such epidemics.

On the technical side, since we have one absorbing state, the hypothesis made in non-equilibrium thermodynamics that such models belong to the universality class of directed percolation applies here (Janssen, private comm.). A future spatial version of our model should therefore behave like one in directed percolation, especially the critical exponents should be the same as for other more basic models in this universality class (which includes a basic SIS-model). However, our model is believed to have a large crossover from dynamic percolation (of SIR-type) due to our additional terms and complications. To show this explicitly is left for future work on spatial versions of our model.

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Appendix A. Solution of size distribution of the epidemic

In this appendix we analyse the stochastic dynamic system given by Eqs. (18)–(22) in the main text. Since the number of X can only increase, we can easily solve the dynamic for the marginal distribution

$$p(Y,\tau) \coloneqq \sum_{X=0}^{\infty} p(Y,X,\tau) \tag{A.1}$$

and still extract the number of cases X after the epidemic has finished.

Hence the dynamic is

$$\begin{aligned} &p(Y,\tau+1) \\ &\quad = \tilde{b}p(Y-1,\tau) + \tilde{a}p(Y+1,\tau) + \tilde{g}p(Y,\tau) \end{aligned} \tag{A.2}$$

with boundary

$$\begin{aligned} &p(Y=0,\tau+1) \\ &\quad = \tilde{a}p(Y+1=1,\tau) + p(Y=0,\tau) \end{aligned} \tag{A.3}$$

and

$$\begin{aligned} &p(Y=1,\tau+1) \\ &\quad = \tilde{a}p(Y+1=2,\tau) + \tilde{g}p(Y=1,\tau) \end{aligned} \tag{A.4}$$

and initial distribution

$$p(Y,\tau=0) = \delta_{Y,1}. \tag{A.5}$$

With the initial condition vector $(p(Y=0,\tau=0), p(Y=1,\tau=0), p(Y=2,\tau=0), p(Y=3,\tau=0), \ldots)^{tr} = (0,1,0,0,\ldots)^{tr}$ this is for time step τ a $(\tau+1)$-dimensional matrix system of equations

$$\begin{aligned} &\begin{pmatrix} p(Y=0,\tau+1) \\ p(Y=1,\tau+1) \\ p(Y=2,\tau+1) \\ \vdots \\ p(Y=\tau+1,\tau+1) \end{pmatrix} \\ &\quad = \begin{pmatrix} 1 & \tilde{a} & 0 & 0 & 0 \\ 0 & \tilde{g} & \tilde{a} & 0 & 0 \\ 0 & \tilde{b} & \tilde{g} & \tilde{a} & 0 \\ & & \ddots & \ddots & \ddots \\ 0 & 0 & 0 & \tilde{b} & \tilde{g} \end{pmatrix} \\ &\quad \times \begin{pmatrix} p(Y=0,\tau) \\ p(Y=1,\tau) \\ p(Y=2,\tau) \\ \vdots \\ p(Y=\tau+1,\tau) \end{pmatrix} \end{aligned} \tag{A.6}$$

with tridiagonal structure.

The solution of the matrix system is for times $\tau = 1,2,\ldots$ and for states $Y = 1,\ldots,\tau+1$ given by

$$p(Y,\tau) = \sum_{\tilde{\alpha}=0}^{\tilde{\alpha}_{max}} k_{\tau,Y,\tilde{\alpha}} \tilde{a}^{\tilde{\alpha}} \tilde{b}^{\tilde{\beta}} \tilde{g}^{\tilde{\gamma}} \tag{A.7}$$

with

$$\tilde{\beta} = Y - 1 + \tilde{\alpha}, \tag{A.8}$$

$$\tilde{\gamma} = \tau - (Y-1) - 2\tilde{\alpha} \tag{A.9}$$

since it has to be $\tilde{\alpha} + \tilde{\beta} + \tilde{\gamma} = \tau$ the number of total transitions. Furthermore,

$$\tilde{\alpha}_{max} = \left\lfloor \frac{1}{2}(\tau - (Y-1)) \right\rfloor \tag{A.10}$$

with 0 or 1 to give an integer $\tilde{\alpha}_{max}$. The coefficients $k_{\tau,Y,\tilde{\alpha}}$ fulfil the recursion

$$k_{\tau+1,Y,\tilde{\alpha}} = k_{\tau,Y-1,\tilde{\alpha}} + k_{\tau,Y,\tilde{\alpha}} + k_{\tau,Y+1,\tilde{\alpha}-1} \tag{A.11}$$

for initially $k_{0,1,0} = 1$ and the other coefficients zero.

The solution of this recursion is given by

$$k_{\tau,Y,\tilde{\alpha}} = \frac{Y(\tau!)}{(Y+\tilde{\alpha})!\tilde{\alpha}!(\tau-(Y-1)-2\tilde{\alpha})!} \tag{A.12}$$

as can be seen by insertion. In terms of $\tilde{\alpha}$, $\tilde{\beta}$ and $\tilde{\gamma}$ it is

$$k_{\tilde{\alpha},\tilde{\beta},\tilde{\gamma}} = \frac{\binom{\tilde{\beta}}{\tilde{\alpha}}}{\binom{\tilde{\beta}+1}{\tilde{\alpha}}} \frac{\tau!}{\tilde{\alpha}!\tilde{\beta}!\tilde{\gamma}!}. \tag{A.13}$$

The general solution $p(Y,X)$ can now be read from the above by reordering the summations such that we sum up the powers of $\tilde{g}$, hence summing over $\tilde{\gamma}$. We will show this now just for the absorbing state $Y = 0$.

The distribution of the absorbing state $Y = 0$ is given from its definition

$$p(Y=0,\tau) \coloneqq \sum_{v=0}^{\tau-1} \tilde{a}p(Y+1=1,v) \tag{A.14}$$

as

$$p(Y=0,\tau) = \sum_{v=0}^{\tau-1} \tilde{a} \sum_{\tilde{\alpha}=0}^{\tilde{\alpha}_{max}} k_{v,1,\tilde{\alpha}} \tilde{a}^{\tilde{\alpha}} \tilde{b}^{\tilde{\alpha}} \tilde{g}^{v-2\tilde{\alpha}} \tag{A.15}$$

or labelling the sum in the number of transitions creating X, i.e. in powers of $\tilde{g}$:

$$p(Y=0,\tau) = \sum_{\tilde{\gamma}=0}^{\tau-1} \tilde{g}^{\tilde{\gamma}} \tilde{a} \sum_{\mu=0}^{\mu_{max}} \kappa_{\tilde{\gamma},\mu} (\tilde{a}\tilde{b})^{\mu} \tag{A.16}$$

with

$$\mu_{max} = \left\lfloor \frac{1}{2} \left(\tau - (\tilde{\gamma}+1) - \begin{Bmatrix} 1 \\ 0 \end{Bmatrix} \right) \right\rfloor \tag{A.17}$$

and

$$\kappa_{\tilde{\gamma},\mu} \coloneqq k_{\tilde{\gamma}+2\mu,1,\mu}. \tag{A.18}$$

Note that here μ and v are summation indices and not to be confused with the mutation rates mentioned in the main text. The coefficients $\kappa_{\tilde{\gamma},\mu}$ can be expressed in terms of the Catalan numbers $C_\mu := [1/(\mu+1)]\binom{2\mu}{\mu}$ as

$$\kappa_{\tilde{\gamma},\mu} = C_\mu \binom{2\mu+\tilde{\gamma}}{\tilde{\gamma}}. \tag{A.19}$$

This completes the calculation of the distribution of the size of the epidemics as

$$p(Y=0,X,\tau) = \tilde{g}^X \tilde{a} \sum_{\mu=0}^{\mu_{max}} \kappa_{X,\mu} (\tilde{a}\tilde{b})^\mu. \tag{A.20}$$

Appendix B. Size distribution of the epidemic for ε zero

For $p(Y=0,X,\tau)$ from Appendix A we consider now the limiting behaviour for time τ going to infinity and then large X. As described in the main text we set μ_{max} to infinity for τ going to infinity. (In the main text we use ω_{max} to avoid confusion with other notations.)

Using the gamma function to express the factorials, $\Gamma(x+1) = x!$, the coefficients κ are given by

$$\begin{aligned}\kappa_{\tilde{\gamma},\mu} &= C_\mu \binom{2\mu+\tilde{\gamma}}{\tilde{\gamma}} \\ &= \frac{1}{\Gamma(\tilde{\gamma}+1)} \frac{\Gamma(\tilde{\gamma}+1+2\mu)}{\Gamma(\mu+2)} \frac{1}{\mu!}.\end{aligned} \tag{B.1}$$

Hence the size distribution of the epidemics is given by

$$p(X) = \frac{\tilde{g}^X \tilde{a}}{\Gamma(X+1)} \sum_{\mu=0}^{\infty} \frac{\Gamma(X+1+2\mu)}{\Gamma(\mu+2)} \frac{(\tilde{a}\tilde{b})^\mu}{\mu!}. \tag{B.2}$$

Using the duplication formula $\Gamma(2x) = 1/\sqrt{2\pi} 2^{2x-1/2} \Gamma(x)\Gamma(x+\frac{1}{2})$ for the Γ-function we can write

$$\begin{aligned}p(X) = &\frac{\tilde{g}^X \tilde{a}}{\Gamma(X+1)} \frac{2^{X+\frac{1}{2}}}{\sqrt{2\pi}} \\ &\times \sum_{\mu=0}^{\infty} \frac{\Gamma(\frac{X+1}{2}+\mu)\Gamma(\frac{X+2}{2}+\mu)}{\Gamma(\mu+2)} \frac{(4\tilde{a}\tilde{b})^\mu}{\mu!}\end{aligned} \tag{B.3}$$

in the form of a Gauss hypergeometric function ${}_2F_1$ which is defined as

$${}_2F_1(u,v;w;x) := \sum_{v=0}^{\infty} \frac{(u)_v (v)_v}{(w)_v} \frac{x^v}{v!} \tag{B.4}$$

(Abramowitz and Stegun, 1972) and with Pochhammer's symbol $(u)_v := \Gamma(u+v)/\Gamma(u)$ and $(u)_0 := 1$ resulting in

$$\begin{aligned}&{}_2F_1(u,v;w;x) \\ &= \frac{\Gamma(w)}{\Gamma(u)\Gamma(v)} \sum_{v=0}^{\infty} \frac{\Gamma(u+v)\Gamma(v+v)}{\Gamma(w+v)} \frac{x^v}{v!}.\end{aligned} \tag{B.5}$$

The hypergeometric function ${}_2F_1(u,v;w;x)$ is the solution of the hypergeometric differential equation

$$\begin{aligned}&x(1-x)\frac{\mathrm{d}^2F}{\mathrm{d}x^2} \\ &\quad = uvF - (w-(u+v+1)x)\frac{\mathrm{d}F}{\mathrm{d}x}.\end{aligned} \tag{B.6}$$

Hence with $u := (X+1)/2$, $v := (X+2)/2$ and $w := 2$ we finally get an expression for the distribution of the total size of the epidemics in terms of a hypergeometric function:

$$p(X) = \tilde{g}^X \tilde{a}\, {}_2F_1\left(\frac{X+1}{2}, \frac{X+2}{2}; 2; 4\tilde{a}\tilde{b}\right) \tag{B.7}$$

again using the duplication formula for the Γ-function.

Using the definitions for $\tilde{a}$, $\tilde{b}$ and $\tilde{g}$ we obtain for the argument of the hypergeometric function

$$4\tilde{a}\tilde{b} = 1 - 2\tilde{g} = 1 - \frac{\varepsilon}{\beta} = 1 - \eta \tag{B.8}$$

and define $\eta := \varepsilon/\beta$ being small when ε is small. For the prefactor in front of the hypergeometric function we then obtain

$$\tilde{g}^X \tilde{a} = \eta^X 2^{-(X+1)}. \tag{B.9}$$

Hence

$$\begin{aligned}p_\eta(X) = &\eta^X 2^{-(X+1)} \\ &\times {}_2F_1\left(\frac{X+1}{2}, \frac{X+2}{2}; 2; 1-\eta\right),\end{aligned} \tag{B.10}$$

which can be simplified further using the formula for the hypergeometric function

$$\begin{aligned}&{}_2F_1(u,v;w;x) \\ &\quad = (1-x)^{w-u-v}\ {}_2F_1(w-u, w-v; w; x).\end{aligned} \tag{B.11}$$

This results in

$$\begin{aligned}p_\eta(X) = &\sqrt{\eta} 2^{-(X+1)} \\ &\times {}_2F_1\left(\frac{3-X}{2}, \frac{2-X}{2}; 2; 1-\eta\right).\end{aligned} \tag{B.12}$$

Now we consider the conditional probability given at least one disease case X, i.e. $p_\eta(X|X\geqslant 1)$. It is given by Bayes' rule $p(X, X\geqslant 1) = p(X|X\geqslant 1)p(X\geqslant 1)$ and $p(X\geqslant 1) = 1 - p(X=0)$. For all $X\geqslant 1$ we can use $p(X, X\geqslant 1) = p(X)$ with $p(X)$ from Eq. (32). In total we obtain

$$\begin{aligned}&p_\eta(X|X\geqslant 1) \\ &\quad = \frac{p_\eta(X)}{1-p_\eta(X=0)} \\ &\quad = \frac{\sqrt{\eta} 2_2^{-(X+1)} F_1\left(\frac{3-X}{2}, \frac{2-X}{2}; 2; 1-\eta\right)}{1-p_\eta(X=0)}.\end{aligned} \tag{B.13}$$

It is $p_\eta(X=0) = \sqrt{\eta} 2_2^{-1} F_1(3/2, 1; 2; 1-\eta)$. Using the integral representation of the hypergeometric function

(Abramowitz and Stegun, 1972, p. 558, Eq. 15.3.1)

$$ {}_2F_1(u,v;w;x) = \frac{\Gamma(w)}{\Gamma(u-w)\Gamma(v)} \int_0^1 z^{v-1}(1-z)^{w-v-1} \times (1-zx)^{-u}\,\mathrm{d}z. \tag{B.14}$$

with $u=3/2$, $v=1$, $w=2$ and $x=1-\eta$ the integral can be solved analytically with elementary algebra obtaining

$$ {}_2F_1(3/2,1;2;1-\eta) = \int_0^1 (1-z(1-\eta))^{-3/2}\,\mathrm{d}z = \frac{2}{1-\eta}\left(\frac{1}{\sqrt{\eta}}-1\right). \tag{B.15}$$

So for $p_\eta(X=0)$ we obtain a very simple expression

$$ p_\eta(X=0) = \frac{1}{1+\sqrt{\eta}}. \tag{B.16}$$

Inserting this result into Eq. (B.13) gives

$$ p_\eta(X|X\geqslant 1) = (1+\sqrt{\eta})2^{-(X+1)} \times {}_2F_1\left(\frac{3-X}{2},\frac{2-X}{2};2;1-\eta\right). \tag{B.17}$$

As opposed to $p_\eta(X)$ from Eq. (32), this expression for $p_\eta(X|X\geqslant 1)$, Eq. (B.17) gives non-vanishing results in the limit $\eta\to 0$. Namely, for $\eta=0$ the hypergeometric function can be given explicitly by

$$ {}_2F_1(u,v;w;1) = \frac{\Gamma(w)\Gamma(w-u-v)}{\Gamma(w-u)\Gamma(w-v)}. \tag{B.18}$$

Hence

$$ \begin{aligned} p_\eta(X|X\geqslant 1) &= (1+\sqrt{\eta})2^{-(X+1)} \times {}_2F_1\left(\frac{3-X}{2},\frac{2-X}{2};2;1-\eta\right) \\ &\to {}_2F_1\left(\frac{3-X}{2},\frac{2-X}{2};2;1\right) \\ &= 2^{-(X+1)}\frac{\Gamma(2)\Gamma(x-\frac{1}{2})}{\Gamma(\frac{1+X}{2})\Gamma(\frac{1+X}{2}+\frac{1}{2})} \end{aligned} \tag{B.19}$$

for $\eta\to 0$. $\Gamma(2)=1$.

Using the duplication formula for Γ-functions again and Stirling's formula for large X-values in the arguments of the remaining Γ-functions we obtain

$$ \begin{aligned} &p_\eta(X|X\geqslant 1) \\ &\to \underbrace{2^{-(X+1)}\frac{\Gamma(X-\frac{1}{2})}{\Gamma(1+X)\sqrt{2\pi}2^{-(X+1)1/2}}}_{\text{for } \eta\to 0} \\ &= \frac{\Gamma(X-\frac{1}{2})}{2\sqrt{\pi}\Gamma(1+X)} \\ &\sim \underbrace{\frac{\mathrm{e}^{3/2}}{2\sqrt{\pi}}\frac{(X-\frac{1}{2})^{(X-1/2)}}{(X+1)^{(X+1)}}}_{\text{for } X\to\infty}. \end{aligned} \tag{B.20}$$

Finally, we obtain for the X-dependent part in the limit $X\to\infty$

$$ \frac{(X-\frac{1}{2})^{(X-1/2)}}{(X+1)^{(X+1)}} \sim X^{-3/2}\mathrm{e}^{-3/2} \tag{B.21}$$

as can be seen by

$$ \begin{aligned} &\ln\left(\frac{(X-\frac{1}{2})^{(X-\frac{1}{2})}}{(X+1)^{(X+1)}}\right) \\ &= \left(X-\frac{1}{2}\right)\ln\left(X-\frac{1}{2}\right) - (X+1)\ln(X+1) \\ &= \left(X-\frac{1}{2}\right)\ln\left(X\left(1-\frac{1}{2X}\right)\right) \\ &\quad -(X+1)\ln\left(X\left(1+\frac{1}{X}\right)\right) \\ &\sim \left(X-\frac{1}{2}\right)\ln(X) - \frac{1}{2} - ((X+1)\ln(X)+1) \\ &= -\frac{3}{2}\ln(X) - \frac{3}{2}. \end{aligned} \tag{B.22}$$

We use the Taylor expansion of $\ln(1+y)$ around $y=0$ for $y := (1/x)$ in $(x+a)\ln(x+a) = (x+a)(\ln x + \ln(1+(a/x)))$ which gives $(x+a)\ln x + a + a^2/x$ plus higher order terms.

In mathematical terms we find in summary

$$ \lim_{X\to\infty}\lim_{\eta\to 0}\lim_{\tau\to\infty}\left(\frac{p_\eta(X,\tau)}{\sqrt{\eta}X^{-\frac{3}{2}}}\right) = \text{const.} = \frac{1}{2\sqrt{\pi}}, \tag{B.23}$$

respectively, for the conditional probability $p_\eta(X|X\geqslant 1)$:

$$ \lim_{X\to\infty}\lim_{\eta\to 0}\lim_{\tau\to\infty}\left(\frac{p_\eta(X,\tau|X\geqslant 1)}{X^{-\frac{3}{2}}}\right) = \text{const.} = \frac{1}{2\sqrt{\pi}}, \tag{B.24}$$

where the sequence of the limits taken is of importance. First we let time τ go to infinity, only leaving considerations for relatively small values of infected X, then look close to the critical value $\eta\geqslant 0$, taking the divergence of $\sqrt{\eta}$ into account. We finally find scaling with a power law for X only for large values of X, but always much smaller than time τ. The actual value of the constant $1/2\sqrt{\pi}$ is of no further importance, apart from numerical checks.

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