

Applying optimal control theory to complex epidemiological models to inform real-world disease management

E.H. Bussell, C.E. Dangerfield, C.A. Gilligan & N.J. Cunniffe

Affiliations: Department of Plant Sciences, University of Cambridge, Cambridge CB2 3EA, United Kingdom

Keywords: optimal control, feedback, model predictive control, disease management

Corresponding Author: Dr. Nik Cunniffe, njc1001@cam.ac.uk

Main Text

Summary

Mathematical models provide a rational basis to inform how, where and when to control disease. Assuming an accurate spatially-explicit simulation model can be fitted to spread data, it is straightforward to use it to test the performance of a range of management strategies. However, the typical complexity of simulation models and the vast set of possible controls mean that only a small subset of all possible strategies can ever be tested. An alternative approach – optimal control theory – allows the best control to be identified unambiguously.

15 However, the complexity of the underpinning mathematics means that disease models used to identify this
16 optimum must be very simple. We highlight two frameworks for bridging the gap between detailed epidemic
17 simulations and optimal control theory: open-loop and model predictive control. Both these frameworks
18 approximate a simulation model with a simpler model more amenable to mathematical analysis. Using an
19 illustrative example model we show the benefits of using feedback control, in which the approximation and
20 control are updated as the epidemic progresses. Our work illustrates a new methodology to allow the insights
21 of optimal control theory to inform practical disease management strategies, with the potential for application
22 to diseases of humans, animals and plants.

23 **1 Introduction**

24 Mathematical modelling plays an increasingly important role in informing policy and management decisions
25 concerning invading diseases [1, 2]. However, model-based identification of effective and cost-efficient controls
26 can be difficult, particularly when models include highly detailed representations of disease transmission
27 processes. There is a variety of mathematical tools for designing optimal strategies, but no standard for putting
28 the results from mathematically motivated simplifications into practice. An open question is how to incorporate
29 enough realism into a model to allow accurate predictions of the impact of control measures, whilst ensuring
30 that the truly optimal strategy can still be identified [3]. In this paper we identify the difficulties – as well as
31 potential solutions – in achieving a practically useful optimal strategy, highlighting the potential roles of open
32 loop and model predictive control by way of a simple example.

33 **Realistic simulation models**

34 The optimisation of disease management involves determining the most appropriate control method(s), e.g.
35 vaccination, quarantine or roguing, and the best deployment strategy for that method or combination of
36 methods to minimise impacts of the disease. This minimisation can be difficult when resources are limited
37 and there are economic costs associated with both control measures and disease. Methods that simulate the
38 expected course of an epidemic and explicitly model effects of interventions can rapidly quantify the potential
39 impact of a given strategy [4]. These simulation models accurately capture the dynamics of the real system
40 and so have become important tools for assessing policy decisions relating to real-time management responses
41 as well as to increased preparedness for future threats. Examples include vaccination policies for human
42 papillomavirus in the UK [5, 6], livestock culling policies [7, 8] and vaccination optimisation [9, 10] for foot-
43 and-mouth disease, and optimal host removal strategies for tree diseases of citrus [11–14] and sudden oak
44 death [15].

45 Various complexities of disease dynamics, for example spatial heterogeneities and inherent individual
46 differences in susceptibility and pathogen transmission (risk structure), have been shown to be important
47 determinants of patterns and rates of epidemic spread [16–18]. To ensure accurate epidemic predictions,
48 these factors must be included in simulation models designed to aid decision making. However, inclusion of
49 these heterogeneities typically results in highly complex models with many possible control measures, making
50 optimisation computationally infeasible when interventions can be combined, and particularly when control
51 measures can also vary over time, in space or according to disease risk [19]. For most simulation models the
52 only viable option is then to use the model to evaluate a small subset of plausible strategies that remain fixed

53 during the epidemic, potentially scanning over a single parameter such as a culling radius. We shall refer
54 to this approach as ‘Strategy Testing’. Using this approach makes it difficult to have high confidence in the
55 best-performing strategy, since with no framework for choosing it, the set of strategies under test is likely to be
56 biased. Further to this, as the set to test cannot span the entire space of control options, it is unlikely that the
57 true optimum will be found.

58 **Optimal control of epidemiological models**

59 Many mathematical techniques exist for characterising the true optimal control for a disease, such as equi-
60 librium or final size analysis, depending on the system being analysed [16]. We here focus on optimising
61 time-varying control of dynamical systems, for which optimal control theory (OCT) is widely used [20]. By
62 analysing a set of equations describing the disease dynamics, OCT can mathematically characterise the optimal
63 deployment strategy for a given control method and provide insight into the underlying dynamics, without
64 the repeated simulation required to optimise simulation models. However, because of the underlying mathe-
65 matical complexity, little progress can be made with OCT unless the underpinning models for disease spread
66 are highly simplified. Early work in OCT focussed on optimal levels of vaccination and treatment [21], with
67 extensions to consider further interventions including quarantine, screening, and health-promotion campaigns
68 appearing later [22]. Disease models can also be coupled with economic effects [23–25], and within OCT this
69 has been used to balance multiple costs, such as surveillance and control [26], or prophylactic versus reactive
70 treatment [27].

71 The optimal strategies identified by OCT can be very complex, often specifying controls that switch strategies
72 at specific times during the course of an epidemic. The added complexity of these switching controls can

73 significantly improve disease management when tested on a spatially explicit model, but can lead to poor
74 performance if the exact time of the switch is not known [28], for example when parameter uncertainty gives
75 a wide range of possible switch times. This demonstrates that uncertainties and additional complexities often
76 prohibit OCT from being directly applicable to the real world. It is also unclear how insight from OCT alone
77 could be translated into practical advice. To move towards robust strategies that could be used practically,
78 more recent work has focussed on including additional features and heterogeneities into the models used in
79 OCT, in particular spatial dynamics. Space is usually only included to a limited extent, for example by using
80 metapopulation models (e.g. [29, 30]), or partial differential equations (e.g. [31]) to optimise spatial strategies,
81 so whether the heterogeneities added are sufficient to identify robust and practical control strategies remains
82 an open question.

83 **Moving towards practical control**

84 Despite finding the mathematically optimal control strategy, major simplifications to the system as modelled
85 are required to allow progress to be made using OCT. It is therefore often unclear how these strategies would
86 perform if adopted by policy makers. On the other hand, models with sufficient realism to inform policy
87 directly are often impossible to optimise fully. Therefore, a framework is needed to combine the optimisation
88 capabilities of OCT with the accurate predictions of simulation type models as required in policy making. The
89 question is then how should we make practical use of OCT?

90 In §2 we describe two methods from control systems engineering for applying OCT results, and compare
91 these versus Strategy Testing using a simple illustrative model in §3. We seek to answer how, under current
92 computational constraints, results from OCT can be applied whilst maintaining the realism required for practical

93 application.

94 **2 Applying optimal control to realistic systems**

95 Outside of epidemiology, OCT has had wider use on approximate models of complex systems. A recent study
96 reviews the use of OCT for agent-based models (ABMs) [32], a type of model that simulates the individual
97 behaviour of autonomous agents. An *et al.* [32] suggest the use of a model that approximates the dynamics
98 of the ABM, designed to be simple enough to allow mathematical analysis of the optimal control. A suitable
99 approximate model is chosen and fitted either to real data, or to synthetic data from the ABM. The OCT results
100 from the approximating model are then mapped onto the ABM to be tested: a process referred to as 'lifting',
101 which could equally well apply to the detailed epidemic simulation models considered in this paper. We
102 now describe two possible frameworks from control systems engineering for making use of this control lifting
103 approach.

104 **Open-loop control**

105 The first method is the simplest application of control lifting, and the framework implicitly suggested by An
106 *et al.* [32]. Control is optimised on the approximate model once using the initial conditions of the simulation
107 model. The resulting optimal control strategy is lifted to the simulator and applied for the full simulation run
108 time (figure 1). Repeated simulation of the OCT strategy on the simulation model allows assessment against
109 other possible control strategies. The optimisation gives a single, time dependent strategy for all simulation
110 realisations, and so does not incorporate any feedback. It is therefore referred to as 'open-loop' control, as it is
111 fully specified by the simulation initial conditions and the trajectory predicted by the approximate model. Use

112 in epidemiology is uncommon, although Clarke *et al.* [33] use OCT in an approximate model to find optimal
113 levels of Chlamydia screening and contact tracing which are then mapped onto a network simulation.

114 **Model predictive control**

115 Open-loop control requires the approximate model to remain accurate over the time scale of the entire epidemic.
116 However, for tractability the approximate model must necessarily omit many heterogeneities present in the
117 simulation model, such as spatial effects and risk structure. When strategies resulting from OCT are then
118 applied to the simulation model or to the real system, the disease progress is likely to deviate systematically
119 from the trajectory predicted by the approximate model. Model predictive control (MPC) is an optimisation
120 technique incorporating system feedback that can take such perturbations into account [34, 35]. At regular
121 update times the values of the state variables in the approximate model are reset to match those in the simulation
122 at that time. The control is then re-optimised and the new control strategy is applied to the simulation until
123 the next update time. The approximate and simulation models are therefore run concurrently, with multiple
124 optimisations per realisation, to ensure that the approximate model and control strategy closely match each
125 individual simulation realisation (figure 1). These multiple optimisations are computationally costly but
126 tractable, unlike performing optimisation on the full simulation model.

127 MPC has had some use within the epidemiological literature, the majority being for control of drug ap-
128 plications for single individuals rather than control of epidemics at the population level. Examples include
129 finding management strategies for HIV that are robust to measurement noise and modelling errors [36, 37], and
130 control of insulin delivery in patients with diabetes [38]. These studies highlight the benefits of MPC for robust
131 control, i.e. control that remains effective despite system perturbations. However, only one study concentrates

132 on epidemic management [39], and that does not explicitly test the feedback control on simulations.

133 **3 Optimising strategies on an illustrative network model**

134 **Methods**

135 To demonstrate open-loop and MPC for epidemic management we use a stochastic SIR network model including
136 host demography and risk structure. The model is deliberately kept simple to show how the underpinning
137 idea is broadly applicable across human, animal and plant diseases. Whilst the model and its parameters are
138 arbitrary and do not represent a specific disease, we use it to represent a scenario in which a simulation model
139 has already been fitted to a real disease system; the network model is therefore used here as a proxy for a
140 potentially very detailed simulation model.

141 **Simulation Model**

142 In our model, infection spreads stochastically across a network of nodes that are clustered into three distinct
143 regions (figure 2a). Each node contains a host population stratified into high and low risk groups. The infection
144 can spread between individuals within nodes and between connected nodes. The net rate of infection of risk
145 group r in node i is given by:

$$146 \quad S_i^r \sum_j \sigma_{ij} \left(\rho^{rH} I_j^H + \rho^{rL} I_j^L \right), \quad (1)$$

147 where S and I are numbers of susceptible and infected hosts respectively, subscripts identify the node, and
148 superscripts specify high (H) or low (L) risk group. The sum is over all connected nodes including the focal
149 node itself, with the relative transmission strength into node i from node j given by σ_{ij} , and risk structure given

150 by the 2×2 matrix ρ . Full details of the model are given in the supplementary material. Although not limited
151 to these applications, the model in Equation 1 could represent crop or livestock diseases spreading through
152 farms, or sexually transmitted infections spreading through towns, cities or countries.

153 Mass vaccination is the only intervention we consider, with the potential to target based on both risk group
154 and region but randomised across host infection status (i.e. the vaccine is given to all hosts but is only effective
155 on susceptibles). Logistical and economic constraints are included through a maximum total vaccination rate
156 (η_{\max}) that can be divided between risk groups and regions. Within each group susceptibles are vaccinated
157 at rate: $f\eta_{\max}S/N$, where f is the proportion of control allocated to that group, and N is the total group
158 population.

159 Optimal allocation of the vaccination resources minimises an epidemic cost J representing the disease
160 burden of the epidemic across all infected hosts over the simulation time (T): $J = \int_{t=0}^T I(t)dt$. In common with
161 the particular control we consider and the risk and spatial structures, this simple choice of objective function
162 was made merely to illustrate our methods, but the framework generalises immediately to more complex
163 settings.

164 **Approximate Models**

165 Exhaustive optimisation of control using the simulation model, across space, risk group and time, is clearly very
166 computationally expensive. To assess the best level of approximation, we consider two different deterministic
167 approximate models of the simulator. The first model is purely risk structured, factoring out all spatial
168 information and leaving one high risk and one low risk population group. This model is deterministic and
169 based on the assumption that all nodes are spatially well-mixed with each other. The second approximate

170 model is more complex, in as much as it is also deterministic and risk structured, but additionally includes a
171 first approximation to the host spatial structure by including the regional host information. Spatial dynamics
172 are included between but not within the three regions to maintain enough simplicity to obtain optimal control
173 results, thereby assuming that nodes are spatially well-mixed within each region. This could represent, for
174 example, optimising control at the country level, but not at the regional level. We refer to this model as the
175 spatial approximate model. A single set of parameters is fitted for each model to data from an ensemble of
176 simulation model runs. We then test which of the two approximate models is the more useful for control
177 optimisation. Full details of the approximate models, fitting and optimisation procedures are given in the
178 supplementary material.

179 **Control Scenarios**

180 We test six different control scenarios, which compare Strategy Testing of controls based purely on the simulation
181 model (scenarios 1 and 2) with open-loop and MPC applied using both of our approximate models (scenarios
182 3 to 6):

- 183 1. 'High': exclusively vaccinate high risk individuals
- 184 2. 'Split': partition control resources between high and low risk groups based on an optimisation performed
185 in advance
- 186 3. 'Risk OL': open-loop control using the risk based approximate model
- 187 4. 'Risk MPC': MPC using the risk based approximate model
- 188 5. 'Space OL': open-loop control using the spatial approximate model

6. 'Space MPC': MPC using the spatial approximate model

The optimal constant allocation for the 'Split' strategy was found by running many simulation model realisations for each of a range of partition values, as in [11], and selecting the value that gave the lowest average epidemic cost (supplementary figure S8). The six strategies are assessed by repeatedly running the simulation model under each control scenario.

Results

The OCT results for optimising the vaccination strategy in the risk based approximate model lead to initial vaccination of high risk individuals only, before switching priorities and treating the more populous low risk group almost exclusively. The OCT results from the spatial approximate model show this same switch (figure 2b), but a number of spatial switches are also seen, allowing control to track the epidemic as it progresses through the three regions (supplementary figure S9). The spatial strategies are therefore much more complex than the risk based controls.

Applying the control scenarios to the simulation model and comparing epidemic costs shows that incorporating greater realism, through a more complex approximate model as well as by using MPC, allows for improved disease management (figure 3 and supplementary figure S10). Of the constant and purely simulation based 'user-defined' strategies, splitting control between risk groups is slightly more effective than just vaccinating the high risk group. The optimal allocation to the high risk group used in the 'Split' strategy is 63% of vaccination resources, with the rest used to vaccinate low risk individuals, although this does occur in a broad minimum of epidemic cost (supplementary figure S8). Applying the optimisations from the risk based approximate model to the simulation model gives an improvement over either of the 'user-defined' strategies,

209 although there is little difference in epidemic cost between the open-loop and MPC frameworks (see below).
210 Adding space into the approximate model improves control further, leading to the smallest epidemic costs
211 when the spatial MPC framework is used.

212 The illustrative model demonstrates the management improvements that can be achieved by combining
213 OCT with both open-loop and MPC. The key results of the OCT analyses are the control switching times.
214 Using the switching controls from either approximate model with open-loop control gives lower epidemic
215 costs than the naively chosen 'user-defined' strategies. The feedback present in the MPC controllers allows
216 further reductions to the epidemic cost. By re-evaluating the timing of the switches during the epidemic,
217 and potentially including additional switches, the control can respond more closely to the exact trajectory of
218 the current simulation realisation (figures 2b–d). This gives control that is more robust to uncertainty and
219 systematic errors in the approximate model, and hence performs better on the complex simulation model.

220 In the risk based strategies there is little difference between open-loop and MPC. This is because the precise
221 timing of the switch from high to low risk group vaccination does not significantly affect the epidemic cost
222 (supplementary figure S11). The timings of disease introduction into regions B and C are highly variable
223 between simulation runs (supplementary figure S2). The potential for additional switches in the spatial
224 approximate model gives more flexibility for the MPC controller to respond to this variability, and so spatial
225 MPC shows a significant improvement over open-loop which cannot adapt to perturbations. The performance
226 of the control is closely linked to the accuracy of the approximate model. In our example, spatial dynamics are
227 clearly important because of the timing of spread between regions, and so the more informed controls of the
228 spatial model outperform the risk based strategies.

229 4 Discussion

230 Our results show that the choice of approximate model affects the performance of both open-loop and MPC
231 strategies. Here we have found a suitable approximate model in an ad hoc manner, but a key challenge for the
232 future is to develop a more formal method for choosing the most appropriate approximate model. A more
233 accurate model may give better predictions, and hence control that is closer to the true optimum, but simpler
234 models are often sufficient [40] and accuracy must be balanced with added complexity and optimisation
235 constraints. One difficulty in doing this is that it is not always clear where the boundary of mathematical
236 or computational feasibility is, and so how complex the model can be made in practice. It is also difficult
237 to determine mathematically, in a systematic way, which aspects of the dynamics are important to capture
238 accurately. This key issue must be considered though, since the implications relate directly to applications in
239 the real world.

240 Practical disease control requires surveys of the real system to assess the state of the epidemic. Both open-
241 loop and MPC optimise control using predictions of the future dynamics, making them both feed-forward
242 controllers. The approximate model underlying these frameworks allows more informed decisions between
243 surveys, resulting in control that is closer to the true optimum. Accurate predictions can avoid continuous
244 or very frequent surveys which may be expensive or logistically challenging. As discussed previously, the
245 repeated updates in the feedback loop of MPC improve these predictions and hence the performance of the
246 control. However, each update will require surveillance of the real system, so the frequency of updates must
247 be chosen so as to balance improved knowledge of the system with any surveillance constraints.

248 In this paper we have focussed on a top-down approach, finding robust, practically-applicable strategies by

249 making use of OCT to optimise simulation models. Equally, many studies use OCT without simulation models,
250 rarely considering practical application of the resulting optimal controls. With this bottom-up approach, a
251 system for testing the results on realistic systems is vital to ensure that these results are robust to additional
252 realism. Using an MPC framework as considered here could be one way in which OCT researchers could
253 demonstrate the potential impact of their work to a wider audience.

254 Exhaustive testing of alternative simulation model parameterisations is beyond the scope of this study, but
255 we generally find that spatial MPC also performs best across other reasonable parameter sets (supplementary
256 material §3). We have assumed throughout that an accurate simulation model of the real system in question
257 can be built, and that a single set of parameters can be fitted for the chosen deterministic approximate model.
258 In reality there may be considerable uncertainty in parameters for the simulator so fitting a single deterministic
259 model may be challenging. A question for future study would be how to handle these uncertainties, perhaps
260 also incorporating improved knowledge of parameters as the simulation proceeds [41].

261 The strategies found by OCT are highly dependent on the exact form of the objective function, which we
262 have here chosen to be very simple. Extending the objective to include costs associated with control as well as
263 with each switch in strategy would allow a more detailed assessment of the practicality of implementing these
264 complex strategies. More research is needed into how to quantify the balancing of very different costs though,
265 for example treatment costs and disease burden [29]. In human disease, cost-effectiveness analyses are usually
266 based on quality adjusted life years [42]. A similar concept could perhaps be used for plant and animal diseases,
267 including calculations of yield losses [43] as well as effects on welfare, biodiversity and tourism for example
268 [44]. The methods we have described however, are not dependent on the form of the control or objective
269 function. For an appropriate approximate model, the feedback in MPC ensures accurate predictions and so

270 should always improve performance over open-loop. The frameworks we describe can be used to provide an
271 additional, unbiased control scenario to the Strategy Testing process that is already in common use.

272 In this paper we have shown that coupling feedback control with simulation models and OCT can help
273 to design effective and robust intervention strategies for managing pathogens of human, animal and plant
274 populations. Whilst these techniques may be able to transfer optimal control results to more realistic simulations
275 and so to practical application, it does raise the issue of communicability of results. With complex feedback
276 strategies between two models, one complex in structure and the other mathematically complex, the overall
277 result is no longer simple to explain. Future research must therefore focus on improving the accuracy of
278 simulation models, and analysing their reliability, so that simulations can be used to establish conclusively the
279 benefit of these complex OCT based strategies.

280 **Additional Information**

281 **Acknowledgements**

282 We thank Andrew Craig, Eleftherios Avramidis and Hola Adrakey for helpful discussions. We also thank two
283 anonymous reviewers for their helpful and constructive comments.

284 **Data Accessibility**

285 All code and animations are available at <https://github.com/ehbusse11/Busse112018Model>.

286 **Authors' Contributions**

287 E.H.B., C.E.D. and N.J.C. designed the study, E.H.B. conducted the analysis and wrote the initial draft of the
288 manuscript. All authors contributed to data interpretation, manuscript editing and discussion.

289 **Competing Interests**

290 We have no competing interests.

291 **Funding**

292 E.H.B. acknowledges the Biotechnology and Biological Sciences Research Council of the United Kingdom
293 (BBSRC) for support via a University of Cambridge DTP Ph.D. studentship.

294 **References**

- 295 [1] Heesterbeek H, et al. 2015. Modeling infectious disease dynamics in the complex landscape of global health. *Science* **347**, aaa4339 doi:10.1126/science.
296 aaa4339
- 297 [2] Metcalf CJE, Edmunds WJ, Lessler J. 2015. Six challenges in modelling for public health policy. *Epidemics* **10**, 93–96 doi:10.1016/j.epidem.2014.08.008
- 298 [3] Cunniffe NJ, Koskella B, E Metcalf CJ, Parnell S, Gottwald TR, Gilligan CA. 2015. Thirteen challenges in modelling plant diseases. *Epidemics* **10**, 6–10
299 doi:10.1016/j.epidem.2014.06.002
- 300 [4] Lofgren ET, et al. 2014. Opinion: mathematical models: a key tool for outbreak response. *Proc. Natl. Acad. Sci. U.S.A.* **111**, 18095–18096 doi:10.1073/pnas.
301 1421551111
- 302 [5] Jit M, Choi YH, Edmunds WJ. 2008. Economic evaluation of human papillomavirus vaccination in the United Kingdom. *BMJ* **337**, a769 doi:10.1136/bmj.
303 a769
- 304 [6] Choi YH, Jit M, Gay N, Cox A, Garnett GP, Edmunds WJ. 2010. Transmission dynamic modelling of the impact of human papillomavirus vaccination in
305 the United Kingdom. *Vaccine* **28**, 4091–4102 doi:10.1016/j.vaccine.2009.09.125

- 306 [7] Keeling MJ, Woolhouse ME, Shaw DJ, Matthews L, Chase-Topping M, Haydon DT, Cornell SJ, Kappey J, Wilesmith J, Grenfell BT. 2001. Dynamics of the
307 2001 UK foot and mouth epidemic: stochastic dispersal in a heterogeneous landscape. *Science* **294**, 813–817 doi:10.1126/science.1065973
- 308 [8] Keeling MJ. 2005. Models of foot-and-mouth disease. *Proc. R. Soc. Lond. B Biol. Sci.* **272**, 1195–1202 doi:10.1098/rspb.2004.3046
- 309 [9] Keeling MJ, Woolhouse MEJ, May RM, Davies G, Grenfell BT. 2003. Modelling vaccination strategies against foot-and-mouth disease. *Nature* **421**, 136–42
310 doi:10.1038/nature01343
- 311 [10] Tildesley MJ, Savill NJ, Shaw DJ, Deardon R, Brooks SP, Woolhouse ME, Grenfell BT, Keeling MJ. 2006. Optimal reactive vaccination strategies for a
312 foot-and-mouth outbreak in the UK. *Nature* **440**, 83–86 doi:10.1038/nature04324
- 313 [11] Cunniffe NJ, Stutt RO, DeSimone RE, Gottwald TR, Gilligan CA. 2015. Optimising and communicating options for the control of invasive plant disease
314 when there is epidemiological uncertainty. *PLoS Comput. Biol* **11**, e1004211 doi:10.1371/journal.pcbi.1004211
- 315 [12] Hyatt-Twynam SR, Parnell S, Stutt RO, Gottwald TR, Gilligan CA, Cunniffe NJ. 2017. Risk-based management of invading plant disease. *New Phytol.* **214**,
316 1317–1329 doi:10.1111/nph.14488
- 317 [13] Adrakey HK, Streftaris G, Cunniffe NJ, Gottwald TR, Gilligan CA, Gibson GJ. 2017. Evidence-based controls for epidemics using spatio-temporal
318 stochastic models in a Bayesian framework. *J. R. Soc. Interface* **14**, 20170386 doi:10.1098/rsif.2017.0386
- 319 [14] Craig AP, Cunniffe NJ, Parry M, Laranjeira FF, Gilligan CA. 2018. Grower and regulator conflict in management of the citrus disease Huanglongbing in
320 Brazil: a modelling study. *J. Appl. Ecol.* **55**, 1956–1965 doi:10.1111/1365-2664.13122
- 321 [15] Cunniffe NJ, Cobb RC, Meentemeyer RK, Rizzo DM, Gilligan CA. 2016. Modeling when, where, and how to manage a forest epidemic, motivated by
322 sudden oak death in California. *Proc. Natl. Acad. Sci. U.S.A.* **113**, 5640–5645 doi:10.1073/pnas.1602153113
- 323 [16] Keeling MJ, Rohani P, 2008. *Modeling Infectious Diseases in Humans and Animals*. Princeton University Press
- 324 [17] Anderson RM, Medley GF, May RM, Johnson AM. 1986. A preliminary study of the transmission dynamics of the human immunodeficiency virus (HIV),
325 the causative agent of AIDS. *Math. Med. Biol.* **3**, 229–263 doi:10.1093/imammb/3.4.229
- 326 [18] Smith DL, Lucey B, Waller LA, Childs JE, Real LA. 2002. Predicting the spatial dynamics of rabies epidemics on heterogeneous landscapes. *Proc. Natl.*
327 *Acad. Sci. U.S.A.* **99**, 3668–3672 doi:10.1073/pnas.042400799
- 328 [19] Bellman R, 2013. *Dynamic Programming*. Courier Corporation
- 329 [20] Lenhart S, Workman JT, 2007. *Optimal Control Applied to Biological Models*. CRC Press
- 330 [21] Sethi SP, Staats PW. 1978. Optimal control of some simple deterministic epidemic models. *J. Oper. Res. Soc.* **29**, 129–136 doi:10.1057/jors.1978.27
- 331 [22] Behncke H. 2000. Optimal control of deterministic epidemics. *Optim. Control Appl. Methods* **21**, 269–285 doi:10.1002/oca.678

- 332 [23] Perrings C, et al. 2014. Merging economics and epidemiology to improve the prediction and management of infectious disease. *EcoHealth* **11**, 464–475
333 doi:10.1007/s10393-014-0963-6
- 334 [24] Epanchin-Niell RS. 2017. Economics of invasive species policy and management. *Biol. Invasions*, 1–22 doi:10.1007/s10530-017-1406-4
- 335 [25] Cunniffe NJ, Laranjeira FF, Neri FM, DeSimone RE, Gilligan CA. 2014. Cost-effective control of plant disease when epidemiological knowledge is
336 incomplete: modelling Bahia bark scaling of citrus. *PLOS Comput. Biol.* **10**, 1–14 doi:10.1371/journal.pcbi.1003753
- 337 [26] Ndeffo Mbah ML, Gilligan CA. 2010. Balancing detection and eradication for control of epidemics: sudden oak death in mixed-species stands. *PLoS*
338 *ONE* **5**, 1–8 doi:10.1371/journal.pone.0012317
- 339 [27] Brown VL, White KAJ. 2011. The role of optimal control in assessing the most cost-effective implementation of a vaccination programme: HPV as a case
340 study. *Math. Biosci.* **231**, 126–134 doi:10.1016/j.mbs.2011.02.009
- 341 [28] Forster G, Gilligan CA. 2007. Optimizing the control of disease infestations at the landscape scale. *Proc. Natl. Acad. Sci. U.S.A.* **104**, 4984–4989 doi:
342 10.1073/pnas.0607900104
- 343 [29] Rowthorn RE, Laxminarayan R, Gilligan CA. 2009. Optimal control of epidemics in metapopulations. *J. R. Soc. Interface* **6**, 1135–1144 doi:10.1098/rsif.
344 2008.0402
- 345 [30] Ndeffo Mbah ML, Gilligan CA. 2011. Resource allocation for epidemic control in metapopulations. *PLoS ONE* **6**, doi:10.1371/journal.pone.0024577
- 346 [31] Neilan RM, Lenhart S. 2011. Optimal vaccine distribution in a spatiotemporal epidemic model with an application to rabies and raccoons. *J. Math. Anal.*
347 *Appl.* **378**, 603–619 doi:10.1016/j.jmaa.2010.12.035
- 348 [32] An G, Fitzpatrick BG, Christley S, Federico P, Kanarek A, Neilan RM, Oremland M, Salinas R, Laubenbacher R, Lenhart S. 2017. Optimization and control
349 of agent-based models in biology: a perspective. *Bull Math Biol* **79**, 63–87 doi:10.1007/s11538-016-0225-6
- 350 [33] Clarke J, White KAJ, Turner K. 2013. Approximating optimal controls for networks when there are combinations of population-level and targeted
351 measures available: chlamydia infection as a case-study. *Bull. Math. Biol.* **75**, 1747–1777 doi:10.1007/s11538-013-9867-9
- 352 [34] Camacho EF, Bordons C, 2012. *Model Predictive Control in the Process Industry*. Springer Science & Business Media
- 353 [35] Lee JH. 2011. Model predictive control: review of the three decades of development. *Int. J. Control Autom. Syst.* **9**, 415–424 doi:10.1007/s12555-011-0300-6
- 354 [36] Zurawski R, Teel AR. 2006. A model predictive control based scheduling method for HIV therapy. *J. Theor. Biol.* **238**, 368–382 doi:10.1016/j.jtbi.2005.05.004
- 355 [37] David J, Tran H, Banks HT. 2011. Receding horizon control of HIV. *Optim. Control Appl. Meth.* **32**, 681–699 doi:10.1002/oca.969
- 356 [38] Hovorka R, et al. 2004. Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiol. Meas.* **25**, 905–920
357 doi:10.1088/0967-3334/25/4/010

- 358 [39] Sélley F, Besenyei Á, Kiss IZ, Simon PL. 2015. Dynamic control of modern, network-based epidemic models. *SIAM J. Appl. Dyn. Syst.* **14**, 168–187
359 doi:10.1137/130947039
- 360 [40] Thompson RN, Hart WS. 2018. Effect of confusing symptoms and infectiousness on forecasting and control of ebola outbreaks. *Clin. Infect. Dis.*, ciy248
361 doi:10.1093/cid/ciy248
- 362 [41] Thompson RN, Gilligan CA, Cunniffe NJ. 2018. Control fast or control smart: when should invading pathogens be controlled? *PLoS Comput. Biol.* **14**,
363 e1006014 doi:10.1371/journal.pcbi.1006014
- 364 [42] Whitehead SJ, Ali S. 2010. Health outcomes in economic evaluation: the QALY and utilities. *Br. Med. Bull.* **96**, 5–21 doi:10.1093/bmb/ldq033
- 365 [43] Savary S, Ficke A, Aubertot JN, Hollier C. 2012. Crop losses due to diseases and their implications for global food production losses and food security.
366 *Food Secur.* **4**, 519–537 doi:10.1007/s12571-012-0200-5
- 367 [44] Boyd IL, Freer-Smith PH, Gilligan CA, Godfray HCJ. 2013. The consequence of tree pests and diseases for ecosystem services. *Science* **342**, 1235773
368 doi:10.1126/science.1235773

369 **Figure and table captions**

370 **Figure 1**

371 Open-loop and model predictive control (MPC). The model hierarchy is shown, with optimised controls from
372 the approximate model directly lifted to the simulation model. The real system is in green, the models and
373 fitting processes are in blue, and the control framework is in orange. Without the orange dashed feedback
374 loop, this is open-loop control. MPC resets the state of the approximate model at regular update steps, before
375 re-optimising and lifting controls to the simulation model until the next update time.

376 **Figure 2**

377 **(a)** shows the network used for the illustrative simulation model, including region labels. The epidemic is
378 seeded in the red node in region A, and can spread between connected nodes (grey lines). In **(b)** the control

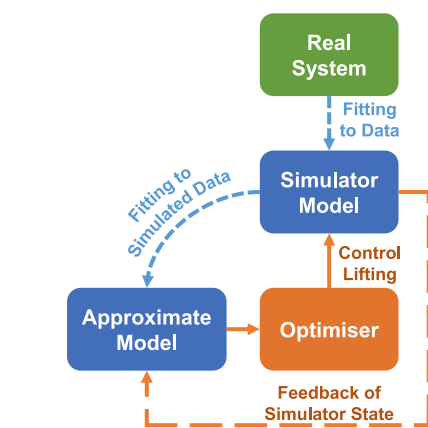
379 allocation is shown for a single space based MPC run, with the corresponding open-loop allocation indicated
 380 by the black dotted line. (c) shows the total number of infected individuals under a single run of space based
 381 open-loop control. Control is based on the prediction of the approximate model starting from the initial
 382 conditions. (d) shows the number of infected individuals in the simulation and space based approximate
 383 model corresponding to the MPC control carried out in (b). Here the prediction is reset to match the simulation
 384 at every update step (0.5 time units) and the control is re-optimised. By repeatedly correcting for differences
 385 between short-term model predictions and realised numbers of infected individuals – rather than relying on
 386 a potentially increasingly inaccurate prediction made at the initial time – MPC gives better predictions of the
 387 simulation state as well as improved control when compared to open-loop (note different y axis scales).

388 **Figure 3**

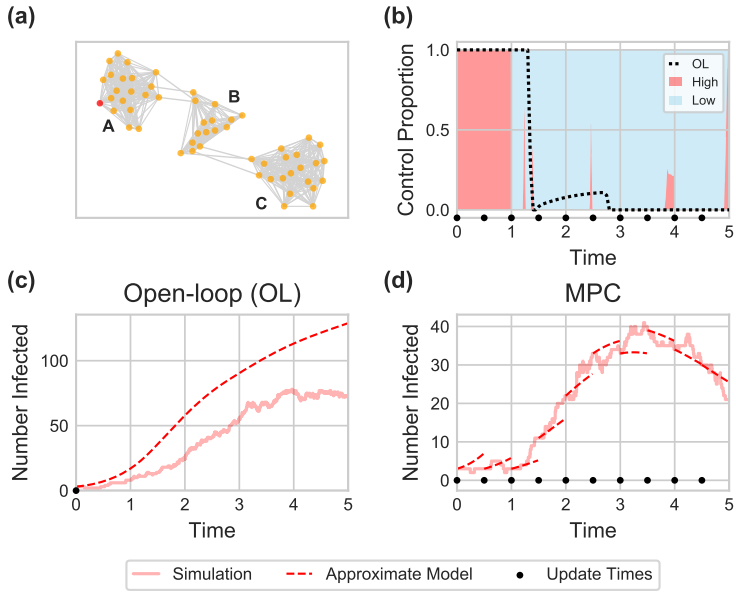
389 Results of different control optimisation schemes on the illustrative simulation model. Spatial MPC performs
 390 best, showing an improvement over both open-loop and user-defined strategies.

391 **Figures**

392 **Figure 1**

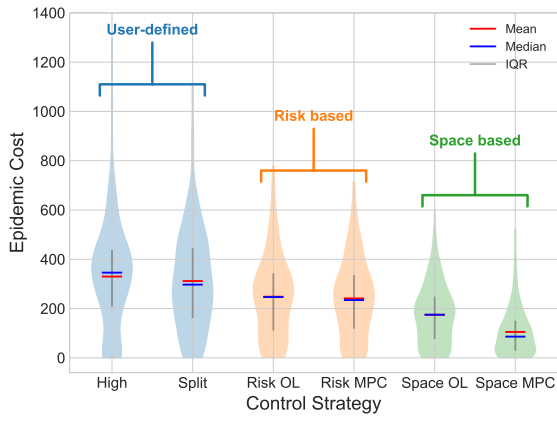


394 **Figure 2**



395

396 **Figure 3**



397