

1 Past and future perspectives on mathematical models of tick-borne pathogens.

2 Norman, R.A.<sup>1</sup>, Worton, A.J.<sup>2</sup> and Gilbert, L.<sup>3</sup>

3 1. School of Natural Sciences, University of Stirling, Stirling FK9 4LA

4 2. Division of Computing Science and Mathematics, University of Stirling, Stirling, FK9  
5 4LA

6 3. The James Hutton Institute, Craigiebuckler, Aberdeen, AB15 8QH

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9 Corresponding author: Rachel Norman, School of Natural Sciences, University of Stirling,

10 Stirling FK9 4LA. Telephone: 01786 467466. Fax: 01786 464551. Email:

11 [r.a.norman@stir.ac.uk](mailto:r.a.norman@stir.ac.uk)

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13 Summary

14 Ticks are vectors of pathogens which are important both with respect to human health and  
15 economically.

16 They have a complex lifecycle requiring several blood meals throughout their life. These  
17 blood meals take place on different individual hosts and potentially on different host species.  
18 Their lifecycle is also dependent on environmental conditions such as the temperature and  
19 habitat type.

20 Mathematical models have been used for the more than 30 years to help us understand how  
21 tick dynamics are dependent on these environmental factors and host availability.

22 In this paper we review models of tick dynamics and summarise the main results. This  
23 summary is split into two parts, one which looks at tick dynamics and one which looks at tick  
24 borne-pathogens.

25 In general, the models of tick dynamics are used to determine when the peak in tick densities  
26 is likely to occur in the year and how that changes with environmental conditions. The  
27 models of tick borne pathogens focus more on the conditions under which the pathogen can  
28 persist and how host population densities might be manipulated to control these pathogens.

29 In the final section of the paper we identify gaps in the current knowledge and future  
30 modelling approaches.

31

32 Keywords:

33 Tick-borne pathogen, mathematical model, Louping ill, Lyme disease.

34 1. INTRODUCTION

35 Ticks are the most important vectors of zoonotic disease-causing pathogens in Europe,  
36 transmitting the tick-borne encephalitis (TBE) complex of viruses, *Anaplasma*  
37 *phagocytophyllum*, *Babesia* and *Rickettsia* species and *Borrelia burgdorferi* sensu lato, the  
38 complex of bacteria that cause Lyme borreliosis, amongst others. *Ixodes ricinus* L. ticks are  
39 particularly implicated in pathogen transmission because they are almost ubiquitous across  
40 Europe and are generalist feeders, which allows for pathogen transmission among different  
41 host species. *I. ricinus* are increasing in number and range in many parts of northern Europe  
42 (reviewed by Medlock et al. 2013).

43 In any given geographical region tick population dynamics are dependent on a number of  
44 biotic and abiotic factors including the density of different host species, and other factors that  
45 influence survival and activity such as temperature and humidity and vegetation types, the  
46 latter of which provide habitats for different hosts and create different microclimates.

47 Mathematical models have been used extensively to predict the dynamics of tick populations  
48 under different conditions including climate change. However, high tick densities do not  
49 necessarily mean high prevalence or risk of tick-borne pathogens, since this is dependent not  
50 only ticks but also competent transmission hosts. Therefore, models have also been used to  
51 predict the tick-borne pathogen dynamics and the theoretical effectiveness of different tick-  
52 borne pathogen control methods under different environmental or management scenarios. In  
53 this paper we will review the use of those models for different systems, summarise they key  
54 results in different contexts and discuss possible future directions of mathematical modelling  
55 of tick-borne pathogens.

57           2. MATHEMATICAL MODELS OF TICK POPULATION DYNAMICS.

58    Although there are a number of different tick species globally this review will focus on *I.*  
59    *ricinus* and we will specify when we cite any papers which refer to other species.

60    The *I. ricinus* life cycle develops from the egg, through two immature stages (larvae and  
61    nymph) to the adult stage. Each immature stage requires a blood meal from a suitable  
62    vertebrate host before developing to the next stage and the adult female requires a blood meal  
63    before producing eggs. Adult females feed primarily on large mammals such as deer, sheep  
64    or hares whilst the immature stages can also feed on smaller vertebrates such as mice, voles  
65    and birds (e.g. Gray 1998). The *I. ricinus* life cycle usually takes 3-4 year to complete (Fig.  
66    1).

67    In winter ticks often enter behavioural diapause induced by cold and/or short day length  
68    (Randolph et al. 2002; but see Gray 1987). Therefore, tick activity is highly seasonal with  
69    ticks in northern Europe being active mainly between spring and autumn when temperatures  
70    are warm enough. Activity is inhibited by cold temperatures but increases with temperature  
71    up to a limit (12-20°C depending on population e.g. Gilbert et al. (2014); Tomkins et al.  
72    (2014)). Tick host-seeking (questing) activity can also be inhibited by low relative humidity  
73    or high saturation deficits (this is a function of relative humidity and temperature and gives  
74    an estimate of the drying power of the air; Perret et al. 2000). After feeding, ticks also  
75    become inactive due to physiological diapause while they develop into the next stage  
76    (Randolph et al. 2002).

77    One of the first mathematical models developed to describe tick population dynamics was  
78    published in 1981 (Gardiner, et al. 1981). This study used empirical data from experiments to  
79    predict how tick development times depend on temperature. They did not put this into a

80 formal predictive modelling framework but they did try to determine functional relationships  
81 between development time and different measures of temperature (i.e. air and soil  
82 temperature). In particular they looked at how experimentally predicted development times  
83 estimated in the laboratory translated to the field where temperature fluctuations are much  
84 less predictable. They found that soil temperatures recorded at a depth of 50mm are useful  
85 predictors for larval and nymphal development phases. In terms of egg development time  
86 they found that air temperatures are useful for predicting the development time of eggs laid in  
87 the spring but soil temperature is a better predictor for those laid in autumn. They suggested  
88 that this might be because during diapause eggs may be conditioned to develop according to  
89 the temperature of their environment rather than air temperature.

90 Mount and Haile (1989) developed a computer simulation model of the American dog tick  
91 *Dermacentor variabilis* (Say). This model simulated the effects of environmental variables  
92 such as ambient temperature, habitat and host density on American dog tick population  
93 dynamics. They validated the model by comparing its predictions with empirical data from  
94 Virginia, Maryland and Massachusetts. The authors concluded that the model produced  
95 acceptable values for equilibrium population densities and seasonal activity patterns and went  
96 on to extend this model to include Rocky Mountain spotted fever dynamics (Cooksey et al.  
97 1990).

98 Over the last 40 years Sarah Randolph and collaborators have written a large number of  
99 papers on tick biology and population dynamics. These are largely empirical; however there  
100 are also some which model tick population dynamics. The first of these came in 1997  
101 (Randolph and Rogers 1997) where they presented a simulation model of the African tick  
102 *Rhipicephalus appendiculatus*. This simulation model incorporated temperature dependent  
103 rates of egg production and development, climate driven density independent mortality rates

104 and density dependent regulation of both nymphs and adults. The model successfully  
105 described both the seasonality and annual range of variation in numbers of each tick stage  
106 observed at each of four test sites in Uganda, Burundi and South Africa.

107 In 2002 Randolph et al. used empirical data on tick counts, various microclimatic factors and  
108 fat contents of ticks to create a population model explaining seasonality of *I. ricinus* in the  
109 UK. This study showed large variation in questing activity between years, but the date of  
110 questing (i.e. host-seeking activity) in one year was used to predict the start of questing for  
111 the next stage the following year, with reasonable accuracy. This was an important paper that  
112 also found evidence of two cohorts of ticks within a life stage within a season. Those nymphs  
113 with higher relative fat contents had emerged and become active more recently than those  
114 with lower fat contents. The suggestion was that spring-questing nymphs had overwintered,  
115 having fed as larvae the previous late summer or autumn; meanwhile autumn-questing  
116 nymphs had fed as larvae in the spring of the same calendar year.

117 More recently, Dobson et al. (2011) used a stage-classified Leslie matrix model to break the  
118 tick life cycle into the key parts, with a particular focus on two types of diapause:  
119 developmental and behavioural, with the latter being important in determining how many  
120 times a year an individual tick might feed. This model was then used by Dobson and  
121 Randolph (2011) to make long-term predictions of the effects of host densities, climate and  
122 acaricide treatment of hosts on tick populations.

123 In 2005 Ogden et. al. developed a model of *Ixodes Scapularis* Say (1821) in which tick  
124 development rates were modelled as temperature dependent time delays. Time spent in egg  
125 and engorged tick states and questing activities were all temperature dependent. The  
126 parameters were estimated using data taken from Ogden et.al. (2004). The model was  
127 validated using data from Ontario and Maryland and in both cases the observed seasonal

128 activity patterns were predicted by the model. The models were then used to predict  
129 theoretical geographical limits for the establishment of *I. Scapularis* in Canada. The model  
130 predicted that the temperature conditions which are suitable for the tick are wider than the  
131 existing distribution, implying that there is potential for spread.

132 At a similar time a different group used an age-structured stochastic model to describe the  
133 dynamics of tick populations (Hancock et al. 2011). They focused on the effect of  
134 temperature on the development between each stage of the tick life cycle, i.e. from egg to  
135 larva, larva to nymph, nymph to adult, and adult laying eggs. This model also introduced  
136 pathogen dynamics into the model. This allowed the model to predict that, if a pathogen is  
137 introduced into the system, it is most likely to persist if it is introduced at a time of year of  
138 peak tick questing.

139 A completely different approach was adopted by Schwarz et al. (2009) who used statistical  
140 methods to identify the relationship between vegetation and tick distribution. *I. ricinus* tick  
141 count data were correlated with plant communities, and the resulting relationship used to  
142 predict *I. ricinus* distribution across the German nature reserve Siebengebirge, using  
143 Geographic Information Systems (GIS). A similar process was undertaken by Braga et al.  
144 (2012) to identify the associations between habitat, host densities, temperature and other  
145 climatic factors on observed tick abundance at sites across Scotland. The resulting output was  
146 used to predict tick abundance over all of Scotland according to GIS-based environmental  
147 data, and visualised as a series of raster maps showing predicted tick abundance. The key  
148 parameters in this basic algorithm were then altered in accordance with environmental change  
149 projections (climate change and woodland expansion), to produce predictions of future tick  
150 abundance over Scotland due to environmental change scenarios.

151 Jore et al. (2011) also used a statistical method to investigate *I. ricinus* tick dynamics. A  
152 principle component analysis provided a model which explained 67% of the variation in past  
153 *I. ricinus* densities in Norway. The study suggests that *I. ricinus* have expanded northwards  
154 since 1983.

### 155 2.1 Summary:

156 For almost 35 years mathematical models of tick dynamics have been developed. The  
157 models have largely focussed on the impact of environmental factors on these dynamics.  
158 Field observations show that tick life stages emerge at different points in the season and  
159 peak at different times in different geographical regions. In some areas we can have  
160 bimodal tick dynamics within a year (e.g. Tagliapietra et al 2011) and in other areas there  
161 is only one peak. The models described above have been able to replicate the observed  
162 tick dynamics for particular geographical areas, tick species and environmental  
163 conditions. However it is clear that in order to be able to predict tick dynamics we would  
164 need to have key pieces of information about the environment (and particularly the  
165 temperature) in which they live.

166 Lorenz et al (2014) explicitly looked at the extrapolation of landscape model results to  
167 other spatial or temporal systems for Lyme disease and *I. scapularis* and concluded that  
168 models based on measures of vegetation, habitat patch characteristics and herbaceous  
169 landcover emerged as effective predictors of observed disease and vector distribution.  
170 These would therefore be important characteristics of an area to measure in order to  
171 predict these distributions.

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173



174 3. MATHEMATICAL MODELS OF TICK-BORNE PATHOGEN DYNAMICS.

175 Modelling of tick-borne pathogens has focussed on a small number of pathogens which are  
176 important for human or animal health and welfare. The three main systems which have been  
177 modelled extensively are louping-ill virus (LIV), western tick-borne encephalitis virus  
178 (TBEV) and *Borrelia burgdorferi* sensu lato, the causative agent of Lyme disease. This  
179 section will focus largely on LIV since this pathogen has the largest body of modelling work  
180 and it is the area of expertise of the authors. It also illustrates many of the biological features  
181 which need to be incorporated into models and so is a good case study for models of other  
182 system.

183 In general transmission of these pathogens can occur in three ways (although also see Park et  
184 al. 2001 discussed below for Louping Ill Virus). The most common form of transmission  
185 occurs when susceptible ticks feed on infected hosts with virus in their bloodstream (viraemic  
186 hosts) and pick up the virus. These ticks then moult into their next developmental stage and  
187 when they take their next blood meal then they can pass the pathogen onto a susceptible host,  
188 this will be a different individual and can also be a different host species (Labuda and Nuttall  
189 2004). The second method is vertical transmission, for some pathogens infection is passed  
190 from adult ticks to eggs and onto larvae (Labuda and Nuttall 2004). Finally, for some hosts  
191 and some pathogens there can be non-viraemic or co-feeding transmission in which  
192 susceptible ticks feeding near to infectious ticks can pick up infection without the host having  
193 a viraemic response (Jones et al 1987).

194 *3.1 Louping Ill Virus*

195 A large body of increasingly complex models have been used to help us understand LIV,  
196 which is the western-most variant of Western tick-borne encephalitis virus. LIV is

197 transmitted by *I. ricinus* and causes disease in livestock, especially sheep *Ovis aries*, as well  
198 as red grouse *Lagopus lagopus scoticus*, a valuable game bird. A vaccine has been developed  
199 for livestock but not for red grouse that are highly susceptible to the disease, with 78%  
200 mortality rates in experimentally infected birds in the laboratory (Reid 1976). The hosts and  
201 transmission cycle of this complex virus system has been recently reviewed (Gilbert 2015),  
202 but mathematical models can be extremely useful in helping to identify gaps in our biological  
203 knowledge of the system, identifying the relative importance of different host species hosts,  
204 and predicting the effectiveness of potential control strategies.

205 The first mathematical model of LIV was presented by Hudson et al. (1995), where a series  
206 of coupled ordinary differential equations describing LIV on red grouse moorland was  
207 presented. This model explored the interactions between ticks and red grouse and their role in  
208 the dynamics of LIV. The model predicted that grouse alone cannot support a tick population  
209 since very few adult ticks feed on grouse, therefore other hosts are required to complete the  
210 tick life cycle. Within this model the alternative hosts were mountain hares *Lepus timidus*,  
211 although similar later studies examined the role of red deer *Cervus elaphus* (Gilbert et al.  
212 2001; Norman et al. 2004) and sheep (Porter et al. 2011). Hudson et al. (1995) also calculated  
213 a formula for the conditions for persistence of both ticks and LIV. For tick persistence a  
214 sufficient number of hosts (or combination of host types) which can feed all stages of ticks  
215 are required, while LIV persistence also requires a competent LIV transmission host (red  
216 grouse in this model) to make up a sufficient proportion of the total tick hosts. This means  
217 that, in order for the pathogen to persist one needs enough tick hosts to maintain the tick  
218 population, with a sufficient number of these being pathogen-transmitting hosts. This  
219 threshold formula comes from the basic reproductive rate or number,  $R_0$ , when  $R_0 > 1$  then the  
220 pathogen persists and when  $R_0 < 1$  the pathogen dies out. Some more complex later LIV  
221 models have also predicted an eventual 'dilution effect' where pathogen prevalence declines

222 if there are too many non-pathogen transmitting tick hosts (hosts which do not transmit the  
223 pathogen such as deer) compared to competent transmission hosts which causes potential  
224 pathogen transmitting bites to be “wasted” and the effect of the pathogen to be diluted  
225 (Norman et al. 1999; Gilbert et al. 2001).

226 Sheep are known to produce a LIV viraemia after infection, and are known to be competent  
227 transmission hosts. However, the role of lambs is less well understood; if ewes have been  
228 bitten by infected ticks, their young lambs acquire immunity from the virus from drinking the  
229 colostrum from their mothers in the first few days or weeks of life. However, as the lambs  
230 age this immunity wanes, leaving them at risk of contracting LIV. Thus, lambs could  
231 potentially have a role as a reservoir host. Therefore, another differential equation model was  
232 created to understand the role that lambs may play as a reservoir of LIV. The model predicted  
233 that, whilst in theory large numbers of lambs could act as a reservoir for the virus, it is more  
234 likely that, in most situations, these numbers are probably small (Laurenson et al. 2000).

235 Laurenson et al. (2003) examined the impact of near-eradication of mountain hares on tick  
236 burdens and LIV seroprevalence in red grouse, using both empirical data and differential  
237 equation models. The models compared the scenario where mountain hares simply act as tick  
238 amplifying hosts to a scenario where hares were both tick hosts and non-viraemic  
239 transmission hosts. It was found that the model which included non-viraemic transmission  
240 produced predictions that fitted the data better than the simpler model did. Laboratory  
241 experiments had already identified mountain hares as competent transmission hosts (through  
242 supporting non-viraemic transmission between co-feeding ticks) in the laboratory (Nuttall  
243 and Jones 1991; Jones et al. 1997). In addition, models have shown that non-viraemic  
244 transmission via co-feeding may allow the virus to persist more readily than it would  
245 otherwise have done, and allow the virus to persist even in the absence of viraemic hosts if

246 the level of non-viraemic transmission is high enough (Norman et al. 2004). However, the  
247 Laurenson et al. (2003) study was important in demonstrating that mountain hares can be LIV  
248 reservoir hosts in the field. There were large management repercussions to this research, as  
249 many grouse moor managers over Scotland began large-scale culls of mountain hares,  
250 leading to political issues (reviewed by Harrison et al. 2010; Gilbert 2015). Models again had  
251 political impact by providing evidence against culling mountain hares: while the Laurenson et  
252 al. (2003) system included only red grouse and mountain hares, most areas in Scotland  
253 managed for grouse hunting also have deer. Therefore, Gilbert et al. (2001) modelled a three-  
254 host system, including deer as well as red grouse and mountain hares. Importantly, this three-  
255 host model predicted that LIV would always persist in the presence of even low densities of  
256 deer, even if all mountain hares were culled. This was because red grouse are transmission  
257 hosts for the virus while deer, although not competent transmission hosts, are important hosts  
258 for all stages of tick, so together both virus and tick life cycles can be maintained. This  
259 Gilbert et al. (2001) model has been crucial in the arguments against large-scale mountain  
260 hare culls (Harrison et al. 2010; Gilbert 2015).

261 Mathematical models have also been used in helping identify which pathogen control  
262 methods could be theoretically most effective in LIV control. Porter et al. (2011) developed  
263 models to predict the effectiveness of using acaricide-treated sheep as a tool to control ticks  
264 and LIV in red grouse. The model predicted that the presence of deer limits the effectiveness  
265 of such a strategy, but for certain conditions the use of acaricide on sheep could theoretically  
266 be a viable method for controlling ticks and LIV providing that high numbers of sheep are  
267 treated and acaricide efficacy remains high, while deer densities must be very low (Porter et  
268 al. 2011). Due to this predicted adverse impact of deer on the success of treating sheep to  
269 control ticks and LIV, and because deer are known to maintain high tick population densities  
270 in Scotland and move ticks between habitats (Ruiz-Fons and Gilbert 2010; Jones et al. 2011;

271 Gilbert et al. 2012), models were then developed to test the theoretical effectiveness of  
272 acaricide-treated deer on controlling ticks and LIV (Porter et al. 2013a). The model predicted  
273 that treating deer could control ticks and LIV if high acaricide efficacies were maintained and  
274 if a large proportion of the deer population was treated. Furthermore, effectiveness was  
275 improved if there were only low densities of deer. However, although the model predicted  
276 that this control method is theoretically plausible, it is unlikely that the conditions could be  
277 met in practical terms, in wild deer. Therefore, using an age-structured differential equation  
278 model, including splitting the grouse life cycle to represent the different behaviour between  
279 chicks and adults, Porter et al. (2013b) investigated whether acaricide treatment of the grouse  
280 themselves could help reduce ticks in the environment and LIV in the grouse population.  
281 Again, this was theoretically possible, but in the presence of deer, high acaricide efficacies  
282 were required and high proportions of the grouse population treated, were needed for  
283 successful control. This is due to the deer amplifying the tick population. These types of  
284 models can therefore be of use in decision-making by land managers for choosing disease  
285 control options, such as whether to try a certain control method or not depending on the  
286 situation in a specific area, taking into account any practical difficulties.

287 It is generally assumed that LIV is transmitted through ticks biting their hosts, and model  
288 parameterisation generally reflects this assumption. However, red grouse chicks frequently  
289 eat invertebrates, including ticks (Park et al. 2001). This is a potentially important route of  
290 transmission: it has been suggested that 73-98% of LIV infection in red grouse in their first  
291 year could stem from ingestion (Gilbert et al. 2004). Introducing this infection route to LIV  
292 modelling has an interesting effect: when using the standard method for calculating the basic  
293 reproduction number for the persistence of LIV, then the algebraic results and numerical  
294 simulations do not match. The standard method of analysis causes virus persistence to be  
295 underestimated, as the ingestion of infected ticks causes a feedback loop where the virus can

296 persist with seemingly insufficient hosts (Porter et al. 2011). This phenomenon requires  
297 further investigation, as it may indicate interesting gaps in our knowledge of the biology of  
298 the LIV system as well as an anomaly in the current modelling approach.

299 In the LIV models described above there has been no explicit spatial component to the  
300 models. However, Watts et al. (2009) investigated the interaction between neighbouring areas  
301 by expanding the previously-existing LIV models into a two-patch system with host  
302 movement between patches. Comparison with empirical data showed that whilst the one-  
303 patch model was a reasonable indicator for tick numbers, it tended to underestimate the  
304 prevalence of the LIV. When considering the two-patch model, the results depended largely  
305 on finding the appropriate balance of deer movement between the two sites (Watts et al.  
306 2009). Jones et al. (2011) developed a different type of differential equation model, which  
307 explicitly tracked the number of ticks on each host, to predict how deer moving ticks from  
308 forest onto moorland might affect ticks and LIV in red grouse on the moorland. The  
309 assumption was that ticks are more abundant in forest than on moorland, which is supported  
310 by empirical data (Ruiz-Fons and Gilbert 2010). This model predicted the highest levels of  
311 LIV in moorland to occur where it is bordering forest regions, due to higher tick numbers  
312 there. Furthermore, this model was important in examining for the first time the impact of  
313 landscape heterogeneity on predicted pathogen levels: virus prevalence was predicted to be  
314 higher in landscapes that have larger forest patches, and higher landscape fragmentation,  
315 which increases the number of borders between the two habitats (Jones et al. 2011).

### 316 *3.1.1 Summary:*

317 The transmission, persistence and dynamics of Louping Ill virus are complex with many  
318 interacting factors to take into account. The focus of the modelling work described above  
319 has been on trying to understand the roles that different hosts play in maintaining these

320 dynamics. Hosts can play three possible roles, they can either simply act as tick amplifiers  
321 (e.g. deer) or they can both amplify ticks and transmit virus (e.g. sheep for viraemic  
322 transmission or hares for non-viraemic transmission) or finally they can transmit the  
323 disease but not support the ticks (e.g. grouse). The ability to control the virus in any  
324 particular system is highly dependent on the densities of other hosts. In addition there are  
325 practical issues involved in trying to control the virus in this system which is made up of  
326 mostly wild hosts. There are both practical difficulties in delivering treatment and  
327 legislative difficulties in which treatments are permitted.

328 Louping ill virus does not infect humans but is of economic importance and has particular  
329 impact in rural areas and on rural livelihoods.

### 330 *3.2 Other tick-borne pathogens.*

331 *3.2.1 Tick-borne encephalitis:* Tick-borne encephalitis is a neurological disease which is of  
332 significant public health interest across mainland Europe. It is caused by the tick-borne  
333 encephalitis virus (TBEV), which is primarily transmitted by *I. ricinus* ticks, where rodents  
334 act as the competent host for the virus.

335 There are two significant ways in which deer can influence TBEV dynamics. Firstly, as deer  
336 are the main host which *I. ricinus* adults feed on, their presence, as with LIV, has an  
337 amplification effect on tick abundance. Secondly, as deer do not support TBEV transmission,  
338 very high deer densities can eventually lead to the dilution effect lowering TBEV levels  
339 (again similar to model predictions of LIV).

340 In both 2003 and 2007 Rosa and co-authors extended the models of Norman et. al. (1999) to  
341 explicitly include the questing and feeding tick stages and the aggregation of ticks on the  
342 hosts. They investigated changes in host densities and different infection pathways to

343 determine when the dilution effect might occur. They found the new result that the dilution  
344 effect might occur at high densities of disease competent hosts. The authors state that better  
345 information on tick demography would be needed before it would be possible to predict  
346 whether this effect would happen in the field. However, there is some evidence that this is the  
347 case in the TBE system (Perkins 2003).

348 In 2012 the same Italian group published a pair of papers taking both an empirical and  
349 theoretical approach to understanding the effect of deer density of tick distributions on  
350 rodents and therefore the risk of TBE. Cagnacci et al. (2012) empirically found a hump-  
351 shaped relationship between deer density and ticks feeding on rodents, and a negative  
352 relationship between deer density and TBE occurrence. Twinned with this, a model was  
353 developed by Bolzoni et al. (2012) to explain these findings. They found hump-shaped  
354 relationships between deer density and both the number of ticks feeding on rodents and  
355 TBEV prevalence in ticks. For low deer densities this can be explained by the tick  
356 amplification effect, for high deer densities the virus dilution mechanism dominates the  
357 dynamics.

358 The role of climate change on tick-borne pathogen prevalence was scrutinised by Randolph  
359 (2008). In this study, TBEV was used as a case example. A statistical model was used to  
360 show that climate change is not enough to explain historical changes in TBE incidence within  
361 Europe. An alternative model was presented, showing how the introduction of further factors  
362 allowed for a better model fit of the data. Crucially, such a model included socio-economic  
363 factors such as unemployment, agricultural practices and income. Zeman et al. (2010) used  
364 GIS analysis to similarly find that heterogeneity in TBE trends cannot be fully explained by  
365 geographic and climatic factors. However, they also found that the inclusion of socio-  
366 economic conditions could not satisfactorily explain the anomalies.



367 3.2.2 Summary

368 As with Louping ill the persistence and dynamics of TBE are dependent on host densities  
369 and deer play a crucial role in this. Some of the papers described above, particularly the  
370 2003 and 2007 Rosa et al papers present general results which could apply to a number of  
371 different tick borne pathogens and, in particular the results that dilution effects are very  
372 dependent on tick demography and density dependent constraints are true more generally  
373 than just for TBE. In most of the models presented here TBE has been a case study of a  
374 model which addresses more general questions.

375 3.2.2 Lyme Disease: *Borrelia burgdorferi* s.l. is the suite of spirochete bacteria which causes  
376 Lyme disease. This is a pathogen which has a wildlife reservoir but infects humans in the  
377 northern hemisphere.

378 Porco (1999) used a time-independent differential equation model to investigate how the  
379 prevalence of *B. burgdorferi* s.l. in *I. scapularis* (Say) nymphs is affected by various model  
380 parameters. The infectivity of white-footed mice *Peromyscus leucopus* (a key transmission  
381 host in the eastern USA) was predicted to be the parameter which increased *B. burgdorferi*  
382 s.l. prevalence the most, whilst a ten-fold increase in the density of deer (which do not  
383 transmit the pathogen) significantly reduced *B. burgdorferi* s.l. prevalence, suggesting that  
384 this is another system where the dilution effect can occur.

385 Zhang and Zhao (2013) presented a seasonal reaction-diffusion model of Lyme disease,  
386 utilising it to study the dynamics of the system in bounded and unbounded spaces. For  
387 bounded habitats a threshold for pathogen persistence was predicted, whilst for unbounded  
388 habitats they were able to predict the speed of pathogen spread.

389 In their 2007 paper Ogden et al considered the work of Wilson and Spielman (1985) and  
390 hypothesized that the transmission cycles of *B. burgdorferi* are very efficient in north-eastern  
391 North America because the seasonal activity of nymphal and larval *I. scapularis* is  
392 asynchronous. They then developed a simulation model which integrated transmission  
393 patterns imposed by seasonal asynchronous nymph and larvae with a model of infection in  
394 white footed mice. They parameterised the model for *B. burgdorferi* and *Anaplasma*  
395 *phagocytophilum* as examples. They found that duration of host infectivity, transmission  
396 efficiency to ticks and co-feeding transmission are the major factors determining fitness of  
397 pathogens in *I. scapularis* in North America.

398 The same group then wrote a series of papers looking *I. Scapularis* in Canada where it is  
399 established in some places and emerging in others. In Wu et al (2013) they developed a  
400 temperature driven map of the basic reproductive number for the ticks and found that for  
401 while the geographical extent of suitable tick habitat is expected to increase with climate  
402 warming the rate of invasion will also increase. In a subsequent paper Ogden et al (2013a)  
403 investigated the speed of *B. burgdorferi* invasion after establishment of ticks. The model  
404 showed that the number of immigrating ticks was a key determinant of pathogen invasion and  
405 so the authors hypothesized that a 5 year gap would occur between tick and *B. burgdorferi*  
406 invasion in Eastern Canada but a much shorter gap in Central Canada. This was consistent  
407 with empirical evidence. This was investigated more generally in Ogden et al (2013b).

### 408 3.2.1 Summary

409 *Borrelia burgdorferi* is another pathogen for which the dilution effect appears to occur. In  
410 this case rodents are the main reservoir host and *B. burgdorferi* is emerging in a number of  
411 different areas as the tick hosts expand their range in response to climate change or socio-  
412 economic factors.

413 3.3 More general models of tick borne pathogen.

414 More generally Hartemink et al. (2008) determined ways of characterising the basic  
415 reproductive number in a tick-borne pathogen system which has multiple transmission routes  
416 using the next generation matrix (e.g. Diekmann et al. 2010). They showed that the  
417 complexities of the tick transmission cycle can be overcome by separating the host  
418 population into epidemiologically different types of individuals and constructing a matrix of  
419 reproduction numbers. They then used field and experimental data to parameterise this next-  
420 generation matrix for *B. burgdorferi* s.l. and TBEV.

421 Dunn et al (2013) used a general model of tick-borne pathogens to study the basic  
422 reproductive number and found that the transmission efficiency to the ticks, the survival rate  
423 from feeding larvae to feeding nymphs and the fraction of nymphs to find a competent host  
424 are the most important factors in determining  $R_0$ .

425 Another general tick-borne pathogen model was created by Zeman (1997), where reported  
426 cases of disease were smoothed over to create risk maps for Lyme disease and TBE in  
427 Central Bavaria. This study indicated that *B. burgdorferi* s.l. is wider spread than TBEV, but  
428 that both pathogens share the same main foci. Similarly, Hönig et al. (2011) assessed the  
429 suitability of various habitats for supporting *I. ricinus* ticks, creating a model with which they  
430 were able to create a tick-borne pathogen risk map for South Bohemia, which was compared  
431 to clinical cases of TBE for validation. The model suggested that the areas most suitable for  
432 tick-borne pathogens were along river valleys. However, when human activity is taken into  
433 account, the surroundings of large settlements are equally likely to provide tick-borne  
434 pathogen cases.

435 Another aspect of transmission which is considerably less well understood is the pattern of  
436 aggregation of ticks on hosts. Ferreri et al (2014) analysed a nine year time series of *Ixodes*  
437 *ricinus* feeding on *Apodemus flavicollis* mice, the reservoir host for TBE in Trentino,  
438 Northern Italy. The tail of the distribution of the number of ticks per host was fitter to three  
439 theoretical distributions. The impact of these distributions on pathogen transmission was  
440 investigated using a stochastic model. Model simulations showed that there were different  
441 outcomes of disease spread with different distribution laws amongst ticks.

442 The models discussed above are not an exhaustive list, but do describe models which help us  
443 to understand many of the different complexities of tick-borne pathogen systems, and  
444 showcase the diversity of models now being developed for a wide range of end uses.

445

#### 446 4. KNOWLEDGE GAPS AND FUTURE DIRECTIONS

447 As we have seen mathematical models have been used for more than 30 years to help to  
448 predict tick dynamics and subsequently pathogen dynamics. The models presented here have  
449 been used in two ways, firstly to predict when tick densities are at their peak within a year  
450 and how that peak varies with environmental factors. Secondly, they have been used to  
451 predict pathogen persistence for different combinations of available host species with  
452 different transmission competencies. In particular, they have looked at the interaction  
453 between tick amplifying hosts and disease transmitting hosts and how densities of these hosts  
454 could be manipulated to control the disease.

455 One of the problems of these modelling studies is the difficulty in gathering empirical data to  
456 validate the model results. This is largely because there is a great deal of variability between  
457 sites in terms of habitat cover, microclimate and host densities. This is not unique to the tick

458 system, it is difficult for a number of reasons to carry out experiments in natural systems. It is  
459 also difficult to measure realistic tick densities (e.g. Dobson 2014).

460 However, most of the models described here have succeeded in doing some type of validation  
461 and they provide useful qualitative results.

462 Future modelling approaches are likely to be focussed in three areas. One is to look at spatial  
463 patterns of tick and disease risk, and in particular to link environmental information in GIS  
464 systems to models of tick and pathogen dynamics in a mechanistic way. These models can  
465 then be used to predict the impact of climate change on tick and disease risk across a given  
466 geographical region. This type of modelling is currently being carried out at the University of  
467 Stirling for Scotland. The advantage of this type of modelling is that it is generalizable and  
468 could be applied to any country with the right type of environmental data available in GIS  
469 form. It can also predict risks are going to change over time rather than only looking at the  
470 end points as has been done before (e.g. Braga et al 2012).

471 If we can identify which areas are going to have significant increases in disease risk then we  
472 can inform policy makers and target control efforts. For example, if we could identify which  
473 areas are going to have higher and lower Lyme disease risk then we could target efforts to  
474 educate the public on how to avoid being bitten in those high risk areas.

475 The second direction which we predict tick modelling will move is to further a new  
476 modelling technique which was introduced in Jones et al (2011). In that paper the authors  
477 developed a model which keeps track of the number of hosts with a particular number of ticks  
478 on it

479 Third route- more work on aggregation and individual differences (Rosa and Pugliese.)

480

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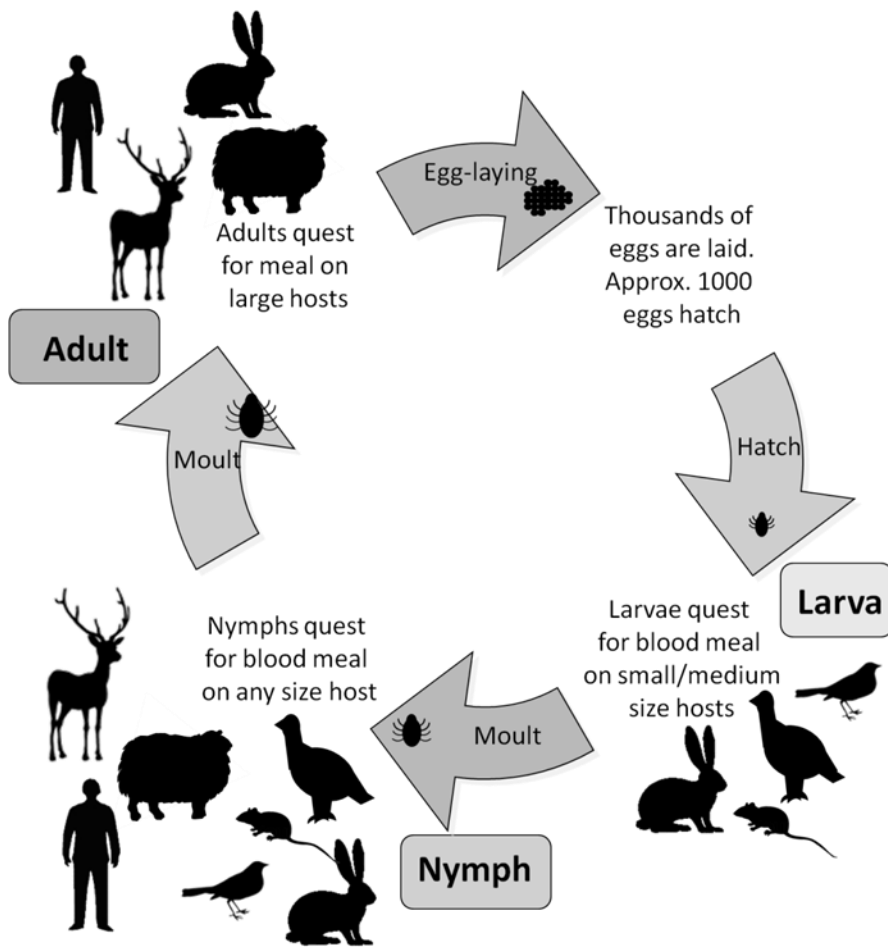
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677 Figure 1: Schematic diagram of the *I. Ricinus* lifecycle with the type of host that they are able  
678 to feed on at each stage.



679