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The Force of Infection in Populations of Varying Size: a Modelling Problem

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Abstract

It is argued that the (quasi-) mechanistic modelling of the incidence of an infectious disease in a population of varying size is a nontrivial problem, deserving careful thinking. The spread of a virus among seals is used to illustrate how a submodel for the contact process may be helpful. In that same context the impact of the disease on the population growth of the host is investigated.

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1. Introduction

The aim of this short note is first of all to take stock of some problems connected with the modelling of the incidence of an infectious disease in a population of varying size. Or, in other words, to give some reflections on the law of mass action as an ingredient for epidemic models. Subsequently, to make the discussion more concrete, we focus on a case study: the spread of Phocid Distemper Virus (PDV) among the harbour and grey seals in the coastal waters of Northern Europe. Here we present an attempt to model the contact process and then deduce the pattern in the effect of the infectious disease on population growth, in the spirit of Anderson & May [1978, 1979], Busenberg & van den Driessche [1990], Busenberg & Hadeler [1990], Diekmann & Kretzschmar [1991], Thieme [1992].

When modelling the spread of an infectious disease one has to consider and compare the time scales of the various processes involved. Roughly speaking one can distinguish three situations (see Diekmann, Heesterbeek & Metz (to appear) and Diekmann [1991] for some more discussion):

- single outbreaks: no inflow of new susceptibles
- endemic state: constant birth rate
- population regulation: exponential growth in the absence of the disease

The third of these, which was introduced as important for animal ecology by Anderson & May [1978], is the one considered here.

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2. NUMBERS OR DENSITY? AND THEN, WHAT IS DENSITY?

So we are interested in populations of varying size. But what does "size" refer to? The obvious alternatives are numbers and density. It should be well-known, but is nevertheless emphasized in DE JONG, DIEKMANN, HEESTERBEEK (to appear), that to model the incidence by *csi*, where c is a constant, s denotes susceptibles and i infectives, the variables s and i should refer to *densities*. The shaky basis for this so-called "law of mass action" is a vague similarity with chemical kinetics: all individuals are assumed to "move" randomly and to "contact" other individuals of various types in proportion to their density; upon contact the infective agent is transmitted with a certain probability, i.e. given a "collision" the "reaction" takes place with a certain probability.
Note that here "incidence" refers to number of new cases per unit of time per unit of area (when the spatial domain is two-dimensional). For a fixed spatial domain Ω we find

$$\frac{c}{|\Omega|} SI$$

for the total number of new cases per unit of time, where S and I denote *numbers* and $|\Omega|$ the area/size of Ω. If, as is done in certain experiments (e.g. the Greenwood experiment (see ANDERSON & MAY [1979], DE JONG, DIEKMANN & HEESTERBEEK (to appear) and the references given there)) and presumably also happens in natural situations, the size of the domain Ω occupied by the population is increased so as to keep the density constant, we obtain

$$\tilde{c} \frac{SI}{N}$$

where N denotes the total number of individuals in the population and $\tilde{c} = ck$ with k defined by $N = k|\Omega|$, i.e. k is the density at which the population is kept (or keeping itself). Some authors (GRENFELL e.a. [1992] and ANDERSON & MAY [1979]) omit the factor N^{-1}, usually without explaining why, at fixed density, the per capita number of "contacts" per unit of time should increase with total population size. The data of the Greenwood experiment more or less equally fit the two models, with and without N^{-1}, DE JONG, DIEKMANN & HEESTERBEEK (to appear). However, the experiments of BOUMA e.a. (in preparation) with the Aujeszky disease virus in pigs clearly demonstrated that the factor N^{-1} is needed.

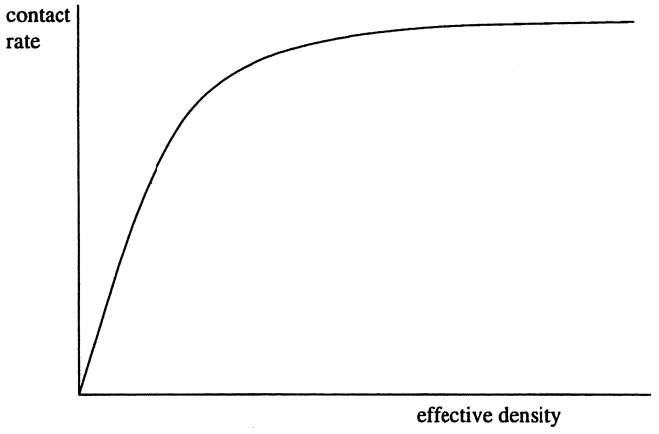
In the paper of HEIDE-JØRGENSEN & HÄRKÖNEN [1992] (which we came across after the first draft of this paper was already written) the model without N^{-1} is used. Subsequently, when comparing the "reaction" coefficients as estimated from data for various more or less isolated populations of different sizes, the authors note that there is, in reasonable approximation, a factor N^{-1}. They explain this dependence by mechanistic arguments which are in the spirit (in fact almost identical) to those of the present paper. Remarkably though, they do not make the logical step of incorporating the factor N^{-1} in the model (perhaps out of unwarranted respect for the mathematical literature in which the factor is missing??).

As indicated above, natural populations may, when growing, gradually expand the area they occupy. This may take the form of spatial spread (see VAN DEN BOSCH e.a. [1990] and METZ & VAN DEN BOSCH (to appear) for a review emphasizing epidemic spread) but it may also (or in addition) take the form of filling in the gaps, e.g. when individuals settle for the proportion of land which forms less favourable habitat, since the best habitat area is all occupied. So we have to scrutinise the definition of "density" as "number per area", especially when it is determined by humans what constitutes the total area in which a population is living. The somewhat vague definition of "effective density" as "the squared inverse of a *typical* nearest neighbour distance" yields an alternative that is worth to be taken serious (of course there are many variants of this "definition").

Rather than taking the law of mass action as a dogma, we may pose the following questions:

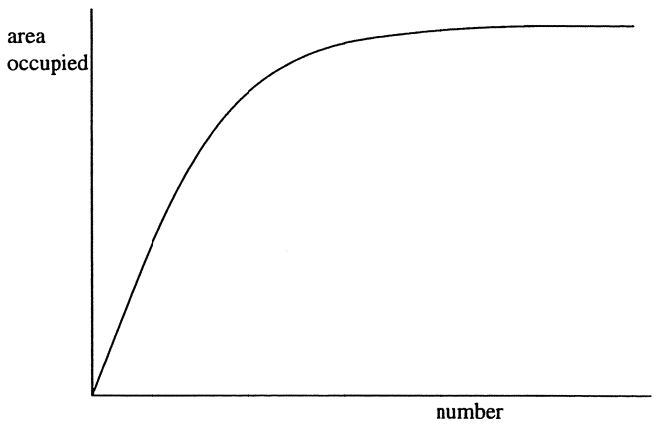
- how does the contact rate, which is a basic ingredient for the force of infection, depend on effective density?
- if, for a given area, numbers change, how does the effective density change?

In general one expects a saturating curve as an answer to the first question.

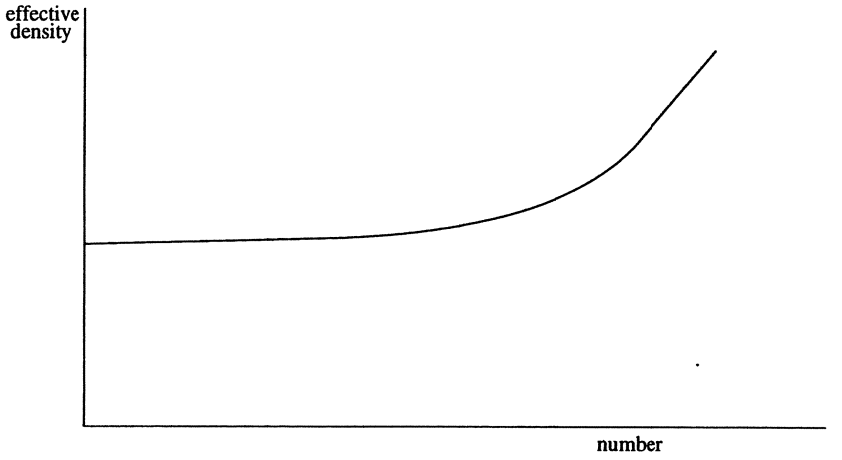


When "satiation" is the basic mechanism (e.g. sexual contacts or mosquitoes taking blood meals) modellers often sacrifice the mechanistic interpretation at very low densities and for simplicity's sake approximate the curve by a constant. When contacts take time and the time budget is the limiting factor one can derive the curve from a submodel for the contact process at a short time scale, in much the same way as one can derive the Holling type II functional response for predation (an essential difference being that now contacts are between two individuals of the *same* population). This was recently carried out by HEESTERBEEK & METZ [1993].

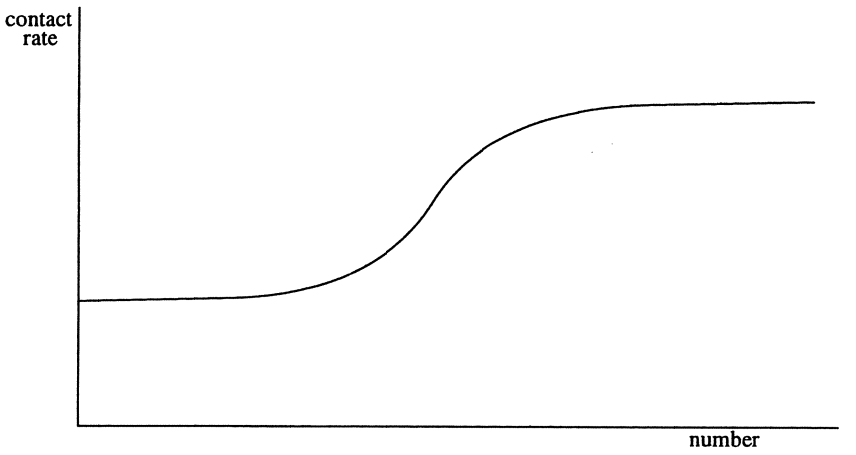
The answer to the second question may be very context dependent (see the next section for a particular example). Yet one may speculate that a graph like



which leads to



captures some universal features when long-range spatial spread is not an option. Composing these graphical answers to the two questions we find the following figure:



Clearly there is a need for submodels for the contact process to give an underpinning as well as a quantitative elaboration of the above, admittedly debatable, qualitative considerations. The main aim of this section has been to signal this need. In the next section we show, by means of an example, what we mean by such a contact submodel.

3. Seals on the beach

In the spring and summer of 1988 an infectious disease caused the death of about half of the population of harbour seals (*Phoca vitulina*) in north-west Europe. Grey seals (*Halichoerus gryphus*) were infected as well. A morbilli virus, similar to the well known Canine Distemper Virus, was later identified as the cause of the disease (Osterhaus & Vedder [1988]) and then baptized Phocid Distemper Virus (PDV).

Building on a computer simulation model developed by M. VAN GRUIJTHUIZEN and E.J.M. VELING [1992] at the RIVM Institute in the Netherlands, a mathematical model for the spread of the PD virus in the seal population was built by A.A. DE KOEIJER [1993]. Here we shall briefly explain the main assumptions underlying the model for disease transmission and then investigate how it combines with a very simple (caricatural) model for population growth. So we focus on the submodel for the contact process and on the possible effects of the disease on population growth. In a separate paper, A.A. DE KOEIJER e.a. (in preparation) will use the same contact submodel to study the epidemic outbreak and the possibilities for an endemic state.

We shall assume that the virus can be transmitted only when seals come out of the water to rest or sun bathe on sand-banks (this takes place at low tide, so roughly twice every 24 hours). More drastically we shall assume that the seals frequenting a particular sand-bank form each time randomly a one-dimensional equidistant row. This is a deliberately simplified description of reality which, as aerial photographs testify, is not too bad an approximation. Note that the assumption entails that the effective density is constant (i.e. we assume that numbers are low enough to neglect the increasing part of the graph of effective density as a function of number in the foregoing section). We assume that transmission of virus can occur only between nearest neighbours.

We shall work with a deterministic model which ignores two aspects of the actual finiteness of the (local) population on which we focus: we shall work with expected numbers and forget about the variance and we shall disregard boundary effects (viz. the fact that the seals occupying the extreme positions of the row have one instead of two nearest neighbours).

Let N denote the total number of seals frequenting a particular sand-bank. When these N seals line up randomly, there are many configurations possible of susceptibles, infectives and immunes. We ignore this fine structure and just note that a susceptible has with probability

$$2\,\frac{I}{N}\,\frac{N-I}{N} \qquad \text{one infected neighbour}$$

and with probability

$$\left(\frac{I}{N}\right)^2 \qquad \text{two infected neighbours}$$

Let p denote the probability that transmission takes place in a nearest neighbour pair consisting of a susceptible and an infective. Then $1-(1-p)^2 = 2p-p^2$ is the probability that a susceptible that happens to have two infective neighbours is infected. Thus we find for the expected number of new cases the expression

$$\left(p2\frac{I}{N}\,(1-\frac{I}{N}) + (2p-p^2)\left(\frac{I}{N}\right)^2\right) S = 2p\,\left(1-\frac{1}{2}p\frac{I}{N}\right)\,\frac{IS}{N}$$

When p is small and we are interested in the dynamics at a time scale at which θ, the number of low-tides per unit of time, is large, we take for the incidence (which is a rate) the expression $\alpha\frac{IS}{N}$, where $\alpha = 2p\theta$.

The fact that, starting from a fairly specific submodel for the contact process, we arrive at such a "general" expression for the force of infection, may seem an anti-climax to some, but encouraging to other readers. The key assumption that underlies the expression is that the density, and therefore the per capita number of contacts per unit of time, remains constant as the number of individuals in the population varies.

The system of ordinary differential equations

$$\dot{S} = bS + bR - \mu S - \alpha \frac{SI}{N}$$

$$\dot{I} = \alpha \frac{SI}{N} - \mu I - \beta I$$

$$\dot{R} = f\beta I - \mu R \qquad \text{where } N := S + I + R$$

embodies a few more assumptions:
1) infectives remain so for an exponentially distributed period of time with parameter β;
2) an infective that does not die from other causes will die with probability $1 - f$ from the disease and will with probability f survive to become immune for the rest of its life;
3) all individuals are exposed to a death rate μ;
4) susceptibles and immunes produce offspring at a per capita rate b, infectives do not produce offspring (since the disease causes abortion).
In the next section we shall study the qualitative behaviour of this system.

In conclusion of this section we emphasize that the configuration is formed at every low-tide anew. It is this aspect which makes the problem different from, say, the Ising model and which motivates us to work with some confidence with expectations only.

4. What does analysis tell us?

Throughout this section we assume $b > \mu$, i.e. the population would grow exponentially in the absence of the disease. Note that the ode system is nonlinear but homogeneous. So we can expect exponential solutions even when the disease is present (Hadeler e.a. [1988] and references given there).

It pays to make first of all the transformation of variables

$$N = S + I + R \qquad y = \frac{I}{N} \qquad z = \frac{R}{N},$$

the main point being that in the new variables we have a decoupling into the two-dimensional system

$$\dot{y} = y\{\alpha(1 - y - z) - \beta + \beta\,(1 - f)y + b\,(y - 1)\}$$

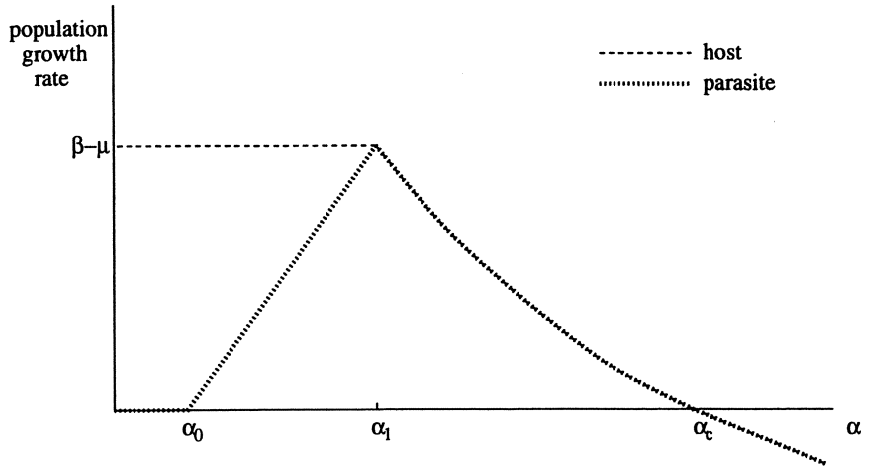
$$\dot{z} = y\,(f\beta + (1 - f)\,\beta z) - bz\,(1 - y)$$

which is independent of N, and the equation

$$\dot{N} = \{b - \mu - \,(b + \beta\,(1 - f))y\}N\,.$$

So we can study the two-dimensional system first, which gives us information about the prevalence of the disease, and then "substitute" the results into the equation for N to deduce the consequences for population growth.

Before giving some more details of the analysis, we summarize the outcome in the following diagram:



The expected duration of the infectious period is $(\beta+\mu)^{-1}$. The basic reproduction ratio R_0 counts the expected number of secondary cases produced by one primary case introduced in a "virgin" population, so in the present context $R_0 = \alpha(\beta+\mu)^{-1}$. At $\alpha = \alpha_0 = \beta+\mu$, R_0 passes the threshold value one. So for $\alpha > \alpha_0$ the virus can increase. Yet it may, and indeed does, happen that the host population grows faster and then the dilution effect is that the proportion of hosts infected still goes to zero. This is the case for $\alpha_0 < \alpha < \alpha_1$, where $\alpha_1 = \beta+b$. The intuitive biological way to derive α_1, is to compute the expected number of secondary cases while discounting for the population growth (recall the interpretation of Lotka's equation in demography):

$$R_1 = \alpha \int_0^\infty e^{-(\beta+\mu)a}\ e^{-(b-\mu)a}\ da = \frac{\alpha}{\beta+b}$$

(the first factor of the integrand is the probability to be still alive and infective, the second is the discount factor that relates absolute numbers to a proportion of the population). R_1 passes the threshold value one at $\alpha = \alpha_1$. For $\alpha > \alpha_1$, the relative prevalence y is positive, host and parasite grow at the same rate, which is reduced relative to $b-\mu$. Whether or not a further increase of α leads to a reduction of the growth rate to below zero, is determined by another quantity admitting a biological interpretation, which was introduced by ANDREASEN [1989]. The expected number of offspring produced by an individual that is infected at birth equals

$$\frac{\beta}{\beta+\mu}\ f\ \frac{b}{\mu}.$$

If this number is bigger than one, the host population (and therefore the parasite population) will increase exponentially no matter how prevalent the disease is. If it is less than one, increasing α will inevitably lead to a situation in which the population will decline. The diagram above is for this last situation.

The mathematical arguments underpinning the conclusions above derive from a phase plane analysis of the (y,z)-system. For $R_1 < 1$ all solutions in the positive quadrant converge to the origin. For $R_1 > 1$ there exists a locally stable nontrivial steady state and the y-coordinate $\bar{y}$ of this steady state depends monotonously increasing on the parameter α, with limit

$$\bar{y} = \frac{\beta+2b-\sqrt{\beta^2+4b\beta f}}{2(b+(1-f)\beta)}$$

for $\alpha \to \infty$. So the population growth rate reduces from $b-\mu$ to the value $\frac{1}{2}\sqrt{\beta^2+4b\beta f} - \mu - \frac{1}{2}\beta$, which is negative if and only if $\beta f b \mu^{-1}(\beta+\mu)^{-1} < 1$. The critical value α_c at which the growth rate becomes zero is given explicitly by $(\beta+\mu)(b+\beta(1-f))(\beta+\mu-f\beta b\mu^{-1})^{-1}$.

At this point we like to remark that when we consider a system that is asymptotically homogeneous, rather than homogeneous, then a branch of steady state solutions bifurcates at the critical value α_c at which the growth rate becomes zero. Moreover, when the population composition affects the per capita birth rate of susceptibles, the bifurcation can be subcritical, in which case we have bistability, and there may also be stable oscillations (see DIEKMANN & KRETZSCHMAR [1991]).

5. DISCUSSION

The simplicity of the model enables us to do explicit calculations. But the qualitative features of the diagram all allow for a biological interpretation and are therefore expected to be robust, that is, insensitive to changes in the details of the model specification.

There are many aspects of the spread of PDV among seals which are not covered by the present analysis. Spatial spread is one of them, epidemic outbreaks in finite populations another (see LEFÈVRE & PICARD [1993], PICARD & LEFÈVRE [1993], DE KOEIJER [1993], DE KOEIJER e.a. (in preparation). A very relevant problem is to determine the odds of endemic persistence.

Here we have chosen the example of PDV among seals to illustrate our thesis that to model the spread of an infectious disease in a population of varying size one has to think carefully about the contact process underlying transmission. The aim of this paper has been to reveal a problem, so that it can be addressed, much more than to present a solution.

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