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Cluster formation for multi-strain infections with cross-immunity

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Abstract

Many infectious diseases exist in several pathogenic variants, or strains, which interact via cross-immunity. It is observed that strains tend to self-organise into groups, or clusters. The aim of this paper is to investigate cluster formation. Computations demonstrate that clustering is independent of the model used, and is an intrinsic feature of the strain system itself. We observe that an ordered strain system, if it is sufficiently complex, admits several cluster structures of different types. Appearance of a particular cluster structure depends on levels of cross-immunity and, in some cases, on initial conditions. Clusters, once formed, are stable, and behave remarkably regularly (in contrast to the generally chaotic behaviour of the strains themselves). In general, clustering is a type of self-organisation having many features in common with pattern formation.

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1. Introduction

Many pathogens have several different antigenic variants, or strains, present in a host population simultaneously. The classic example is influenza (Andreasen et al., 1997; Lin et al., 1999; Plotkin et al., 2002; Gog and Grenfell, 2002; Cliff et al., 1986), where there are several circulating subtypes, with many minor variants within each subtype. Other important examples are meningitis (Gupta et al., 1996; Gupta and Anderson, 1999), dengue (Gog and Grenfell, 2002) and malaria (Gupta et al., 1994).

Because of similarities in, for example, their mechanisms of infection, strains may interact with each other (Gupta et al., 1996). Infection with one strain may partially protect the host against infection with other strains. Cross-immunity is included in different ways in different models, but the general idea is the same: infection with one strain of the disease produces a lasting immune memory in the host which acts to protect against subsequent infection by other strains. That is, for two sufficiently close strains A and B, infection by strain A reduces the chance of a secondary infection by strain B. For instance, in the case of influenza, the surface protein hemagglutinin seems to be under strong positive selection because it is the target of the immune response, and therefore it presents high antigenic diversity in the virus population (Andreasen et al., 1997; Lin et al., 1999; Plotkin et al., 2002; Gog and Grenfell, 2002). This immune response may be

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enhanced because of a previous infection with a close variant.

There are different approaches to the cross-immunity problem (Gog and Swinton, 2002). For instance, we can assume that a fraction, say γ_{BA}, of individuals infected with strain A gain complete immunity to strain B; alternatively, all the individuals infected with strain A may be assumed to acquire partial immunity against B (with a consequence that the force of secondary B-infection is reduced by a factor γ_{BA}). Another possible hypothesis is that the secondary infection is weaker and thus less transmissible by the infective host. These differences in the approaches to cross-immunity lead to a variety of models which can provide controversial outcomes. Under such circumstances it is reasonable to look for such features of the multi-strain system which are intrinsic to this system and are robust irrespective of model choice.

A system of multiple strains interacting via host cross-immunity tends to self-organise into groups, or clusters. The tendency for strains to occur in clusters reflects the observed influenza dynamics (Gog and Grenfell, 2002; Plotkin et al., 2002). Cluster formation was observed and discussed by Gupta et al. (1996, 1998). The phenomenon of clustering appears to be typical for many systems with internal order and may occur in such systems as multi-species predator–prey systems. For example, it was observed in neuronal networks (Rubin and Terman, 2000a,b; Terman and Lee, 1997; Terman et al., 1998).

In this paper we consider formation of clusters in ordered multi-strain systems. We show that for complex systems several different types of cluster structure may arise. We also demonstrate that cluster structures are not specific to a particular model—on the contrary, they appear to be intrinsic to the given strain system. In general, cluster formation is a self-organisation phenomenon bearing many similarities to pattern formation. A remarkable feature of clusters is that they exhibit exceptional regularity even when the dynamics of every strain is chaotic.

2. Model

Due to different approaches to cross-immunity, a variety of models of multi-strain infections has been developed. These models sometimes lead to different outcomes. It is important, therefore, to find such indicators which are characteristic to the system itself and robust to choice of model.

We start from a comparatively simple model of a multi-strain infection suggested by Gupta et al. (1998). This model is composed of only three compartments (and, respectively, three differential equations) for each strain. If $z_i(t)$ is the fraction of individuals who have been or are infected with the strain i (either they are infectious or not), $y_i(t)$ is the fraction of the infectious individuals with the strain, and $w_i(t)$ is the fraction of individuals who have been infected (or are infected) by any strain sufficiently close to the strain i including i itself (that is $w_i = \cup_{j\sim i} z_j$), then the model equations are:

$$\begin{aligned}
\frac{\mathrm{d}z_i}{\mathrm{d}t} &= \beta_i y_i(1-z_i) - \mu z_i,\\
\frac{\mathrm{d}w_i}{\mathrm{d}t} &= \sum_{j\sim i} \beta_j y_j (1-w_i) - \mu w_i,\\
\frac{\mathrm{d}y_i}{\mathrm{d}t} &= \beta_i y_i[(1-w_i) + (1-\gamma)(w_i - z_i)] - (\mu+\sigma_i) y_i. \qquad (1)
\end{aligned}$$

For this model, cross-protection does not affect susceptibility but reduces transmissibility by a factor $1-\gamma$ (where the parameter γ measures the degree of cross-protection between two strains). Here, $j \sim i$ means that the jth strain is related to the ith strain and can induce cross-protection (that is if $j \sim i$ then $\gamma_{ij} \neq 0$). The parameters $1/\mu$ and $1/\sigma$ are, respectively, host life expectancy and average period of infectiousness, β is transmission rate. We refer to this model as Gupta's model. This simple model has been analysed in Gupta et al. (1998) and provided important insights into pathogen formation and the genetic organisation of strains.

To study the phenomenon of clustering we need to consider several levels of cross-protection. Whereas the original model implies only one level of cross-protection (γ if two strains are related, or zero if they are not) and neglects possible multiple infections by strains related to i. We relax these assumptions below to make the model more generally applicable, while striving to keep the model simple. We assume that the probability of cross-protection between strains i and j is γ_{ij} (that is, infection by the strain j reduces the probability that the host will be infected by the strain i by a factor γ_{ij}), and consider the barycentre of γ_{ij}, defined as

$$\Gamma_i = \left(\sum_{j\sim i, j\neq i} \gamma_{ij}\beta_j y_j\right) \Big/ \left(\sum_{j\sim i, j\neq i} \beta_j y_j\right). \qquad (2)$$

We replace the coefficient γ in the system (1) with the barycentre Γ_i. Substituting the barycentre Γ_i into (1) and using the variables $V_i = 1 - z_i$, $X_i = 1 - w_i$, $Y_i = \frac{\beta_i}{\mu} y_i$ and $\tau = \mu t$, we obtain the system

$$\begin{aligned}
\frac{\mathrm{d}V_i}{\mathrm{d}\tau} &= 1 - (1+Y_i)V_i,\\
\frac{\mathrm{d}X_i}{\mathrm{d}\tau} &= 1 - \left(1 + \sum_{j\sim i} Y_j\right) X_i,\\
\varepsilon_i \frac{\mathrm{d}Y_i}{\mathrm{d}\tau} &= ((1-\Gamma_i)V_i + \Gamma_i X_i - r_i) Y_i. \qquad (3)
\end{aligned}$$

Here $\varepsilon_i = \mu/\beta_i$ and $r_i = (\mu+\sigma_i)/\beta_i$. Obviously, $\Gamma_i \equiv \gamma$ for Gupta's model (when γ_{ij} is either γ, or zero).