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Evolution towards criticality in an epidemiological model for meningococcal disease

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Abstract

In a model for bacterial infections with various mutants we find the epidemiological system evolving towards criticality without outer tuning of a control parameter. This is an indication for self-organized criticality. The epidemic model is a susceptible–infected–recovered hosts system (SIR) for the harmless agent infecting hosts I, 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 of critical states. Furthermore, in this approximation we can show analytically that the control parameter, the pathogenicity in this model, evolves to be predominantly in its critical value zero. These findings are then confirmed by simulations of the full SIRYX-system.
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1. Introduction

The universality of critical phenomena in phase transitions has attracted attention from physicists for more than 25 years [1]. Soon after its importance became clear also the relevance for epidemiological and, in general, birth–death processes was recognized [2,3]. For a recent popular account of universality see [4]. Not only criticality as such but also development of a system towards criticality has been postulated for physical systems [5,6] with the paradigmatic system of a sand pile (see for an overview [7]). This scenario of a system evolving on its own towards criticality is called self-organized criticality, SOC.

We investigate an evolutionary biological model describing the epidemiological interactions of a host population subject to asymptomatic bacterial infection. We then include mutations of these bacteria which sometimes lead to disease with often fatal consequences. This is effectively a negative selection of these mutant bacteria in the epidemiological process.

The probability rate of hosts being infected with mutant bacteria making the transition to the disease is called pathogenicity. We show explicitly that the state of small pathogenicity is critical, and furthermore, that the system evolves towards this state of small pathogenicity in the host population.

Our model is designed along the realistic interactions in the epidemiology of meningococcal dis-

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ease caused by the bacterium *Neisseria meningitidis*, named in 1879 after its discoverer Albert Neisser [8]. Infection with the bacterium normally is harmless and leads to asymptomatic carriage. Occasionally, however, infection can lead to menigococcal disease. Different strains of the bacterium differ in their propensity to cause disease. The model is parametrized and could, in principle, be tested with empirical epidemiological data as it uses realistic parameters for the basic epidemic processes [9,10]. However, this system is of broader interest, since it potentially provides an explanation for uncertainties and huge fluctuations for more general models in evolutionary biology. This approach is more realistic than previous attempts in simplified evolutionary models [11,12]. We show explicitly that a parameter is automatically driven towards its critical value. The pathogenicity evolves to small values near its critical value of zero. In the analysis it evolves to zero, since for analytic treatability we use approximations which show the qualitative behaviour correctly. In the full system the pathogenicity will evolve to small values, in the order of magnitude of the mutation rate where competing strains can replace each other.

Epidemics with critical fluctuations have been described before [13,14] in forest fire like scenarios [7, p. 68]. We present a non-spatial stochastic model, in the form of a master equation (time-continuous Markov process), leading in criticality to power laws with exponents of mean field type (essentially the branching process exponent $3/2$ [15]), confirming that the system under investigation establishes critical fluctuations with fat-tail behaviour.

A spatial system analysis would require a renormalization approach to path integrals which are derived from the spatial master equation. This method is still under controversial debate, even in chemical systems' analysis [16–18].

2. The meningitis model

Since meningitis and septicaemia are two forms of meningococcal disease we will refer to the model we describe as the meningitis model. It has been described in its basic structure and first analysis of the critical state in an earlier paper [10]. We derive here for the first time the evolution of a mixture of mutant bacteria with initially different pathogenicities towards the critical state of vanishing or small pathogenicity.

We start with a basic SIR-system for asymptomatic infection, for which the infected hosts are called I, susceptible hosts S and recovered and immune hosts R. Then in the next section we introduce one competing strain with non-vanishing pathogenicity. This gives the two new host classes of infected with the mutant strain, Y, and disease cases X, to wich the Y hosts can change with small transition rate ε, the pathogenicity. Finally, in the last section we consider an ensemble of mutant infected hosts with a variety of pathogenicities, hence $Y(\varepsilon)$, and investigate the distribution of infected hosts with each ε.

2.1. The SIR-model for asymptomatic infection

The basic SIR-model for a host population of size N divided in subclasses of susceptible, infected and recovered hosts [19] is constructed as follows. With a rate α a resistent host becomes susceptible, or as a reaction scheme $R \xrightarrow{\alpha} S$. Then, a susceptible host meets an infected host with a transition rate β and proportional to the fraction of infected hosts in the population. As a reaction scheme we have $S + I \xrightarrow{\beta} I + I$. Finally, infected hosts can recover and become temporally resistent with the rate γ, hence $I \xrightarrow{\gamma} R$. We could call this basic SIR-model also SIRS-model, since transitions from R to S are allowed, but use SIR, since later in an 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 5 classes in the more complicated model [10].

The corresponding deterministic ordinary differential equation (ODE) system reads

$$\begin{aligned}
\frac{dS}{dt} &= \alpha R - \beta \frac{I}{N} S, \\
\frac{dI}{dt} &= \beta \frac{I}{N} S - \gamma I, \\
\frac{dR}{dt} &= \gamma I - \alpha R,
\end{aligned} \tag{1}$$

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 $(\beta/N)IS$.

2.2. Stochastic modelling of demographic noise

We include demographic stochasticity in the description of the epidemic. Since we will describe fluctuations near critical states we have to consider stochastic models, Markov processes explicitly formulated in master equations, as used in physics and chemistry (see, e.g., [20]). 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 infected and R recovered at time t, which is governed by a master equation [20,21], and in a recent application to a plant epidemic model [22,23]. For state vectors $\underline{n}$, here for the SIR-model $\underline{n} = (S, I, R)$, the master equation reads

$$\frac{dp(\underline{n})}{dt} = \sum_{\underline{\tilde{n}} \neq \underline{n}} w_{\underline{n},\underline{\tilde{n}}} p(\underline{\tilde{n}}) - \sum_{\underline{\tilde{n}} \neq \underline{n}} w_{\underline{\tilde{n}},\underline{n}} p(\underline{n}), \tag{2}$$

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

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

This formulation defines the stochastic process completely and will be the basis for the extended SIRYX-model for competing bacteria strains.

Now, we introduce pathogenic mutant strains which infect hosts in the same way as the asymptomatic strain does, but occasionally cause disease, and allow for mutation transitions between the two strains. We will call the additional host classes for the infection with mutant bacteria Y hosts, and diseased cases X. With this model we can show that huge fluctuations occur when the chance of a mutant causing a diseased case, called pathogenicity, is small [10]. For small values of the pathogenicity we can furthermore show power law behaviour of the size distribution of epidemics (see [10] for details), hence demonstrate that the system is in criticality.

2.3. The SIRYX-model for infection with competing strains

In order to describe the behaviour of pathogenic strains we add a new class Y of individuals infected with a potentially pathogenic strain to the basic SIR-system. 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 mutate back with rate ν, hence $S + Y \xrightarrow{\nu} I + Y$.

The main 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 symptomatic disease. These are the cases which are detectable as opposed to hosts in classes Y and I who are asymptomatic carriers who 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

$$w_{(S-1,I,R,Y+1,X),(S,I,R,Y,X)} = \mu \frac{I}{N} S.$$

In order to denote the total contact rate still with the parameter β, we keep the balancing relation

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

and obtain for the ordinary infection of normal carriage the transition rate

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

Respectively, 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 obey

the balancing equation

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

for $\underline{m} = (I, R, Y, X)$. With the above mentioned transitions this fixes the master equation rate

$$w_{(S-1,I,R,Y+1,X),(S,I,R,Y,X)} = (\beta-\nu-\varepsilon)\frac{Y}{N}S.$$

For completeness, we introduce a recovery from the disease with rate φ, hence $X \xrightarrow{\varphi} S$. With regard to meningitis and septicaemia in many cases the disease is fatal, hence $\varphi = 0$. With medication the sufferers often survive, but are hospitalized for a long time and then most of the time will 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 $w_{\underline{\tilde{n}},\underline{n}}$ are then given (omitting unchanged indices in $\underline{\tilde{n}}$, with respect to $\underline{n}$) by

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

along with the respective reaction schemes. Again from $w_{\underline{\tilde{n}},\underline{n}}$ the rates $w_{\underline{n},\underline{\tilde{n}}}$ follow immediately. This defines the master equation for the full SIRYX-system. The ODE system for the SIRYX-model, including all transitions mentioned above, reads as

$$\begin{aligned}
\dot{S} &= \alpha R - \beta\frac{S}{N}(I+Y) + \varphi X,\\
\dot{I} &= (\beta-\mu)\frac{S}{N}I - \gamma I + \nu\frac{S}{N}Y,\\
\dot{R} &= \gamma(I+Y) - \alpha R,\\
\dot{Y} &= (\beta-\nu-\varepsilon)\frac{S}{N}Y - \gamma Y + \mu\frac{S}{N}I,\\
\dot{X} &= \varepsilon\frac{S}{N}Y - \varphi X,
\end{aligned} \tag{8}$$

again assuming mean field approximation.

2.4. 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 simulations of the master equation, using the Gillespie algorithm, also known as minimal process algorithm [24–26]. This is a Monte Carlo method, in which after an event, i.e., a transition from state $\underline{n}$ to another state $\underline{\tilde{n}}$, the exponential waiting time is calculated as a random variable from the sum of all transition rates whereupon 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

$$\begin{aligned}
S^* &= N\frac{\gamma}{\beta}, \qquad I^* = N\frac{\alpha}{\beta}\frac{\beta-\gamma}{\alpha+\gamma},\\
R^* &= N\frac{\gamma}{\beta}\frac{\beta-\gamma}{\alpha+\gamma},
\end{aligned} \tag{9}$$

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* [8]. 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 parameter values, but rather the order of magnitude.

After fixing the basic epidemic parameters α, β and γ for the SIR-subsystem, we now consider the mutation towards infected in the Y-class, fixing the mutation rate $\mu := 0.0001$ to be orders of magnitude smaller than the infection process, and foreward mutations equal to backward mutations $\nu = \mu$.

Interesting behaviour is observed if 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 we show two simulations in this ε-region, first $\varepsilon = 0.05$, Fig. 1(a), (b), then a ten times smaller ε, Fig. 1(c), (d). For high pathogenicity ε we find relatively low levels of mutants Y, in Fig. 1(a) less than 20 cases, and at the end of the simulation roughly between 15 and 80 hospital cases X, Fig. 1(b). For smaller pathogenicity ε, Fig. 1(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 ten times smaller than in the previous simulation we find at the end of this simulation similar numbers of disease cases X, Fig. 1(d). We observed larger fluctuations and sometimes a much higher number of outbreaks of dis-

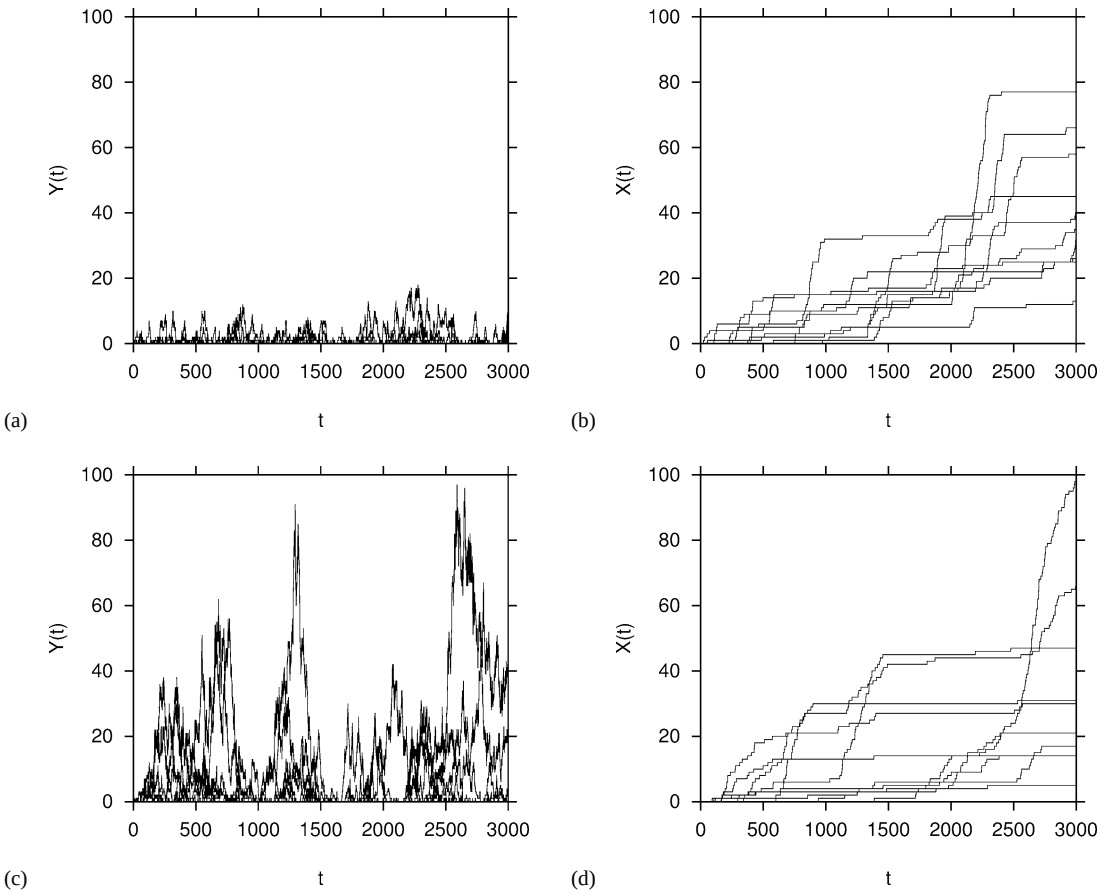

Fig. 1. (a) Time series of ten runs showing the mutant carriage Y for pathogenicity $\varepsilon = 0.05$. (b) Number of seriously diseased cases X for pathogenicity $\varepsilon = 0.05$. (c) and (d) as (a) and (b) with pathogenicity ten times smaller, hence $\varepsilon = 0.005$. Although the pathogenicity ε is of the factor ten smaller, the damage in the number of seriously diseased cases X remains high and even varies more than for larger ε.

eased cases though the probability to cause disease is smaller.

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

2.5. Dynamics of mean numbers of infected

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 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 into account Eqs. (9) for the stationary values of the SIR-system we obtain for the transition rates (compare Eqs. (7)) of the remaining YX-system:

$$\begin{aligned}
&w_{(S^*,Y+1),(S^*,Y)} = \mu\frac{S^*}{N}I^* =: c,\\
&w_{(S^*,Y+1),(S^*,Y)} = (\beta-\nu-\varepsilon)\frac{S^*}{N}Y =: bY,\\
&w_{(S^*,X+1),(S^*,X)} = \varepsilon\frac{S^*}{N}Y =: gY,\\
&w_{(Y-1,R^*),(Y,R^*)} = \gamma Y =: aY,\\
&w_{(X-1,S^*),(X,S^*)} = \varphi X = 0.
\end{aligned} \tag{10}$$

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 meningococcal disease, hence $\varphi = 0$, we are only left with Y-dependent transition rates. Hence, for the YX-system we get the master equation:

$$\begin{aligned}
&\frac{d}{dt}p(Y,X,t)\\
&\quad=\big(b(Y-1)+c\big)p(Y-1,X,t)\\
&\qquad+a(Y+1)p(Y+1,X,t)+gYp(Y,X-1,t)\\
&\qquad-(bY+aY+gY+c)p(Y,X,t).
\end{aligned} \tag{11}$$

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 $b := (\beta-\nu-\varepsilon)\frac{S^*}{N}$, death rate $a := \gamma$ and a migration rate $c := \mu\frac{S^*}{N}I^*$. 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. We will check the validity of this assumption later with simulations of the full SIRYX-system.

Hence, we have

$$\begin{aligned}
\frac{d}{dt}p(Y,t) &= \big(b(Y-1)+c\big)p(Y-1,t)\\
&\quad+a(Y+1)p(Y+1,t)\\
&\quad-(bY+aY+c)p(Y,t)
\end{aligned} \tag{12}$$

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

$$\frac{d}{dt}p(Y=0,t) = ap(Y=1,t) - cp(Y=0,t). \tag{13}$$

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

$$\frac{d}{dt}\langle Y\rangle = (b-a)\langle Y\rangle + c. \tag{14}$$

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 ODE for the mean $\langle Y\rangle(t)$, 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 ODE then reads

$$\langle\dot{Y}\rangle = -g\langle Y\rangle$$

under suitable initial condition $Y(t=0) = 1$. The solution is

$$\langle Y\rangle(t) = e^{-g(t-t_0)}. \tag{16}$$

For non-vanishing mutation rate μ we obtain as solution

$$\langle Y\rangle(t) = \frac{c}{g}\big(1-e^{-g(t-t_0)}\big). \tag{17}$$

We will use Eqs. (16) and (17) to analyse the behaviour of an ensemble of different pathogenicities ε in the next section.

2.6. Power law at criticality

We have shown previously that the probability of the final size of the epidemics follows a power law as observed in branching processes [10]. These power laws are a characteristic sign for criticality.

In a simplified model, where the SIR-subsystem is assumed to be stationary (due to its fast dynamics), we can show analytically divergence of variance and power law behaviour for the probability of the size of the epidemics $p(X)$ as soon as the pathogenicity is developing towards 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 (see [10] for details).

For the final size distribution of the epidemic we get power law behaviour

$$p_\varepsilon(X) := \lim_{t\to\infty} p(Y=0,X,t) \sim \frac{1}{2\sqrt{\pi\beta}}\varepsilon^{1/2}X^{-3/2}, \tag{18}$$

for $\varepsilon \to 0$ and large X [10]. The exponent $-3/2$ is exactly the one given in [15] for the critical branching process. This behaviour 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 [29], see also [27].

3. Evolution towards criticality

In sand pile models two time scales appear, the slow time scale of sand dropping onto the sand pile and the fast time scale of avalanches running down the pile. In simulations and theoretic models often these time scales are separated by making the avalanches infinitely fast. Likewise, in our epidemic model we have the slow time scale of mutations of different bacteria strains, characterized by the mutation rate μ, and the fast time scale of the infection process for these strains, characterized by the contact rate β (and rates α and γ). The former parameter ε, the pathogenicity, will now become a state variable which the system adjusts on its own, like the slope of the sand pile being adjusted on its own in the paradigmatic model of SOC.

We consider two scenarios to investigate how the distribution of different mutants with various pathogenicities changes with time in the system. In our first consideration we look at the case of complete separation of time scales by making the mutation process infinitely slow, hence $\mu := 0$. The analytic solution will be very simple and easy to analyze, showing the evolution towards the critical state with ε towards zero. In the second consideration we analyze the more realistic situation of finite mutation rate, and still find an analytic solution in terms of an infinite sum. This solution can be similarly treated as the first case, again showing evolution towards criticality. In both cases the above simplifications of stationarity of the SIR-subsystem are used to obtain analytic solutions. And in both cases simulations of the full SIRYX-subsystem agree well with the analytic results.

3.1. Model 1: Ensemble of initially introduced mutants

We show now that in a population of equally distributed pathogenicity ε after a certain period only the hosts with mutants of low pathogenicity remain in the system. Therefore, we investigate an ensemble of realizations each starting with one mutant infected. In each realization the initial mutant infected has pathogenicity ε. Now the different realizations have different pathogenicities ε with relative frequency $p(\varepsilon,t_0)$ uniform for starting time t_0. We follow the relative frequency of infected with a certain pathogenicity over the time course

$$p(\varepsilon,t) := \frac{\langle Y\rangle(\varepsilon,t)}{\int_0^{\varepsilon_m}\langle Y\rangle(\varepsilon,t)\,d\varepsilon}. \tag{19}$$

Analytically, we can approximate $\langle Y\rangle(\varepsilon,t)$ by Eq. (16)

$$\langle Y\rangle(\varepsilon,t) = e^{-gt}, \tag{20}$$

with $g := \varepsilon\gamma/\beta$, derived from the ODE $\frac{d}{dt}\langle Y\rangle = (b-a)\langle Y\rangle$ with $b-a=-g$. The result for $p(\varepsilon,t)$ is

$$p(\varepsilon,t) = \frac{\frac{\gamma}{\beta}te^{-\varepsilon\frac{\gamma}{\beta}t}}{1-e^{-\varepsilon_m\frac{\gamma}{\beta}t}} \tag{21}$$

with initial distribution $p(\varepsilon, t_0) = 1/\varepsilon_m$ for $\varepsilon \in [0, \varepsilon_m]$ and for time going towards infinity $p(\varepsilon, t \to \infty) = \delta(\varepsilon)$, hence all mass concentrates at $\varepsilon = 0$.

In a full SIRYX-model the present assumptions, especially $I = I^*$ as the stationarity for the harmlessly infected, would be violated for the pathogenicity being in the order of the mutation rate, $\varepsilon \approx \mu$, since the I can then be completely replaced by the Y mutant infected with I going towards very small numbers or extinction [10]. The distribution $p(\varepsilon, t)$ for model 1 from Eq. (21) is shown for three different times in Fig. 2.

3.2. Simulation of the full SIRYX-system for model 1

In simulations of the full SIRYX-system we consider a variety of pathogenicities ε_i and for each of those we perform a large number of runs j, recording the number of mutant infected $Y_j(\varepsilon_i, t)$ over time. Hence the distribution of pathogenicities in an ensemble of hosts infected with different mutant strains is given by

$$\hat{p}(\varepsilon_i, t) := \frac{\sum_j Y_j(\varepsilon_i, t)}{\sum_i \sum_j Y_j(\varepsilon_i, t)\Delta\varepsilon}, \tag{22}$$

with $\Delta\varepsilon$ the length of the considered ε-interval times the number of ε-values. We compare the simulation results with the previous theoretical results in Fig. 3. The simulation results (crosses) lie well in the vicinity of the theoretical curve (full line).

3.3. Model 2: Mutations during the process

In a second consideration we assume that no mutant infected are present initially, but with mutation rate μ mutants with equally distributed pathogenicity are created. Since all pathogenicities are equally likely to appear during mutations, the initial distribution $p(\varepsilon, t_0)$ is expected to be uniform. After some time, the strains with low pathogenicity will create more and more mutant infected overruling the newly few incoming mutant infected with higher pathogenicity from the mutation process.

Analytically, we take the above definition of $p(\varepsilon, t)$, and now calculate from Eq. (17)

$$\langle Y\rangle(\varepsilon, t) = \frac{c}{g}\left(1 - e^{-gt}\right),$$

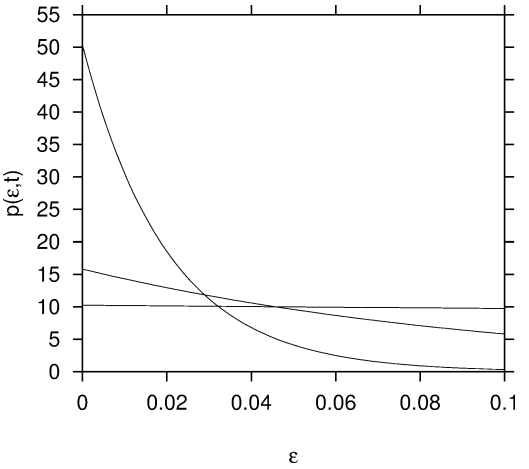

Fig. 2. For our first model we show distributions $p(\varepsilon, t)$ for times $t = 1$, $t = 20$, $t = 100$ (times $t = 1$, horizontal line, $t = 20$, slightly tilted line, and $t = 100$, where all the probability is going towards small pathogenicity values).

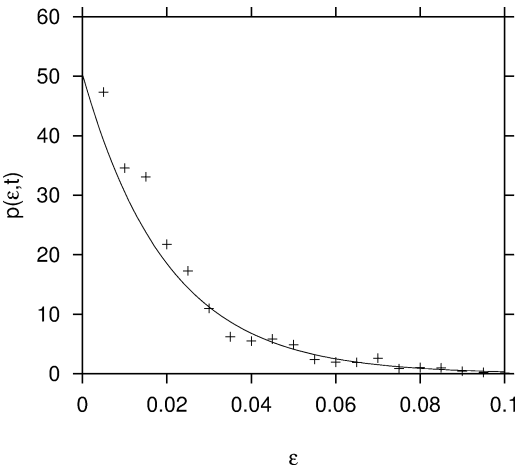

Fig. 3. Comparison of simulations of the complete SIRYX-system with the theoretical curve from the YX-subsystem and assumption of SIR in stationarity for the first model. Here time $t = 100$ is shown.

with import rate $c = \mu I^* S^*/N = \mu I^* \gamma/\beta$, hence $c/g = \mu I^*/\varepsilon$. This is derived from the ODE $\frac{d}{dt}\langle Y\rangle = (b-a)\langle Y\rangle + c$. The solution can now only be obtained numerically (or with $\int (e^x/x)\,dx$ as given function).

Explicitly it is

$$p(\varepsilon, t) := \frac{\langle Y\rangle(\varepsilon, t)}{\int_0^{\varepsilon_m} \langle Y\rangle(\varepsilon, t)\,d\varepsilon} = \frac{\frac{1}{\varepsilon}\left(1 - e^{-\varepsilon\frac{\gamma}{\beta}t}\right)}{\int_0^{\varepsilon_m} \frac{1}{\varepsilon}\left(1 - e^{-\varepsilon\frac{\gamma}{\beta}t}\right) d\varepsilon} \tag{23}$$

and

$$\int_0^{\varepsilon_m} \frac{1}{\varepsilon}\left(1-e^{-\varepsilon\frac{\gamma}{\beta}t}\right)d\varepsilon = \lim_{\varepsilon_0\to 0}\left(\int_{\varepsilon_0}^{\varepsilon_m}\frac{1}{\varepsilon}\,d\varepsilon - \int_{\varepsilon_0}^{\varepsilon_m}\frac{1}{\varepsilon}e^{-\varepsilon\frac{\gamma}{\beta}t}\,d\varepsilon\right). \quad (24)$$

With the substitution in the last integral $z := -\varepsilon\frac{\gamma}{\beta}t$, hence $\frac{dz}{d\varepsilon} = -\frac{\gamma}{\beta}t$ we find the exponential integral function defined as $\mathrm{Ei}(y) := \int_{-\infty}^{y}\frac{e^z}{z}\,dz$ with explicit series expansion $\mathrm{Ei}(y) = \ln|y| + \sum_{\nu=1}^{\infty}\frac{y^\nu}{\nu\cdot\nu!} + C$. Hence,

$$\int_0^{\varepsilon_m} \frac{1}{\varepsilon}\left(1-e^{-\varepsilon\frac{\gamma}{\beta}t}\right)d\varepsilon = \lim_{\varepsilon_0\to 0}\left(\ln(\varepsilon_m) - \ln(\varepsilon_0) + \int_{-\frac{\gamma}{\beta}t\varepsilon_0}^{-\frac{\gamma}{\beta}t\varepsilon_m}\frac{1}{z}e^z\,dz\right), \quad (25)$$

and taking the limit

$$\lim_{\varepsilon_0\to 0}\left(\ln(\varepsilon_m) - \ln(\varepsilon_0) + \mathrm{Ei}\left(-\frac{\gamma}{\beta}t\varepsilon_0\right) - \mathrm{Ei}\left(-\frac{\gamma}{\beta}t\varepsilon_m\right)\right) = \sum_{\nu=1}^{\infty}(-1)^{\nu+1}\frac{\left(\varepsilon_m\frac{\gamma}{\beta}t\right)^\nu}{\nu\cdot\nu!}, \quad (26)$$

with the result

$$p(\varepsilon,t) = \frac{1}{\varepsilon}\left(1-e^{-\varepsilon\frac{\gamma}{\beta}t}\right)\left[\sum_{\nu=1}^{\infty}(-1)^{\nu+1}\frac{\left(\varepsilon_m\frac{\gamma}{\beta}t\right)^\nu}{\nu\cdot\nu!}\right]^{-1}. \quad (27)$$

The distribution $p(\varepsilon,t)$ for model 2 from Eq. (27) is shown for three different times in Fig. 4(a).

3.4. Simulation for model 2

In simulations for our second model we start with a resident strain with vanishing pathogenicity and allow for mutations to various strains with different pathogenicities ε_i. For all strains the mutation rate is the same. Again we consider the distribution of the various ε_i in a population of mutant infected over time (see Eq. (22)) and compare with theoretical results in Fig. 4(b).

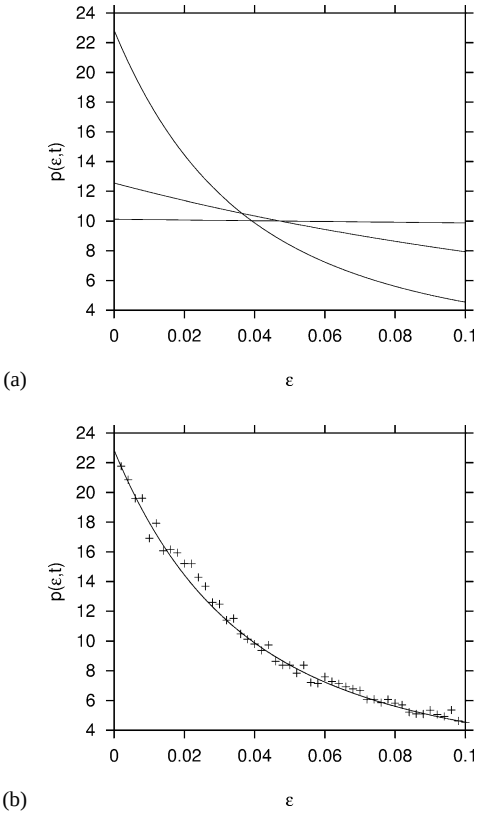

Fig. 4. Second model. (a) Theoretical curves for times $t = 1$, $t = 20$, $t = 100$ and (b) comparison between model and simulations for time $t = 100$. Each data point of the simulation is an average over 5000 runs, and 50 values for ε are taken.

Remarkably, the result for the lowest value of $\varepsilon = 0.002$ still is in very good agreement with the theoretical curve though ε is only twenty times larger still than the mutation rate μ.

4. Summary

Our results show that in an ensemble of strains with different pathogenicity the strains which are least pathogenic are selected over the more pathogenic strains. This brings about an evolution towards reduced pathogenicity, and thus, criticality. If no new mutant strains are produced eventually the only remaining strains will be completely non-pathogenic

strains. However, small mutation rates will continuously produce pathogenic strains of which only the weakly pathogenic ones will remain in the system for some time. In this sense the criticality of this system is a robust feature and evolution will drive this system towards criticality. In this sense the meningitis model provides a biologically realistic example of self-organized criticality. Future work to eventually obtain more formal proofs of self-organized criticality, possibly along the lines of work done on simpler models [28], might give a detailed understanding of the mechanisms we found.

Preliminary analysis of empirical data of meningitis and septicaemia show large outbreaks of often unlinked cases between extended periods of silence, indicating that the structural behaviour of the system can be understood from the implications of our model. Future work will be spent on the disentanglement of our model's features and additional effects like, for example, seasonality in already seen data and comparison with further data from different climatic and cultural backgrounds (peoples' meeting habits seem to have effects on the contact rate). Parameter estimation techniques used previously in [22] and [23] could be applied to the present system under investigation.

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