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Modelling the spread of Bovine Viral Diarrhoea Virus (BVDV) in a managed metapopulation of cattle herds

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Abstract (172 words)

In numerous epidemiological models developed within a metapopulation framework, it is assumed that a single infected individual introduced into a patch infects the whole patch and that the proportion of infected individuals into infected patches is consistent over time and among patches. If this approach is relevant for rapidly-spreading pathogens, it is less appropriate for moderately-spreading pathogens, like the Bovine Viral Diarrhoea Virus (BVDV), characterized by a variability in within-patch prevalence. Our objective is to study the respective influence of neighbouring relationships and animal movements on the spread of BVDV in a managed metapopulation of 100 cattle herds. Infection dynamics is represented by two coupled stochastic compartmental models in discrete time: a within-herd and a between-herd models. Animal movements are mechanistically modelled. They largely influence the BVDV persistence, the prevalence in infected herds and the epidemic size. Neighbouring relationships only influence epidemic size. Whatever the neighbouring relationships, the infection does not persist in the metapopulation without animal movement between herds. The proposed model can be easily adapted for different herd contact structures.

Keywords: contact network, structured population, epidemic model, migration, pestivirus, livestock.

1. Introduction

Bovine Viral Diarrhoea Virus (BVDV) is a pathogen of major concern in Europe. BVDV infection is widespread among cattle herds (Houe, 1999). Of considerable economic impact (Houe, 2003), it is characterized by abortions or congenital deformities, induces milk production losses and growth delays, and increases occurrence of other diseases. As an example, the total annual losses were estimated in Denmark to US$ 20 millions in 1992 (Houe, 1999), while the annual incidence of acute infections was estimated to 34%. To limit BVDV spread and its consequences, control strategies are implemented in several regions in Europe (Greiser-Wilke et al., 2003; Lindberg et al., 2006). However, their efficiency is hard to evaluate or to compare to each other by field observations because no reference situations (without control) is generally available, and because observations on the long term should be performed, which is costly and sometimes unfeasible. Modelling is then a convenient approach to evaluate control strategies of BVDV spread. However, at a regional level, i.e. taking into account interactions between herds, no model of BVDV spread between cattle herds is available yet.

Between herds, BVDV spreads mainly through purchases of animals carrying the virus (equivalent to migration or movement in unmanaged systems) and through neighbouring relationships between infected and BVDV-free herds (Lindberg and Alenius, 1999). There are three types of animals carrying the virus. Two types are infectious animals: persistently infected (PI) immunotolerant animals shed the virus in large amounts during their whole life, whereas transiently infected (TI) animals shed the virus in low amounts during a few days (Tremblay, 1996; Houe, 1999). The third type consists of pregnant cows that have been infected and that may carry a PI foetus due to vertical transmission (Fray et al., 2000).

Such cows are immune and thus hard to detect by diagnostic tests (Lindberg et al., 2001). The probability to purchase an animal carrying the virus is directly related to the within-herd prevalence in the source herd and to the characteristics of the control strategies implemented (if some are implemented), such as detection tests which can be performed at purchases. If the characteristics of such tests are well known (Beaudeau et al., 2001; Baxi et al., 2006), the within-herd prevalence of infected animals is variable over time and among infected herds. Moreover, introducing an infected animal into a herd does not necessarily lead the infection to spread in that herd (Ezanno et al., 2008). Hence, infected herds heterogeneously contribute to the BVDV regional spread. In terms of control, it may lead to specific issues, as strategies efficiency might be largely influenced by the within-herd prevalence and its variability.

At a regional scale, a population of cattle herds forms a metapopulation, defined as a set of unstable local populations living each on discrete patches of habitat connected by migrants (Hanski, 1998). A metapopulation dynamics is based on a balance between patch extinction and subsequent patch recolonisation by dispersing individuals. This concept is well-known in ecology and genetics to study dynamics of fragmented populations and gene flow in heterogeneous landscapes (Grenfell and Harwood, 1997). Each metapopulation has its own contact structure. Four types of contacts can be distinguished: migrations or dispersal (an individual moves from one patch to another and does not come back to the initial patch), neighbourhood (individuals in patch *i* have contacts with individuals in patch *k* but no individual leaves its own patch), visits (an individual leaves its patch, reaches another one

and then comes back to its initial patch) and indirect contacts (individuals do not meet, the pathogen being transmitted by an inert or animal vector or by the air).

Recently, epidemiological models have been developed in this framework, taking into account infection dynamics of patches in addition to an extinction-recolonisation balance. In such an approach, each patch is a potential localization for a group of hosts. Hess (1996) was a precursor by conceptualising an epidemiological model based on the Levin's model: migrations of infected individuals were a source of infection for healthy populations. With such a model, the persistence of a metapopulation in the presence of a pathogen can be studied (Hess, 1996; Gog et al., 2002; McCallum and Dobson, 2002). Currently, this kind of models is often used to study pathogen spread and persistence in connected populations, particularly for rapidly-spreading animal diseases such as Avian Influenza (Le Menach et al., 2006). In this case, the infection dynamics is represented at the metapopulation level in a deterministic way without care about what exactly happens within each patch. It is thus assumed that introducing one infected individual into a patch is sufficient to lead to infecting this patch and that the prevalence of infection (proportion of infected individuals) in infected patches is consistent over time (the equilibrium is immediately reached) and among infected patches. If this argument seems adequate for rapidly-spreading pathogens, we can wonder what happens for moderately-spreading pathogens. For example, an infected individual with bovine tuberculosis can disappear long before infecting congenerics. In such a case, infectious statuses have to be defined at the individual level and the within-patch infection dynamics has to be modelled (Jesse et al., 2008). This approach is all the more relevant when heterogeneity in the within-patch infection process is assumed, either over time or among patches (Hess, 1996; Park et al., 2002; Cross et al.,

104 2005). If this kind of models better reflects the variety of situations, it is far more complex.
105 Nevertheless, a lot of major animal pathogens spread moderately, such as BVDV. When
106 studying the spread of such a pathogen, well-adapted epidemiological models have to be
107 developed.
108
109 The objective of this paper is to represent the spread of BVDV in an initially fully
110 susceptible metapopulation of cattle herds. The respective influence of animal movements
111 and neighbouring relationships on the regional BVDV spread and persistence is evaluated
112 using a modelling approach. Such an approach allows to better understand the dynamics of
113 this moderately-spreading, to test a wide range of situations and to evaluate the influence of
114 unobservable parameters.
115
116 **2. The modelling approach**
117 We consider a metapopulation of n small animal populations, each inhabiting a distinct
118 habitat patch. Patches are assumed to be connected by migrations of animals and by
119 neighbouring contacts between patches. Space is assumed to be homogeneous and
120 populations to all have the same number of neighbours.
121 Here we assumed that the within-patch pathogen spread varies among infected patches.
122 Actually, a newly infected animal can quickly disappear (mortality, recovery, migration to
123 another patch) or persist for a long time in a given patch. To take into account this
124 heterogeneity in the within-patch force of infection and the potential effect it may have on
125 the global infection dynamics at the metapopulation level, a within-patch model is coupled
126 with a between-patch model (Fig. 1).

Within a patch, a population can be structured into different groups with different contact structure. For example, young individuals of an age-structured population can be assumed neither to migrate nor to have neighbouring contacts. Such a population structure influences the within-population spread of pathogens (Keeling and Rohani, 2008) and should be accounted for to model the within-patch infection dynamics.

As populations are small, the model is stochastic. The resulting model is a patch-based model in discrete-time, the state of each patch at time t being defined by the number of animals per health status and per group at this time in the patch. For example, for a SIR (susceptible / infected / recovered) within-patch model in a population structured into groups, the local probability of infection in patch (or population) X in group l at time t depends on the within-group infection process and on the between-group probability of transmission. Assuming a frequency-dependent infection function, this can be written as:

$$p_l^X(t) = 1 - \exp\left(- \Delta \left(\frac{\beta_w I_l^X(t)}{N_l^X(t)} + \sum_{g \neq l, g \in x} \frac{\beta_b I_g^X(t)}{N_g^X(t) N_l^X(t)} \right) \right), \quad (1)$$

with β_w the within-group transmission rate of the infection between an infectious and a susceptible animal, β_b the between-group transmission rate, Δ the length of the time step, g a group other than group l also belonging to population X, $I_g^X(t)$ the number of infectious animals in group g in population X at time t, $N_g^X(t)$ the total number of animals in group g in population X at time t. The between-group transmission function takes into account both the influenced and the influencing populations. This is convenient in order to model indirect transmission, by contaminated material for example. In such a case, only a fraction of population encounters the contaminated material. Hence, the probability of infection per

individual depends on the size of the influenced population. Such an infection function has been proposed to model epidemics in highly mobile populations (Ögren and Martin, 2002), as well as for modelling the spread of a pathogen in a cattle herd (Ezanno *et al.,* 2007), which is typically structured into groups (feedlots, reproductive groups, etc.).

Between patches, the pathogen can locally spread by neighbouring contacts. This could be the case when patches of habitat are contiguous or when a common resource (such as a temporary pool) is used by several populations. The probability of infection of patch X by neighbouring relationships is assumed to depend on the prevalence of the infection in neighbouring populations and to be frequency-dependent:

$$P_n^X(t) = 1 - \exp\left(- \beta_n \Delta \frac{\sum_{Y \in \zeta_X} I^Y(t)}{N^X(t) \sum_{Y \in \zeta_X} N^Y(t)} \right), \quad (2)$$

with β_n the transmission rate between an infectious animal and a susceptible one belonging to neighbouring patches, ζ_X the set of neighbours of patch X, $I^Y(t)$ the number of infectious animals in patch Y at time t, and $N^Y(t)$ the total number of animals in patch Y at time t. As for the between-group within-population transmission, the proposed function takes into account the sizes of both the influenced and the influencing populations. Here again, only a fraction of the animals from a herd are influenced by infected animals from neighbouring herds at each time period. Contacts between neighbouring herds may involve for example uncontrolled movements of susceptible animals (escape) or contacts above the fence at pasture influenced by the available space. Hence, the function has to combine the

probability of encountering infected animals of the herd a ($k\frac{P_t^a}{N_t^a}$) and the probability for a susceptible animal in herd l to be in contact with it ($\frac{\beta_n}{k}\frac{1}{N_t^l}$).

Moreover, a global spread of the pathogen between patches is due to migrations of individuals. Here, explicit movements are modelled using a complete random network, i.e. animals from a patch can go to any other patches. Actually, in a small patch infected with a moderately-transmitted pathogen, the prevalence of infection can be low. The movement of a single individual can thus influence the infection dynamics in both source and destination patches, especially if the moving individual is the only infected one in its source patch. We assume that there is no infection during the migration process, i.e. migrants form a pool of individuals without any contact with other individuals or with each other (Fig. 1).

3. Application to BVDV spread between cattle herds

3.1. Main characteristics of BVDV infection

BVDV is a pestivirus which does not survive well in the environment (Tremblay, 1996). Direct contacts between animals are then required for transmission of the infection. Thus, animal purchases and contacts at pasture between animals of neighbouring herds (contact above the fence or pasture on common land areas) are the most important ways of introducing BVDV into a herd (Lindberg and Alenius, 1999). Potential introductions by people or equipment, inoculations during vaccination, artificial reproduction (sperm or embryos) or insects are assumed to have a negligible impact (Tremblay, 1996).

187 The virus can also be vertically transmitted. Foetuses infected in utero by their mother
188 infected between 40 and 125 days of pregnancy become persistently infected (PI) animals.
189 They shed the virus in large amounts during their whole life (Tremblay, 1996). Moreover,
190 PI dams give birth to PI calves. On the contrary, transiently infected (TI) animals have been
191 horizontally infected. They shed the virus in low amounts during a few days (Houe, 1999).
192 Afterwards, they are considered resistant for their whole life (Brownlie *et al.,* 1987). Their
193 epidemiological importance is generally considered to be weak except that transient
194 infection occurring during the first third of gestation can lead to the future birth of a PI calf,
195 the dam certainly becoming resistant.
196
197 *3.2. Within-herd model*
198 The within-herd model is described in details in Ezanno *et al*. (2007). It is a stochastic
199 compartmental model in discrete-time that represents the BVDV spread in a dairy herd.
200 The herd is structured in 5 groups of animals (calves, young heifers, heifers, lactating cows
201 and dry cows). Animals change groups function of their age and their physiological state.
202 The two kinds of infectious individuals are represented : transiently infected (T) and
203 persistently infected (P). A diagram of this model as well as the related equations are
204 published elsewhere (Ezanno *et al*., 2007).
205 Direct horizontal transmission occurs between PI or TI animals and susceptible ones of the
206 same group and between PI and susceptible animals of different groups. By extending
207 equation (1) to model the local probability of BVDV infection in population X for group l,
208 we have:

$$P_l^X(t) = 1 - \exp\left(-\Delta\left(\frac{\beta_w^P P_l^X(t)}{N_l^X(t)} + \frac{\beta_w^T T_l^X(t)}{N_l^X(t)} + \sum_{g \neq l,\ g \in x} \frac{\beta_b^P P_g^X(t)}{N_g^X(t) N_l^X(t)}\right)\right)$$

considering the same notations as in equation (1) and with β_w^P the within-group transmission rate for PI animals, β_w^T the within-group transmission rate for TI animals, β_b^P the between-group transmission rate only due to PI animals, $Z_g^X(t)$ the number of animals of status *Z* in group *g* in population *X* at time *t*, and $N_g^X(t)$ the total number of animals in group *g* in population *X* at time *t.*

3.3. Between-herd model

We consider a metapopulation of 100 dairy herds assimilated to patches with two ways of contacts between those patches: neighbouring contacts and animal purchases (comparable to between-patch migrations).

As observed in the field (Ezanno *et al*., 2006), each dairy herd buy a given number of heifers per year, the source herd being chosen randomly for each purchase. Animal purchases lead to a random network structure.

The neighbouring contact structure is stated initially and is kept identical over time and for all realizations of a given scenario. It is a symmetric structure (if A is B neighbour, then B is A neighbour). For each herd, neighbours are selected among all herds, without accounting for between-herd distances. As only a small region with a few herds is modelled, distance is not highly influential. Actually, pastures of a given herd can be anywhere in the modelled area and thus can be in the neighbourhood of any other herd. As a result, due to such a fragmented farming landscape, pastures of a given herd can be in the

neighbourhood of pastures of two herds which have no contact with each other (A is the neighbour of B and C, without B and C being neighbours). Hence, the chosen structure is not transitive. However, the model can be easily adapted to other contact structures, including a distance-dependent or transitive network structure, by initially specifying the matrix of neighbouring contacts.

Neighbouring contacts are assumed to occur from mid-March to mid-November. Only dry cows, heifers and young heifers over 6 months are grazing and thus may have neighbouring contacts. We assume that only PI animals shed the virus in sufficient amount to give rise to infection of their neighbours at pasture. By extending equation (2) to model the probability of infection of patch X by neighbouring relationships, we have:

$$P_n^X(t) = 1 - \exp\left(- \beta_n \Delta \frac{\sum_{Y \in \zeta_X} P_o^Y(t)}{O^X(t) \sum_{Y \in \zeta_X} O^Y(t)} \right)$$

considering the same notation as in equation 2 and with β_n the transmission rate between a PI animal and a susceptible one belonging to neighbouring patches, $P_o^Y(t)$ the number of PI animals at pasture in patch Y at time t, and $O^Y(t)$ the total number of animals at pasture in patch Y at time t.

3.4. Parameters and initial conditions

Initially, every herds are of the same size, being composed each of 85 animals (45 cows, 20 heifers and the associated young stock). The size varies over time but each herd cannot have more than 60 cows and/or 25 heifers, numbers above which cows or heifers randomly

leave the herd. Demographic parameters (birth, mortality, slaughter, achievement in AI) are the same for all herds. They are chosen to represent typical Holstein dairy herds (see Ezanno *et al.* (2007) for more details). For sake of simplicity, we assume that all herds introduce the same number of heifers per year and have the same number of neighbours. Because no information is available to rationalize the value taken for the rate of BVDV transmission at pasture, it is taken to be equal to the between-group transmission rate within a herd because both events are closely related. As a result, the within-group within-herd transmission rates are equal to 0.50 and 0.03 per day for the PI and TI animals, respectively. The between-group and between-herd transmission rates are equal to 0.10 per day (transmission only du to PI animals).

BVDV is initially introduced in a fully susceptible metapopulation by the purchase of a PI heifer in one herd. No re-introduction is further allowed.

3.5. Scenarii

Three neighbouring contact structures (0, 5 or 10 neighbours per herd) and five purchase intensities (0, 2, 5, 7 or 10 heifers yearly purchased per herd) are modelled to study their relative influence on the regional spread of BVDV, leading to a total of fifteen scenarii. The reference scenario is '5 neighbours per herd and 2 purchases per year per herd'.

For each scenario, 150 realizations are run, which is enough to stabilize model outputs (results not shown). We simulate the evolution of the system over a 15-year period. It has to be noted that studying such a managed system on a longer term will not be appropriate because herd structure and management obviously change on such a time scale.

3.6. Output

First, we observe the influence of stochastic events on the modelled system by comparing two almost extreme realizations of the reference scenario and the global average of the number PI animals over time in the metapopulation.

Second, we analyse the probability of persistence of the metapopulation infection (equal for each scenario at any time interval to the proportion of realizations for which the virus is still present in the metapopulation), the distribution of the metapopulation infection duration and the related probability of pathogen endemicity (assumed when the pathogen persists more than 10 years in the metapopulation), the mean number of infected herds over time in a metapopulation still infected, and the distribution over all realizations of the epidemic size in infected herds (cumulated number of herds that have been infected for at least one time interval).

4. Results

As the model is stochastic, the infection dynamics is variable both over time and among realizations for a given scenario. The infection can disappear in a few years or persist over a long time with a high number of persistently infected animals in the metapopulation (as shown for example for the reference scenario in Fig. 2). In the reference scenario, the prevalence of PI animals in the metapopulation reaches a pseudo-equilibrium equal to 8%.

The infection does not persist in the metapopulation when no animals are purchased (Fig. 3), whereas the probability of persistence is high and maintains over time when animals are purchased. The number of animals that are purchased does not influence the probability of

295 persistence, which is almost the same for 2 to 10 animals yearly purchased per herd (results
296 not shown).
297 Animal purchases also highly influence the duration of the metapopulation infection
298 (Fig. 4a). This duration is shorter without purchases (on average 4.6 years) than with
299 purchases (on average 10.8 years), whatever the number of neighbours. The median
300 duration increases with the number of purchased animals until reaching a maximum
301 duration (equal to the simulated period) after which increasing further the number of
302 purchased animals slightly decreases the median duration (here obtained for 10
303 purchases/year/herd). On the contrary, the neighbouring contacts do almost not influence
304 this output. The related probability of pathogen endemicity is lower than 6% when no
305 animal is purchased, whereas it is larger than 50% when animals are purchased (Fig. 4b),
306 whatever the number of animals purchased and the number of neighbours per herd.
307 Without purchase, the mean number of infected herds in an infected metapopulation
308 decreases to reach extinction on average in 10 years, without any influence of neighbouring
309 contacts (Fig. 5). On the contrary when animals are purchased the average number of
310 infected herds in an infected metapopulation reaches an pseudo-equilibrium, the herd level
311 prevalence being almost equal to 5%. The presence of neighbours slightly increases this
312 prevalence (Fig. 5).
313 Both increasing neighbouring contacts and increasing purchases increase the herd epidemic
314 size (Fig. 6). The median epidemic size only slightly increases with the number of
315 neighbours per herd. However, the number of realizations showing an extreme epidemic
316 size (queue of the distribution) increases with the number of neighbours per herd (Fig. 6).
317 Moreover, until 7 animals are purchased per herd per year, the more animals are purchased,

the larger is the epidemic size. As the median infection duration, the epidemic size slightly decreases for a large number of purchases (10 purchases/year/herd).

5. Discussion

5.1 The modelling approach

A stochastic compartmental model in discrete time is proposed, which couples within- and between-patch infection dynamics in a metapopulation framework. Because the model is stochastic, different evolutions of the system over time for a given scenario are possible: the infection can early disappear or persist with a variable number of infected patches and infected individuals. This type of dynamics is important for pathogens which spread moderately in a heterogeneous way, especially in small-size patches in which stochastic events have a major impact (Jesse *et al.,* 2008). However, for such realistic a model, the running time becomes important. Concerning BVDV, it has been shown that the herd structure largely influences the pathogen spread within a herd (Ezanno et al., 2008). Therefore, the within-herd infection and population dynamics should be explicitly modelled. Furthermore, the between-patch contact structure is related to both neighbouring relationships and mechanistically modelled individual migrations. In order to clearly evaluate the effect of both these types of between-patch contact on pathogen spread and persistence, independently of other possible causes of persistence, no reintroduction of the virus in the metapopulation is allowed. Accounting for an external source of infection would have largely contributed to the pathogen persistence (e.g. Fromont et al., 2003; Gog et al., 2002), and would have been appropriate if a pathogen surviving in the environment had been modelled. Actually, for such indirectly transmitted pathogens, a delay may appear

between environment contamination and subsequent animal infection, which can occur even if no infected animal is present. However, in case of directly transmitted pathogens, it would have led to quite an artificial persistence of the pathogen. For the model to be extended to the case of indirectly transmitted pathogens, the transmission function should be modified and a compartment stating the level of environment contamination over time should be added (e.g. in livestock pathogens within a managed herd, Lurette et al., 2008).

In addition, the way subpopulations influence each other is generally modelled with a frequency-dependent function of the form $\lambda_i = \sum_{j=1}^{j=n} \beta_{ij} \frac{I_j}{N_j}$, with β_{ij} the transmission rate between subpopulation i and j, I_j the number of infected individuals in subpopulation j and N_j the total number of individuals in subpopulation j. If such a function has the convenient property of simplifying in case of just one subpopulation to the function of the unstructured model, it seems inappropriate when subpopulations greatly differ in size (Ogren and Martin, 2002). In case of travelling between subpopulations, the fraction of travellers from the source population has to be taken into account as well as the proportion of infected individuals in the destination population. Ogren and Martin (2002) propose the following function: $\lambda_i = \sum_{j=1}^{j=n} \beta_{ij} \frac{1}{N_i} \frac{I_j}{N_j}$, with $\beta_{ij} = \beta M_{ij}$, M_{ij} being the number of travellers between subpopulations i and j. Such a function takes into account the sizes of both the influenced and the influencing populations. In case of managed herds, herd sizes vary among herds. Moreover, not all the animals from a herd are influenced by infected animals from neighbouring herds at each time period. Hence, such a function appears to be appropriate to model the between-herd transmission when direct contacts between animals are involved.

In the absence of knowledge on the intensity of contacts over the fence at pasture, the between-group transmission rate is assumed to be the same within-herd and between-herd. However, within a herd, between-group transmission involves indirect contacts like contaminated equipments, whereas between herds, direct contacts are concerned during which transmission is frequent. This can lead to underestimate the probability of infection at pasture.

The neighbouring contact structure is a symmetric structure but not a transitive one (even if A is the neighbour of B and C, B and C have not a higher probability of being neighbours). It is kept identical over time and for all realizations of a given scenario. As only a small region with a few herds is modelled, distance can be assumed not to be highly influential. In addition, in farms, pastures are often scattered in the countryside and sometimes located far from the farm. Hence, even if A has a pasture contiguous to one of farm B and another contiguous to one of farm C, B and C are likely not to have neighbouring pastures. As a result, we do not represent space as continuous or as a grid made of contiguous cells of habitat, but place our modelling work in the metapopulation framework. In such a framework, moreover, no edge effect are encountered as space is not explicitly modelled. In contrast, in ecology, patches can be spatially aggregated in clusters (Matthews *et al.* 2003; Favier et al., 2005), and distance may play a major role in pathogens spread (Keeling et al., 2001), as for example in vector-borne diseases (Tran and Raffy, 2006). Therefore, for areas of larger sizes or for a biological system explicitly related to space, the proposed model should be extended to represent geographical clusters, i.e. sets of patches in which neighbourhood contacts are more frequent, which could be more spatially realistic. Such an

384 explicit representation of space can be easily incorporated in our model by modifying the
385 neighbouring matrix.
386 In our approach, we consider a homogeneous exposure to infection at pasture due to
387 neighbouring relationships. We assume that all individuals from a given patch are
388 consistently exposed to infectious individuals of all neighbours. This assumption is
389 appropriate if contacts between individuals from neighbouring patches occur because
390 individuals all use a common resource such as water, food or cover, because of random
391 local movements of individuals among neighbouring patches, or because of frequent
392 changes in neighbours. Here, we are in this latter case, pasture turn-over leading to
393 homogenizing infection exposure at pasture. However, in some other cases, the contact
394 related to neighbouring relationships may be heterogeneous, some specific groups of
395 individuals from a patch meeting some specific groups from other patches. This is
396 particularly true concerning wild structured populations, for example because of sexual
397 segregation such as in deer (Bonenfant et al., 2004) which leads to a heterogeneous contact
398 structure between males and females.
399
400 Like in the island model of Hess (1996), animal movements are random in the proposed
401 model, such that each patch can be reach from any other patch. This assumption is realistic
402 here as more than 90% of the pairs between dairy herds which do not have any fattening
403 unit on a given year are not renewed the next year (Ezanno *et al*., 2006). Hence, there is no
404 preference in animal exchanges. However, in some managed populations, herds can sell
405 (buy) animals preferentially to (in) given herds. Some authors thus consider that individuals
406 migrate between patches function of the localization (Matthews *et al.* 2003) or the carrying

capacity (Fulford *et al.* 2002) of patches. Such a random pattern in animal movements can be adapted to more specific networks by specifying the purchase / movement matrix: for each herd, a set of herds is defined in which animals can be purchased. This would improve the model realism when animal movements are not random (Keeling and Eames, 2005).

5.2 BVDV spread and persistence

The model has been applied to modelling the spread of BVDV in a bovine metapopulation in order to study the persistence of such a directly transmitted and moderately-spreading pathogen. When only neighbouring relationships are involved in the between-herd contact structure, the infection does not persist within a metapopulation of 100 dairy herds without fattening units. Purchases are required. However, even with few animal movements and assuming no further reintroduction of the pathogen after the initial contamination of the metapopulation, the infection highly persists over time, which is coherent with field observations. In Brittany (France) for example, BVDV infection is assumed to be endemic and even dairy herds introducing almost no animal may be infected (Joly, pers. comm. 2007).

A non linear relationships between the median epidemic duration and animal movements has been recently highlighted using a stochastic SIR model in metapopulation (Jesse *et al.,* 2008). The median epidemic duration first increases with an increasing movement rate, then decreases for intermediate values until the movement rate becomes large enough to permit an endemic behaviour of the infection. Here, we observe the same tendency using a far more complex model applied to a realistic biological system and pathogen, even for only very few between-herd animal movements.

In the model, the prevalence of infected herds within the metapopulation is lower than 6%. This is consistent with field observations made in Brittany (France): before control strategies have been implemented, around 10% of the dairy herds (with and without fattening units) had at least one persistent infected animal (Joly, pers. comm. 2007). Moreover, in most infected herds, the prevalence of infected individuals is low, which could have consequences on virus screening. A large number of animals should be tested before ensuring an area to be BVDV-free. In the model, if the average herd level and individual level prevalences are low, they highly vary among realizations of a given scenario. This is consistent with literature: from 37 to 100% of the herds of a country could contain seropositive animals (Houe, 1999). Hence, our model catches the heterogeneity in the BVDV dynamics in a realistic way.

5.3 Application to BVDV control

We study how neighbouring contacts and animal movements may influence the dynamics of a moderately spreading pathogen in a metapopulation, applied to BVDV spread among dairy herds. Our model shows that animal movements highly contribute to the persistence of the infection and to the herd level prevalence. Without any purchase, the average number of infected herds in an infected metapopulation decreases and extinction may be reached in less than 10 years, whereas only few animal movements are needed to lead the infection to persist. However, animals of any health states are allowed to be exchanged between herds, whereas control strategies may be implemented in the field to reduce the risk of introducing infected animals within uninfected herds. In fact, preventing re-introduction of the infection in free herds because of movements of animals is one of the central elements of control

453 strategies (Lindberg *et al*, 2006). This can be achieved by defining herd status towards
454 BVDV and by introducing trade regulations for such certified herds: the latter have to buy
455 animals only in herds of equivalent or better status. Testing individuals before purchase is
456 another way to prevent from introducing PI animals. It seems therefore valuable to further
457 evaluate such strategies using a modelling approach, especially in the case of endemic
458 infection. In particular, whereas neighbouring relationships have been shown here to only
459 slightly influence BVDV epidemic size, we can wonder if their influence will change when
460 certification of herds or tests on purchased animals will be systematically implemented.
461

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467

468 **7. Conflict of interest statement**

469 None.
470

471 **8. References**

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553 **Figure legends**

554 **Figure 1:** Model diagram for a SIR (susceptible/infectious/recovered) infection dynamics
555 within patch x structured into juveniles (group 1) and adults (group 2), accounting for
556 infection within and between groups and for between-patch migrations, with a the mean
557 juvenile stage duration, b the birth rate, $1/\gamma$ the mean infectious period duration, μ the
558 mortality rate, p_1^x the infection rate in age class l (l = 1 or 2) in patch x, P_n^x the infection
559 rate by neighbouring contacts in patch x, m_{in} and m_{out} the migration rates into and from a
560 patch. Migrants form a pool of individuals (Z_l^m for migrants in state Z and group l) having
561 no contact with each other, mimicking a complete random network.

562 **Figure 2:** Influence of stochastic events on the number of persistently-infected (PI) animals
563 in the metapopulation over time, as shown by two extreme realizations (thin black and grey
564 lines) of the reference scenario (5 neighbours and 2 animals purchased per herd per year)
565 compared to the average over 150 realizations (bold line).

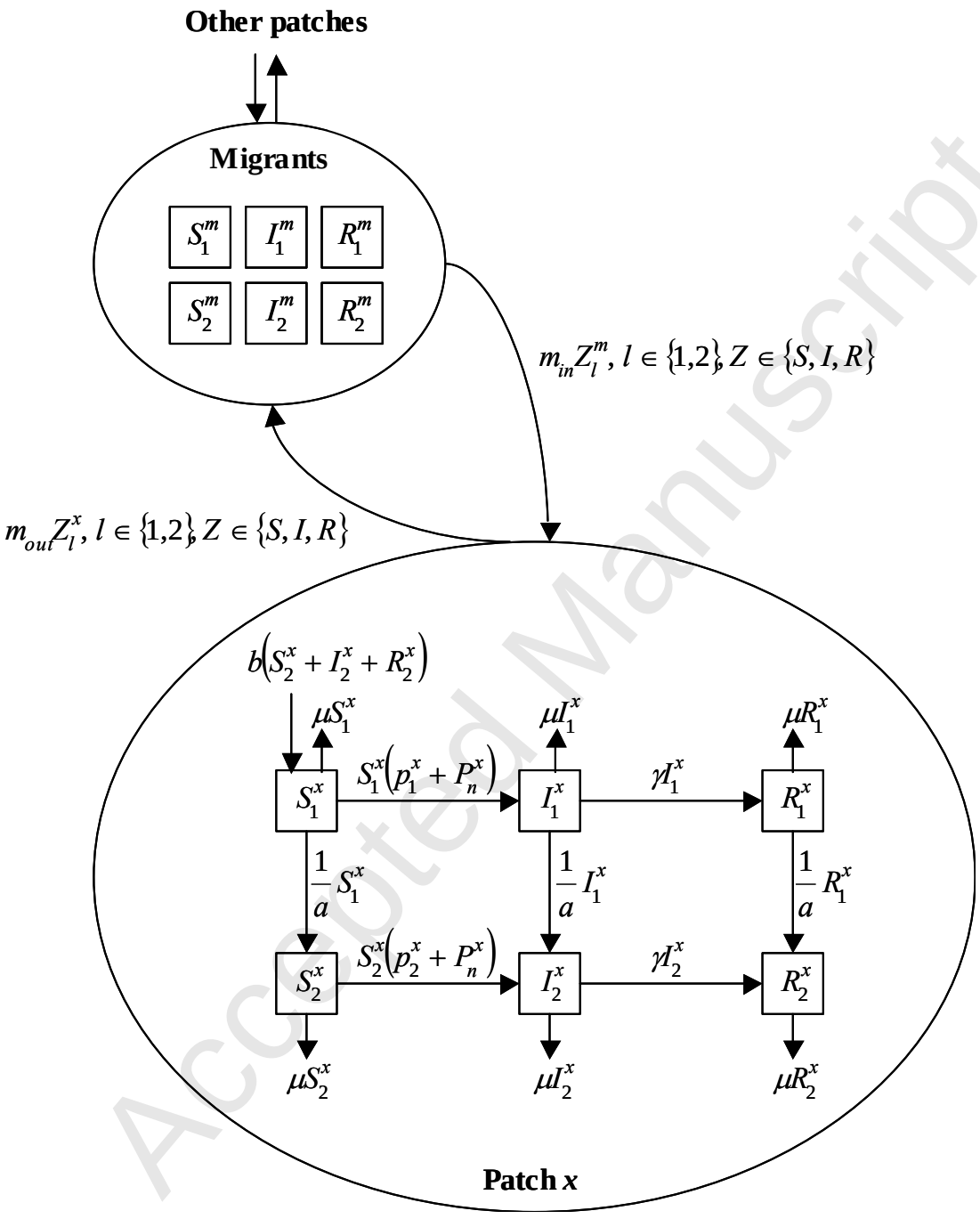
566 **Figure 3:** Probability of infection persistence in the metapopulation according to the
567 number of neighbours per herd, without purchase vs. with 5 animals purchased per herd per
568 year.

569 **Figure 4:** Infection duration of the metapopulation: (a) distribution of the duration (in
570 years) according to the number of animals purchased per herd per year and to the number of
571 neighbours per herd (–: median; +: average; □: percentile 0.25 to 0.75; O: lowest and
572 highest values; -: percentile 0.10 and 0.90); (b) probability of endemicity defined as the
573 proportion of realizations showing an infection duration longer than 10 years.

574 **Figure 5:** Average number of infected herds in a metapopulation still infected according to
575 the number of neighbours per herd, without purchase vs. with 5 animals purchased per herd
576 per year.
577 **Figure 6:** Distribution of the herd epidemic size (cumulative number of infected herds over
578 the simulation period) according to the number of animals purchased per herd per year and
579 to the number of neighbours per herd (–: median; +: average; □: percentile 0.25 to 0.75; O:
580 lowest and highest values; -: percentile 0.10 and 0.90).
581

581 **Short title for page headings:** BVDV spread in a bovine metapopulation

582

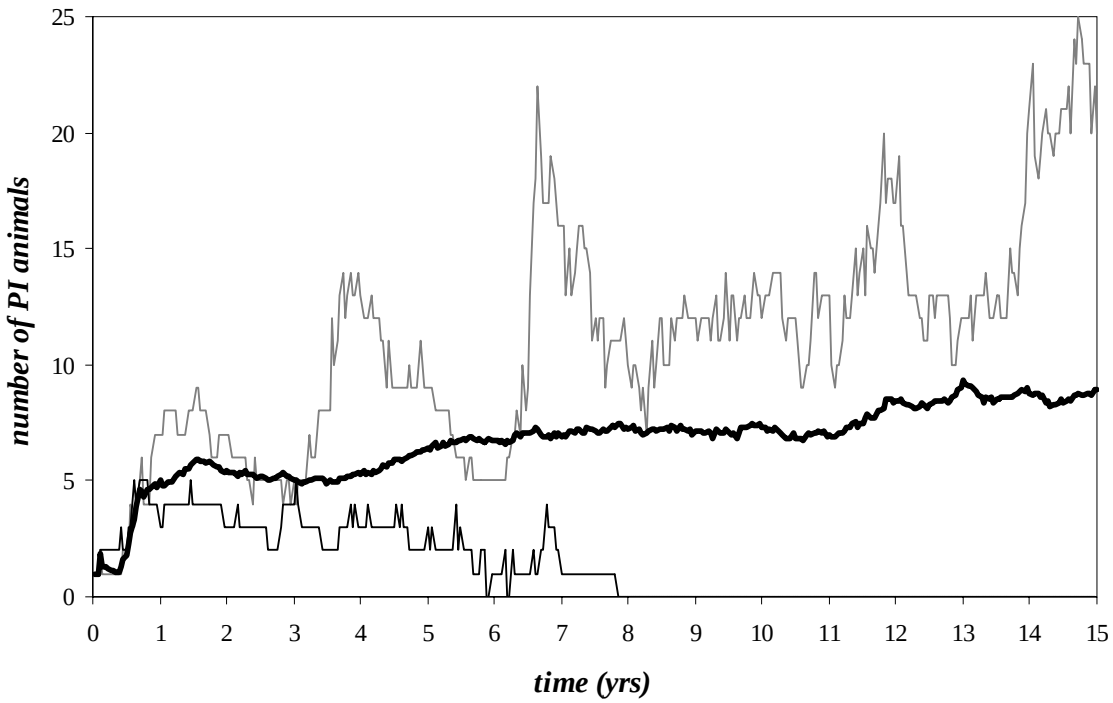


582

583

584 Figure 1

585



585

586 Figure 2

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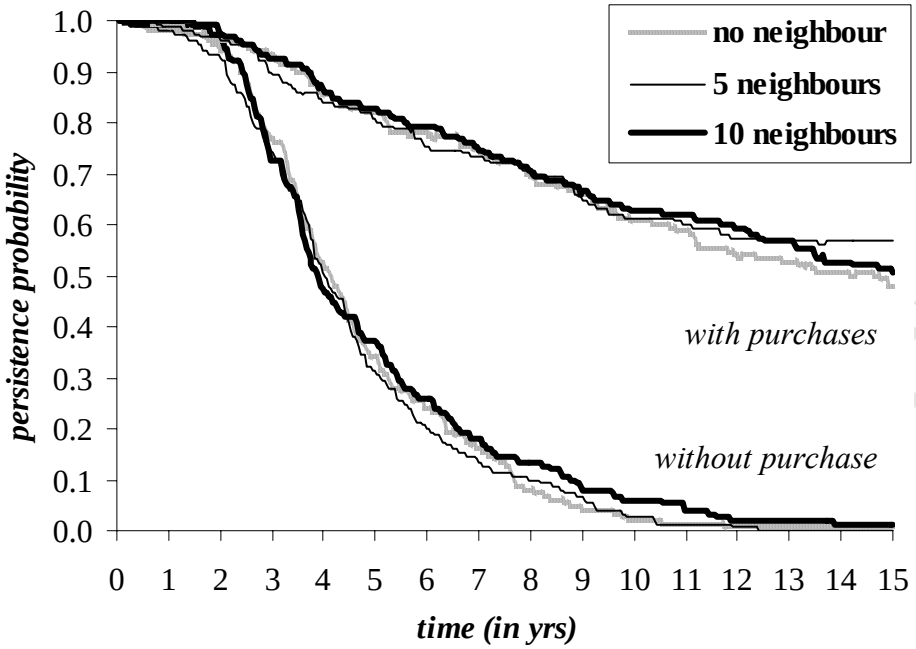

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588 Figure 3

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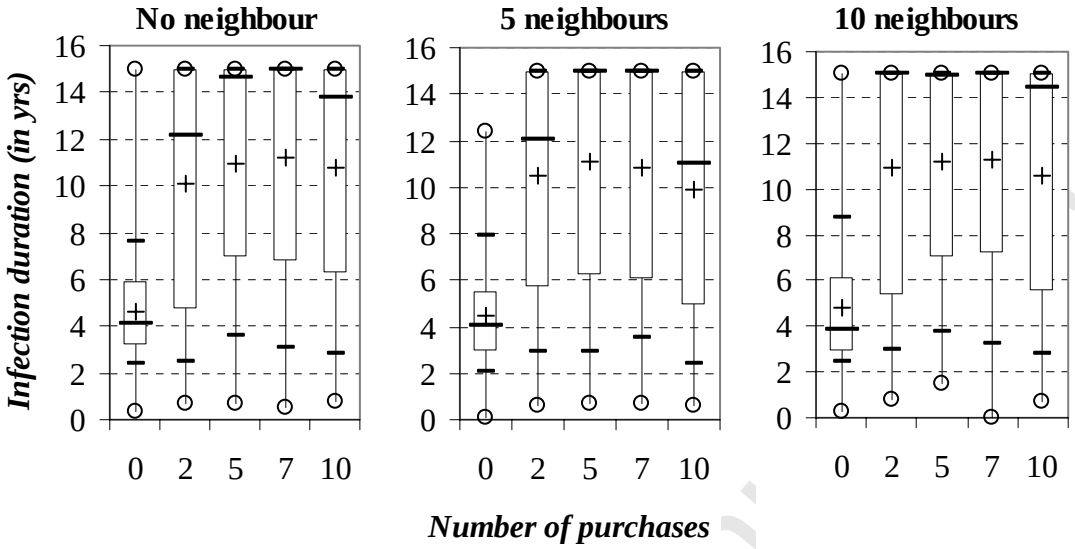
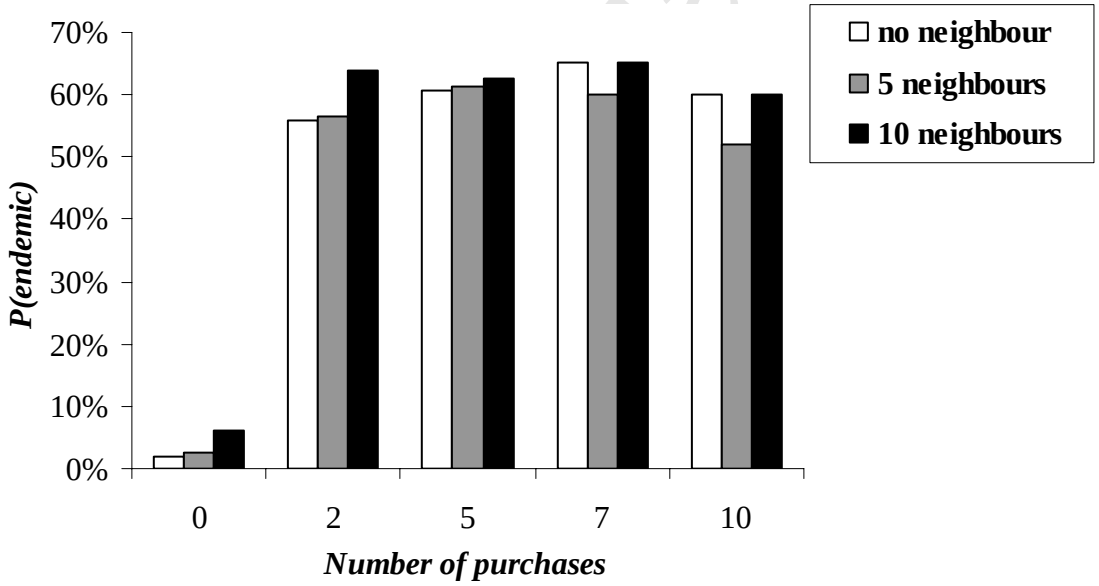


589 (a)



590 (b)

591 Figure 4

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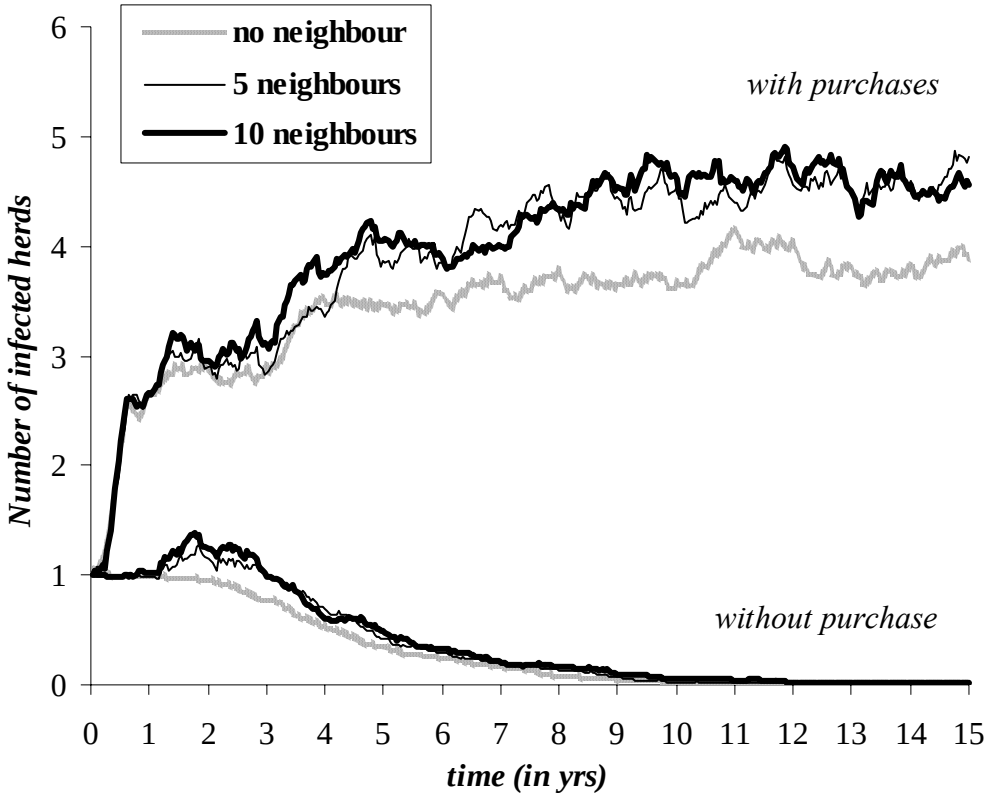

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593 Figure 5

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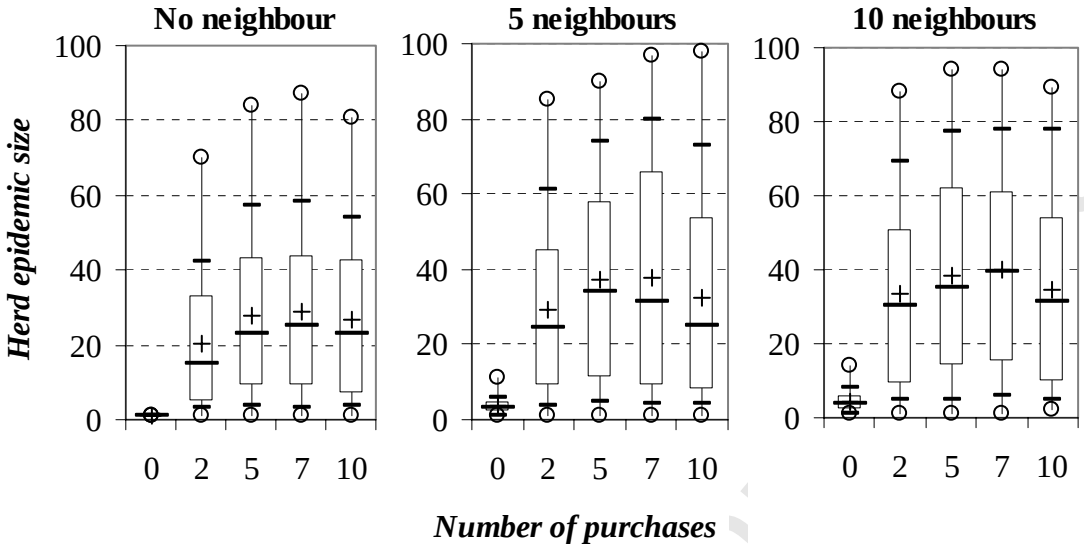

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595 Figure 6