<u>Parallel Session</u>

Ecology IV

ANALYSIS OF THE CATTLE TRADE NETWORK IN FRANCE TO INFORM EPIDEMIOLOGICAL RISK

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Keywords: Dynamical network, Graph theory, Epidemiology.

Effective control of livestock infectious diseases is a major issue for sustainable animal farming and competitive agri-food chains, as well as for public health. Livestock trade movements is one of the most important pathways for pathogen transmission between holdings. Therefore, it is crucial to understand and be able to predict the temporal evolution of the network of animal movements, and assess the risk related to epidemics unfolding on this network.

Here, we focus on the study of cattle trade network in France, based on a fully detailed dataset spanning over more than ten years (2005-2015), extracted from the French database of cattle movements, which records life histories of all French cattle from birth to death. These data, formalized by a time-varying network (with holdings as nodes and commercial transactions as links), were analyzed using tools from graph theory and cluster analysis. Whereas this kind of analysis is often straightforward for static networks, it becomes highly challenging when dealing with time-varying networks, such as animal trade networks, which are, in addition, of high dimension (more than 200,000 active nodes and more than 8,000,000 animal movements per year in our data).

Results on two aspects, the analysis of the temporal dynamics of cattle movements and the assessment of the associated epidemiological risk, will be presented. On the first axis, we focus on the characterization of the temporal stability of the main descriptors of cattle trade networks and the fidelity over time of transaction partners. On the second axis, proxies for pathogen spread, such as the reachability ratio (accounting for the average number of nodes to be reached during an outbreak, using time-respecting paths in the network), are provided. This second analysis was performed for various assumptions on the transmission probability associated to each link and epidemiological parameters (such as the duration of the infection in each node), and computed using efficient algorithms of network exploration.

A STOCHASTIC SIR MODEL FOR CATTLE DISEASES ON A POPULATION GRAPH

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Keywords: Multitype SIR model with demography, Continuous-time multitype branching processes, Major outbreak probability, Epidemic final size, Endemicity.

Animal trade movements are a major pathway of epidemic propagation between holdings at large spatial scales. The large amount of data collected by European authorities over the last two decades makes it possible to track the position over time of every single animal within national territories, allowing to design and calibrate predictive models for pathogen spread.

We define and study an open stochastic SIR model on a graph (with vertices standing for cattle holdings and edges for trade routes between them) in order to describe the spread of an epidemic on a cattle trade network with epidemiological and demographic dynamics occurring over the same time scale. Population entries in various nodes are assumed to be density-dependent with a constant component, the amplitude of which is proportional to a scaling factor determining the overall size of the population process. More specifically, the whole demographic process is a continuous-time multitype branching process with constant immigration. In addition to that process, we consider one-level mixing SIR dynamics, that is, a SIR stochastic model is defined within each node and pathogen spread only occurs through contacts between infectives and susceptibles that are present in the same node. Displacement of infectives between nodes allows for the spread of infectives at the metapopulation level. The SIR processes are assumed to be driven by Poisson processes that are independent from those determining demographics.

Standard branching approximation results for the epidemic process are given along with a numerical computation method for the probability of an epidemic major outbreak. This procedure is then illustrated numerically: we use real data on 2015 cattle trade for the French department of Finistère to set our demographic parameters, and choose epidemiological parameters corresponding to the fast-evolving bovine Foot-and-Mouth Disease. Virtually slowing down the course of the epidemic by dividing the latter parameters by a fixed quantity — and hence obtaining the same time scale for epidemiological and demographic processes

— yields higher discrepancies between the major outbreak probabilities of infections starting in various nodes.

The stochastic model we describe is associated with a deterministic dynamical system that may admit an endemic equilibrium – that is, a steady state associated with a positive number of infectives. Our main result consists on exhibiting an exponential lower bound for the total size of the epidemic in the case where such an endemic equilibrium exists and is globally asymptotically stable, using the Freidlin-Wentzell theory of large deviations from a dynamical system. This differs from closed population models results that predict a mean epidemic final size proportional to the population scaling parameter. It illustrates the role of population renewal in allowing infections to persist over large time scales in a metapopulation connected through an explicit network with a complex structure.

USING TEMPORANK TO IDENTIFY CENTRAL NODES IN CATTLE TRADE NETWORKS

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Commercial exchanges of cattle are an important propagation vector of livestock disease. Hence, network analysis of cattle trade networks can help understand the mechanics at work behind empirical cattle trade data. Crucially, node centrality measures are used to identify the nodes (markets or farms) that are most important in the transmission chains of infectious disease. However, an important feature of cattle trade networks is their variability over time, commercial links being extremely volatile ([3]). Thus, methods taking temporality into account are needed, in order to correctly identify possible transmission chains (pathogens can only spread through links that occur successively). In this work, we present the first application of temporal PageRank methods to cattle trade networks.

Temporal networks are networks in which each edge $e = (x, y)$ has an associated timestamp $t \geq 0$. They can be thought of as a sequence of static graphs $(\mathcal{G}_0, \mathcal{G}_1, \mathcal{G}_2, \dots)$. The classical PageRank centrality measure was extended to the framework of temporal networks ([2]) by considering the behavior of random walks on the graph that can, at time t, only follow edges with timestamp t or stay in the same place with probability $q \in (0, 1)$. For a given temporal network $(\mathcal{G}_1, \dots, \mathcal{G}_T)$, the TempoRank then corresponds to the stationary density of such random walks on the network with periodic boundary conditions defined by $(\mathcal{G}_1, \dots, \mathcal{G}_T, \mathcal{G}_1, \mathcal{G}_2, \dots)$. In order to circumvent the assumption of strong connectivity that is sufficient for a non-trivial stationary measure to exist, we add a random teleportation element that guarantees the existence of a temporal PageRank vector.

We implemented the TempoRank algorithm on a dataset describing cattle trade in France from 2005 to 2009, involving 53 million movements between 274,000 holdings [1]. These movements were sampled daily, which leads to a temporal network representation of this data comprising 1826 one-day snapshots. The holdings included are of three distinct types : farms, assembly centres and markets. The last two are much less numerous than the first (about 1,250 and less than 100, respectively, compared to more than 272,000 farms). We were able to use advanced sparse matrix manipulation tools from the PETSc package to compute the TempoRank scores directly from the definition.

Our work shows that the TempoRank centrality measure can be efficiently computed even for large-scale networks such as the one present in this study. We also explore the relationship between the TempoRank and classical centrality measures such as temporal betweenness and closeness or temporal Katz centrality. Finally, we show how TempoRank scores can be used to prevent transmission of infectious diseases spreading on contact structures such as cattle trade networks.

References

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INFERENCE IN A METAPOPULATION MODEL VIA A COMPOSITE-LIKELIHOOD APPROXIMATION

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Keywords: Parameter estimation, Composite likelihood, Mechanistic epidemic model, Metapopulation model, Mycobacterium avium subsp. paratuberculosis.

Processes related to the spatio-temporal spread of pathogens in metapopulations are most often partially observed, and available data are usually incomplete, spread over time and heterogeneous. Moreover, the representation of this type of biological systems often leads to complex models. In this case, classical inference methods (i.e. maximum likelihood) are not usable because the likelihood function can not be specified. Bovine paratuberculosis (agent *Mycobacterium avium* subsp. *paratuberculosis - Map*) is a worldwide enzootic disease of economic importance whose screening in the field is difficult due to its long incubation period and the low sensitivity of routine diagnostic tests.

Our objective was to estimate key parameters of a multiscale dynamic model of *Map* spread from a longitudinal and spatial dataset collected in Brittany (Western France), using a specific approach taking into account accurately the characteristics of the census data, and to provide additional knowledge on the propagation of *Map*.

Our approach is based on a stochastic mechanistic model of Map spread between dairy herds through animal trade movements. Comprehensive data on cattle movements in 12,857 dairy herds in Brittany and partial data on animal infection status (2,013 herds sampled from 2005 to 2013) were available. Inference was performed with a Monte-Carlo approximation of a composite likelihood coupled to a numerical optimization algorithm (Nelder-Mead Simplex-like). The six estimated key parameters of this model are: (i) the proportion of initially infected herds, (ii and iii) their infection level (distribution of within-herd prevalence), (iv) the probability of purchasing infected cattle from outside the metapopulation, (v) the indirect local transmission rate, and (vi) the sensitivity of the diagnostic test.

Empirical identifiability was verified on simulated data. The optimization algorithm converged after appropriate tuning. Point estimates and profile likelihoods indicate a very large

proportion (¿ 0.80) of infected herds with a low within-herd prevalence on average at the initial time (2005), a low risk of introducing an infected animal from outside (0.10) and a low sensitivity of the diagnostic test (0.25).

Estimations of previously unknown key parameters provide new insights on Map spread at the regional scale, mainly showing a high prevalence in the number of infected herds, in agreement with qualitative opinions of experts. These estimates of previously unknown parameters provide new insights on Map status in Western France.

The inference framework could easily be applied to datasets from other regions concerned by paratuberculosis and adapt to estimate key features of other spatio-temporal infection dynamics, most often imperfectly observed, especially for long-lasting endemic diseases. It is of particular interest when ABC-like inference methods fail due to difficulties in defining relevant summary statistics.

USING FIELD AND EXPERIMENTAL DATA TO ESTIMATE KEY EPIDEMIOLOGICAL PARAMETERS TO DECIPHER PRRSV EPIDEMIOLOGY

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The outputs of epidemiological models are strongly related to the structure of the model and input parameters. The latter are defined by fitting theoretical concepts to actual data derived from field or experimental studies. Such data were recently analyzed to gain insights on the epidemiology of porcine reproductive and respiratory syndrome (PRRS), a disease with significant economic impact for pig producers throughout the world. Although vaccination with modified-live vaccines is a current practice in pig farms, with positive outcomes on clinical expression, the results in terms of transmission are more contrasted.

We first aimed at characterizing the kinetics of post-vaccine antibodies against PRRS virus in vaccinated sows. Twenty-two serological profiles were fitted to a Wood's function using a Bayesian approach. Individual projections allowed for the evaluation of antibody waning distribution according to the time post-vaccination (26.5 weeks). MDA kinetics from piglets with maternally derived antibodies (MDA) was also characterized from a longitudinal dataset including 360 individual up to 14 weeks of age. A nonlinear mixed effect model assuming an exponential decay of antibody titers was used. The initial serological titer $A_0(1.9; SE\ 0.34)$ was found positively correlated with the levels of antibodies of the dams and the decay rate r was estimated to $0.33d^{-1}(SE\ 0.07)$. Based on individual projections, the average duration of passive immunity was estimated to 4.8 weeks.

An experimental study was then developed to analyze how the interference between Maternally Derived Neutralizing Antibodies (MDNA) and vaccination, proved in a previous study [1], affect the transmission of PRRS virus in vaccinated piglets. Fifty-six conventional pigs were selected and grouped according to their MDNA statuses at one weeks of age. Two weeks later, they were transferred in Anses biosafety level 3 animal facilities in pens containing four animals with similar serological statuses. Eight groups of four animals were vaccinated with a modified live vaccine, half of which were MDNA-positive. Two groups were kept unvaccinated for each MDNA status. Finally, in each group, two pigs were intranasally inoculated with a field isolate of PRRS virus, 4 weeks after vaccination. All pigs were monitored twice a week up to day 42 post-challenge through blood sampling, to follow

the transmission events to contact penmates. The latency period and the transmission rate were estimated depending on the vaccination and MDNA status of the animals. Vaccination of MDNA-negative animals was found to halve the transmission rate when compared to unvaccinated animals ($\beta_{A_-V_+} = 0.15[0.07 - 0.29]$ versus $\beta_{V_-} = 0.32[0.14 - 0.68]$). In contrast, the transmission was found the highest in the groups of animals being MDNA-positive and vaccinated ($\beta_{A_+V_+} = 0.44[0.18 - 1.76]$).

A strong interference was evidenced between vaccine and MDA decreasing the benefit of vaccination in terms of transmission. The initial level of MDA in piglets was found correlated with the antibody level in their dams, found maximal between week 5 and week 9 post vaccination . Based on the distribution of maternal immunity waning probability, 90% of piglets would be seronegative at 10 weeks of age. Altogether, these results may help designing strategies optimizing the vaccination efficiency in sows and growing pigs.

References

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