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APPLICATIONS OF MATHEMATICAL PROGRAMMING TO GENETIC BIOCONTROL

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Abstract

We review existing approaches to optimizing the deployment of genetic biocontrol technologies —tools used to prevent vector-borne diseases such as malaria and dengue—and formulate a mathematical program that enables the incorporation of crucial ecological and logistical details. The model is comprised of equality constraints grounded in discretized dynamic population equations, inequality constraints representative of operational limitations including resource restrictions, and an objective function that jointly minimizes the count of competent mosquito vectors and the number of transgenic organisms released to mitigate them over a specified time period. We explore how nonlinear programming (NLP) and mixed integer nonlinear programming (MINLP) can advance the state of the art in designing the operational implementation of three distinct transgenic public health interventions, two of which are presently in active use around the world.

Keywords

nonlinear programming; mixed integer programming; biomathematics; dynamic population model; genetic modification technology; public health; vector-borne disease

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1. Introduction.

Biological control uses living organisms to manipulate the dynamics of an unwanted population [12]. Historic examples include introducing foxes to regulate rabbits and employing entomogenous fungi to combat the spotted alfalfa aphid [35, 31]. Genetic biocontrol includes a subset of biological control approaches that directly alter the genes of a species or change the expression of certain traits, including via radiation or the artificial

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introduction of pathogenic microorganisms [6, 39, 4, 67]. Modified individuals are then released into the environment to mate with their wild counterparts and either suppress or substitute the population of interest over the course of multiple generations. The recent derivation of a synthetic CRISPR-Cas9 genome editing system that allows scientists to create novel gene drives—a phenomenon wherein the allele of a diploid gene present in a heterozygote is inherited more than 50% of the time, temporally accelerating and spatially expanding potential results—holds great promise for the efficacy of future genetic biocontrol tools [10].

This paper focuses on an entomological use case of genetic biocontrol for epidemiological ends: the mitigation of mosquito vectors. The illnesses transmitted by mosquitoes—including malaria, dengue fever, and the chikungunya and Zika viruses—generate massive human health and economic burdens, with dengue alone estimated to infect 390 million people and cost $8.9 billion annually [27, 35, 52]. Such numbers are expected to increase; escalating land-use change and global warming are growing the regions suitable for these arthropods [48, 15, 51, 45, 18] even as insecticide resistance rises [31, 32, 54]. Managing the current and future threats presented by mosquitoes requires augmenting traditional prevention mechanisms with the novel technologies enabled by genetic methods. However, it also demands a precise analytical approach to defining the operational application of such tools under diverse scenarios: it is this need that motivates the present work.

Currently, the design of transgenic public health interventions—their spatial layout as well as the timing and size of modified organism deployments—is informed by field trial experimentation and expert opinion [8, 46, 43]. Computational simulations can also furnish guidance about the potential release requirements of a given scenario [41, 66]. However, empirical measurement in ecology comes at great effort and with a large possibility for error. Meanwhile, simulation carries no guarantees of mathematical optimality. Optimal control has been explored as a means of optimizing the strategic implementation of both suppression and replacement-based genetic tools; mathematicians have succeeded in identifying, for example, the necessary temporal and spatial distribution to achieve specified reductions in wild population levels [2, 22]. But release strategies derived using optimal control have limited operational relevance to the domain of genetic biocontrol. Biological systems are complex; incorporating the multiple dimensions of information necessary to prescribe action for a realistic intervention program can quickly prohibit obtaining the closed-form solutions that characterize optimal control approaches.

Mathematical programming offers a viable alternative wherein more details may be accommodated and numerical solutions obtained. In section 2, following a brief review of the state of the art, we formulate a mathematical program grounded in dynamic population equations to obtain optimal intervention policies across a network. In section 3, we share the outcomes of computational experiments applying this mathematical program to three genetic-based methods designed to mitigate vector-borne disease: release of Insects carrying a Dominant Lethal gene (RIDL), an engineered suppression technology currently undergoing multiple field trials; *Wolbachia* population replacement, a now widely deployed approach that in our featured example employs transfected *w*Mel bacteria as stably inherited pathogen blockers; and Homing Gene Drive (HGD), a representative single-locus homing

replacement gene drive that has to date been strictly tested in laboratory settings. In section 4, we analyze these results. Each optimized release strategy accounts for the unique properties of the genetic system being tested, the regional temperature conditions under which releases are simulated, the thermal biology of both wildtype and modified organisms, geographic topology, and operational constraints. We close with a discussion of how mathematical programming may be used to enhance the epidemiological effectiveness of transgenic interventions while curtailing their environmental and monetary expense.

2. Methods.

2.1. Current practice in biology.

Optimal control has been explored for both suppression and replacement-based genetic interventions, with some works seeking to optimize these technologies as one facet of an integrated vector management (IVM) strategy [3, 16, 38, 36, 2, 14, 47, 1]. But this customary approach to optimization in the biological sciences uses continuous time models rather than discrete ones. It therefore involves synthesizing a function called the Hamiltonian —an instantaneous increment of the Lagrange expression of the problem to be optimized over the time horizon—to find the adjoint equation for each state and solve the dynamical system [24].

The states in these formulations represent constraints of the minimization (or maximization) problem, and the adjoints can be interpreted as Lagrange multipliers associated with the state equations which constitute the marginal cost of violating those constraints [57]. The technique, as applied to deterministic ordinary differential equations in the context of minimization, is to solve a set of necessary conditions to be satisfied by the optimal control u* and corresponding state x*. Those necessary conditions are derived according to the inverse of the inequality in the Pontryagin maximum principle. This principle converts the problem into one of minimizing the Hamiltonian pointwise with respect to the controls [49].

Because the systems of interest in questions of genetic biocontrol can include multiple states—for example, states representing susceptible, infected, and recovered individuals, or states differentiating female disease vectors from their nonbiting male counterparts and wildtype organisms from genetically modified ones—the derivation of the Hamiltonian soon becomes intractable if too many such details are included [40]. Extensive reformulations or system simplifications are therefore necessary to apply optimal control methods to research questions in this domain. Unfortunately, abridging the genetic, biological, or ecological features included in a problem's formulation can limit the utility of its results.

2.2. Advantages of mathematical programming.

Mathematical programming is a computational method that can be used to optimize the application of genetic-based vector control technologies with comparative comprehensiveness and ease [56]. While this subset of analytical tools—which includes a variety of problem classes, from linear to quadratic to second-order cone programs—is not conventionally used in the biological sciences, it is common to optimization efforts in other domains, among them engineering, management, and transportation [29]. Discretizing

continuous models and solving them numerically is less mathematically demanding and more accommodating to large state spaces. Mathematical programs are well-suited to hypothesis testing once the first formulation is created, enabling quick iteration via alternative objective functions and constraints [29]. Further, robust software libraries like Interior Point OPTimizer (IPOPT) available to solve them either supply the assurance of an optimal solution or return a statement of infeasibility.

One notable example of an integer linear program (ILP) developed for the public health arena seeks to spatiotemporally allocate a series of five malaria interventions alone or in combination and subject to budget constraints, with the objective of minimizing person days of infection over all timesteps [20]. This is an innovative multiyear extension of a previously formulated single-stage model that identifies one action (intervention or no intervention) per approximately 270,000 total geographic regions [19]. The work also exhibits a powerful pairing of ILP and ordinary differential equation (ODE) techniques: the mathematical program takes as inputs the outputs of a compartmental ODE model portraying malarial disease dynamics, such that the person days of infection can be minimized by the prescribed intervention(s). By including disease dynamics, the authors connect their ILP with the epidemiological process at the core of the public health problem for which they are optimizing solutions.

2.3. A mathematical program for genetic biocontrol.

The work presented here is not a top-down planning model intended to select from an array of available intervention types. Rather, our objective is to demonstrate how a fine-scale model can guide the operationalization of individual interventions using genetic tools. Therefore, we directly optimize the vector dynamics that underpin epidemiological patterns of mosquito-borne disease by using the Euler approximation method and a daily timestep to discretize a system of ODEs representing a mosquito population. The discretized population equations furnish the equality constraints of our nonlinear program (NLP). The control variable in the optimization problem constitutes modified individuals of the same species as the target vector. Operational factors enter the problem via inequality constraints on these control variables, e.g., bounds on the timing, size, and frequency of releases. We then extend the model to enable binary constraints on the spatial location and timing of interventions. This converts the problem into a nonlinear mixed integer program (MINLP) and permits optimization of the decision to realize an intervention (or not) in a particular node of the modelled network at a given timestep.

This approach is an advance over important optimal control efforts that are also grounded in vector population dynamics, or those which also employ constraints on both states and controls. First, our model does not exclude the juvenile periods in a mosquito's stage-structured life cycle that are crucial to density dependent mechanisms and environmentally sensitive development. Second, there is a notable distinction between constraints on the controls of comparable optimal control problems versus the controls of the mathematical program developed in this work. The former must first determine the restrictions on the controls that guarantee the optimal solution. While theoretically very interesting, the results of this process require adaptation to inform realistic operational design, and it is difficult

to determine the optimality—or feasibility—that might be lost in that conversion. Our mathematical program, on the other hand, enables a numeric search for the optimal schedule of interventions given operational constraints.

We augment the realism of the present problem formulation and differentiate it from earlier optimization efforts in the realm of genetic biocontrol by considering geography explicitly, that is, by defining discrete nodes that are connected via bidirectional migration into a network. Because alternative parameterizations can be accommodated in a straightforward way using mathematical programming, our model also accounts for the differences in dynamics that result from allowing critical data values such as mortality and maturation duration to respond to fluctuating daily temperatures. Additional variability enters via the three genetic tools examined, each of which drives different population dynamics and therefore leads to diverse optimal intervention strategies.

Figure 1 illustrates basic information underlying all computational experiments described in this work—namely temperature inputs, baseline population dynamics, and the topology of the network. The implementation of the NLP is detailed in subsection 2.4; the MINLP implementation is explained in subsection 2.7. The model is written in JuMP, the domain-specific modeling language embedded in Julia [21, 9]. Solvers used include IPOPT, HSL-ma86, Pardiso, Gurobi, Cbc, Juniper, and Bonmin [65, 28, 37, 11]. All code used to run the individual experiments draws on the GeneDrive.jl software package [58] and is accessible on Github [64], with resulting data outputs stored on Figshare [62, 63, 61, 59, 60].

2.4. Implementation: Nonlinear program.

The nonlinear program formulation defines sets, parameters, and decision variables of both biological and operational significance. Sets include the following:

- *Geographic nodes (N)*: The spatial structure across which an intervention is deployed informs population dynamics according to the network layout (e.g., linear, circular, on a grid, etc.), the degree of connectedness between nodes, and the rate at which organisms disperse between discrete locations. This in turn affects the optimal distribution of transgenic releases necessary to achieve a given objective. Nodes are denoted by the index n.
- *Organisms (O)*: An environmental benefit of genetic biocontrol is that interventions strictly target a particular vector species. These unique biological dynamics can therefore be isolated and modelled. Our model reflects the dynamics of the Ae. *aegypti* mosquito, a primary vector of dengue fever, chikungunya, and Zika; this is achieved via the parameterization described below. Organisms are defined by the index o. Because only one species is modelled in this work, o is not explicitly reflected in (2.1).
- *Stages (S)*: Mosquitoes, like other hemimetabolous and holometabolous arthropods, are well represented by stage-structured population equations that subset their life cycle into juvenile and adult phases, with adults evenly divided between males and females. To enable temperature-sensitive development using

Erlang-distributed bins, each stage constitutes a uniquely sized set. The index s is used to model Stages.

- *Genes (G)*: Genetic-based intervention mechanisms rely on the propagation of specific modifications through subsequent generations. Implementing and monitoring the introgression of those changes therefore requires distinguishing the genotypes present in a population. Each of the three interventions modelled here requires distinctly sized genotype sets; *Wolbachia* features two dimensions, RIDL has three, and HGD has six (considering the case of a single homing-resistant allele). Genotypes are defined by the index g.
- *Time (T)*: The time horizon over which a population is modelled and within which an intervention is implemented. All examples presented in this work assume a one year period in 365 daily timesteps. Time is denoted by the index t.

2.5. Parameters and state variables.

State variables E, L, and P represent the juvenile mosquito life cycle periods of egg, larva, and pupa, respectively, while adults are evenly divided between males and females as state variables m[1] and F. All are indexed by genotype g and time t as well as i, with the latter representing the *Erlang*-relevant modeling artifact used to subset each stage s.

The number of eggs laid per genotype is calculated using β_g and σ_g, which are genotype-specific female and male fecundity and fertility parameters, and the inheritance and survival probability of the specified genotypes, namely $\mathbf{\Gamma_g}$ and $\mathbf{T_g}$. The θ_g parameter dictates the male to female emergence ratio of offspring, while η_g prescribes male mating fitness. The data values for genetic parameterizations in the RIDL examples are derived from Carvalho et al. [17], while that of the *Wolbachia* and HGD examples are sourced from Hoffman et al. [33] and Gantz et al. [25], respectively [17, 33, 25]. The implementation of all three constructs is reflected on Github and draws from Sánchez [55]. While both RIDL and *Wolbachia* implementations reflect midrange field estimates of fitness costs on modified organisms, the HGD examples presume equivalent fitness between wildtype mosquitoes and their transgenic counterparts. Mortality rates μ and development rates q are dynamically calculated for each timestep according to temperature inputs using empirically calibrated functional forms; the same values apply to both wild and modified organisms [50]. Data used as temperature inputs is representative of seasonal fluctuations in a temperate location of the southern hemisphere endemic to *Ae. aegypti* mosquitoes. Logistic density dependence d_L is implemented in the larval stage L for all genotypes per timestep in each node.

2.6. Decision variables.

The decision variables enter as the $c_{\hat{g},t}$ terms added to the equality constraint for the life stage appropriate to the mechanisms of a given genetic-based intervention method (adult males in the case of RIDL and HGD; both adult males and adult females in the case of

[1]"m" rather than "M" is used to denote the fact that males are modelled as a vector rather than a matrix, and thus the capitalization of the variable follows convention.

Wolbachia). Each is indexed by g to denote the genotype responsible for the biocontrol action (suppression or replacement) and t to specify the time of deployment.

2.7. Implementation: Mixed integer nonlinear program.

The mixed integer formulation, which takes the form of an MINLP, builds on the sets, parameters, and decision variables described above. It extends the problem by constraining the release variable $R_{n,t}$ to be binary, such that the decision to deploy interventions or not in a particular node n of the network and timestep t becomes a binary choice.

2.8. Model.

Using these sets, parameters, and decision variables, we define the following mathematical program:

$$\min_{c_{g,t}} J(F_{n,g,t}, \alpha c_{g,t}) \quad \text{s.t.} \tag{2.1a}$$

$$E_{g,t,1} = \sum_{s=1}^{N} (\beta_g \sigma_g (\mathbf{\Gamma}_g \odot \mathbf{T}_g)_s F_{t,s}) - E_{g,t,1}(\mu_E + q_E s_E) \quad \forall g, t, \tag{2.1b}$$

$$E_{g,t,s} = E_{g,t-1,s-1} - E_{g,t,s}(\mu_E + q_E s_E) \quad \forall g, t, s = 2 \ldots s_E, \tag{2.1c}$$

$$L_{g,t,1} = E_{g,t,s_E} - L_{g,t,1}(\mu_L d_L + q_L s_L) \quad \forall g, t, \tag{2.1d}$$

$$L_{g,t,s} = L_{g,t-1,s-1} - L_{g,t,s}(\mu_L d_L + q_L s_L) \quad \forall g, t, s = 2 \ldots s_L, \tag{2.1e}$$

$$P_{g,t,1} = L_{g,t,s_L} - P_{g,t,1}(\mu_P + q_P s_P) \quad \forall g, t, \tag{2.1f}$$

$$P_{g,t,s} = P_{g,t-1,s-1} - P_{g,t,s}(\mu_P + q_P s_P) \quad \forall g, t, s = 2 \ldots s_P, \tag{2.1g}$$

$$m_{g,t} = P_{g,t,s_P} q_P s_P (1 - \theta_g) - m_{g,t}\mu_m + c_{\hat{g},t} \quad \forall g, t, \tag{2.1h}$$

$$F_{g,t,s} = P_{g,t,s_P} q_P s_P \theta_g \frac{m_{g,t}\eta_g}{\sum_{k=1}^{N} m_{k,t}\eta_k} - F_{g,t,s}\mu_F + c_{\hat{g},t} \quad \forall g, t, s, \tag{2.1i}$$

$$c_{\hat{g},t} \leq R_{n,t} D_{max}^{day} \quad \forall t \in \mathcal{T}_d, \tag{2.1j}$$

$$c_{\hat{g},t} \geq R_{n,t} D_{min}^{day} \quad \forall t \in \mathcal{T}_d, \tag{2.1k}$$

$$\sum_{t \in \mathcal{T}_d} c_{\hat{g},t} \leq D_{max}^{trial}. \tag{2.1l}$$

The objective function jointly minimizes the number of vector competent mosquitoes F and the number of transgenic organisms c released to mitigate them, where α is a modeling artifact used to weight the controls with a value of e^{-8}. We seek to reduce the count of females because it is the sex that obtains blood meals and is therefore responsible for transmitting disease. The particular goals of a given public health intervention in suppressing the standing genotype g using the modified genotype $\hat{g}$ may differ according to node n or across time t; this is also influenced by the constraining set $\mathcal{T}_d \subset \mathcal{T}$, which is defined as the days when releases $\mathcal{R}$ in node n and time t are permitted. D_{max}^{day} and D_{min}^{day} denote, respectively, the maximum and minimum number of organisms released daily. To conduct the computational experiments featured in section 3, we study the outcome of two alternative versions of the function J in the objective. These are defined below. The sets $N_i \in N, G_i \in G$, and $T_i \in T$ refer to the node, genotype, and time period of operational interest, respectively:

$$\min_{c_{\hat{g},t}} \sum_{n \in N_i} \sum_{t \in T_i} \left(\sum_{g \in G_i} (F_{n,g,t} - \psi F_{n,g,1})^2 + c_{\hat{g},t} \right), \tag{2.2}$$

$$\min_{c_{\hat{g},t}} \sum_{n \in N_i} \sum_{t \in T_i} \left(\sum_{g \in G_i} \left(F_{n,g,t} - \gamma^t F_{n,g,1} \right)^2 + c_{\hat{g},t} + \rho R_{n,t} \right). \tag{2.3}$$

The first implementation of the objective function, (2.2), minimizes the count of vector competent females in each time step from $t = 200$ of the simulation through the end of the horizon ($t = 365$) by a factor of ψ with respect to the first day of simulation $t = 1$, using the minimum number of modified organisms $c_{\hat{g}}$. The value of $\psi = 0.20$ for all experiments. This objective assigns equal priority to all five nodes of the network.

The second version of the objective function, (2.3), minimizes the count of vector competent females in each time step by a factor of γ^t with respect to the first day of simulation $t = 1$, again while using the minimum number of modified organisms $c_{\hat{g}}$. In this case, the value of $\gamma = 0.98$ for all experiments. The variable $R_{n,t}$ and weighting parameter $\rho = e^{-8}$ are used to minimize the number of nodes in which releases are designated; this only impacts the strategies produced by the MINLP, wherein $R_{n,t}$ is binary. In the featured NLP and MINLP examples, objective function (2.3) targets a single location (node four) rather than the entire network, simulating a localized outbreak that demands the design of a regional public health intervention strategy. It demonstrates the difference in decisions enabled by the MINLP versus the NLP when taking spatial structure into account.

The equality constraints in (2.1) comprise the population dynamics of the mosquito vectors across the five life stages, biologically bounding the feasibility of the program. Constraints representing nonbiological or operational limitations, such as resource availability and geographic reach, enter as inequality constraints on the decision variable ($c_{\hat{g},t}$ for the NLP; both $c_{\hat{g},t}$ and $R_{n,t}$ for the MINLP) in (2.1). Because the constraints are defined on a per-node basis within the network, spatially explicit policies can be explored across heterogeneous topologies. For the experiments whose descriptions follow in subsection 3.1, D_{max}^{day} were set to 50, 000.00 modified organisms and D_{max}^{trial} to $9e^9$. The same D_{max}^{day} and D_{max}^{trial} values were used for the results shown in subsection 3.2. The minimum constraint of D_{min}^{day} was additionally employed in the MINLP runs, representing the size of a single unit (containing box) of transgenic mosquitoes. This enforced the requirement that the binary decision $R_{n,t}$ be contingent on making a release of an operationally realistic magnitude.

3. Experimental outcomes.

The first set of results in subsection 3.1 reflect simulations conducted using objective functions (2.2) and (2.3) in turn to optimize the model as an NLP; the second set of results in subsection 3.2 employs objective (2.3) to rerun the model as an MINLP. All outcomes are calculated assuming the temperature inputs, population dynamics, and five-node network structure shown in Figure 1. The per-individual migration rate of adult males and adult females is the same in both directions for all connected nodes and for all timesteps; juvenile stages do not migrate.

Each computational experiment is replicated using the three different technologies, two of which—*Wolbachia* and RIDL—are being actively deployed and one of which—HGD—is representative of a single locus homing drive that employs CRISPR-Cas9 and remains under laboratory development. The decision variable $c_{\tilde{g},t}$ required to model these technologies differs in the sex of the released organism: For RIDL and HGD, only male modified organisms are released. For *Wolbachia*, both males and females are released. In all plots showing results of the latter, female population dynamics for both released organisms and wildtypes are shown in the same panels.

3.1. Results: Nonlinear program.

First we present the outcome of applying objective function (2.2) to the NLP, with the left-hand panels of Figure 2 displaying the optimal schedule of modified male releases and the right-hand panels reflecting the corresponding female dynamics. Figure 2(d) depicts both modified and wildtype females.

Next, we show the results of objective function (2.3), which targets a localized outbreak in node 4 when employed with the NLP model. Figure 3 illustrates outcomes using the RIDL construct, Figure 4 using *Wolbachia* replacement, and Figure 5 using HGD. In each set of figures, we show decisions and the corresponding dynamics across individual nodes of the network, again with all left-hand panels featuring the optimal schedule of modified male releases and right-hand panels reflecting the female dynamics that are produced by those releases.

3.2. Results: Mixed integer nonlinear program.

Here we display the results of objective function (2.3) applied to the MINLP formulation. Because an initial MINLP experiment using RIDL parameters did not produce binary 1.0 or 0.0 values for all locations and timesteps of the $R_{n,t}$ variable, we established a methodology to postprocess results and consistently applied it to all MINLP outcomes.

Two algorithms were developed to assess the effect of different heuristic approaches; these are specified in the supporting information on Github and can be described generally as follows: For the first approach, hereafter described as heuristic “A,” the only control decisions that were retained in the refined policy schedule were those which met or exceeded the D_{min}^{day} value. Under heuristic “B,” the only releases preserved were those corresponding to within 0.1 of a binary $R_{n,t} = 1.0$.

Figure 6 illustrates outcomes using the RIDL construct. Figure 7 displays MINLP results using *Wolbachia* population replacement technology.

4. Discussion.

4.1. Analysis of NLP results.

Results from the initial set of computational experiments in subsection 3.1 were generated employing objective function (2.2), which sought to minimize disease competent mosquitoes across the entire network. This produced the same optimal schedule of releases for all 5

nodes of the network per simulated technology. While the experimental inputs are equivalent aside from the parameterization reflecting choice of genetic biocontrol tool, a notably different intervention policy is prescribed under the RIDL, *Wolbachia*, and HGD scenarios. This outcome reflects the need for mathematical approaches that can account for the unique population dynamics driven by a particular transgenic technique.

Even genetic tools that employ comparable mechanisms can have distinct impacts on the dynamics of the standing population. For example, both the timing and magnitude of releases optimized for *Wolbachia* and HGD vary greatly as shown in Figure 2(c) through Figure 2(f). The difference in deployment schedules illustrate the relatively greater invasiveness of *Wolbachia* compared to HGD despite modeling assumptions that imbue the former with a greater fitness cost. This superior introgression enables a single release of infected organisms at the beginning of the simulation period to achieve more suppression of wildtypes than was realized by the HGD construct using deployments at the end of the simulation period that are larger and more frequent.

None of the simulations featured in this work is designed to emulate the results of a real study. However, the optimized policy output for the sole suppression method shown here, RIDL, broadly supports the “prophylactic” logic that has governed the implementation of field trials using it [5, 26, 17]. Figure 2(a) depicts a schedule of initial overflooding (repeated large releases) followed by a lesser rate of deployments that serve to maintain levels of population reduction as illustrated in Figure 2(b). Because the biological and operational constraints of the NLP are straightforward to iterate, alternative environmental inputs and the resource limitations encountered in actual field cases—including material and time costs—can be used to further refine this release policy, tuning it for regionally relevant recommendations.

The NLP results shown in Figures 3, 4, and 5 apply objective function (2.3), which prioritizes the minimization of disease vectors in node 4. These simulations highlight the utility of mathematical programming in addressing spatial questions and serve as a point of comparison with the MINLP results that follow in subsection 3.2. Geographic information such as topological layout and connectivity was also included in the first cadre of NLP computational experiments, but a spatially relevant objective function in the second set of experiments presents the opportunity to exploit these details in the design of a regional strategy to reduce disease risk (the count of wild adult female *Ae. aegypti*) at a single “outbreak” location (node 4).

While the specifics of the NLP release schedules under objective function (2.3) differ for each technology, all three examples expend fewer releases of lesser magnitude in nodes 1–3 than in nodes 4 and 5. Independent of tool type, deployments in the first three more densely interconnected locations would be comparably less effective in achieving the objective. Because the NLP is able to accommodate details such as dispersal direction, migration rate, and degree of connectedness, unnecessary actions can be minimized. From an operational perspective, interventions guided by such outputs can stand to benefit by cutting costs in the form of the materials, time, and labor that might otherwise be expended to conduct a less targeted public health campaign. Releases do nonetheless occur in nodes 1–3 because the

NLP is not afforded the opportunity to entirely forgo action in those locations: to analyze the impact of including that optionality in the optimization, we turn to the results of the MINLP exhibited in subsection 3.2.

4.2. Analysis of MINLP results.

The MINLP formulation constrains the release variable $R_{n,t}$ to be binary. This extension enables the program to waive deployments entirely in a particular location. To explore the potential utility of optimizing over this choice, and to furnish the opportunity to make a direct comparison with the NLP alternative, the MINLP simulations employ the same geographically pertinent objective function (2.3) that minimizes disease vectors in one node of the larger network. MINLPs are NP-hard, uniting the "challenges of handling nonlinear functions with the combinatorial difficulty of optimizing over discrete variable sets" [7, 42, 44]. In recent years, there has been increased attention to this class of problems, corresponding with significant improvements in the solution methods required to solve the NLP and MILP subproblems that comprise them as well as a heightened recognition that MINLPs are well-suited to modeling real-world questions [23].

In this work, we weigh the complexity of formulating and solving MINLPs against their potential for enhancing the efficiency of a genetic biocontrol intervention. The problem at hand is nonconvex; therefore, we are interested in the possibility of producing a high-quality *feasible* solution in the spirit of D'Ambrosio and Lodi [23], wherein "solving" does not imply a global outcome [23, 13]. We employ two alternative heuristics to postprocess the results of the MINLP and subsequently assess the effect of these refined release schedules on the objective function value. In Figure 6(e), Figure 6(f), Figure 7(e), and Figure 7(f), we also qualitatively compare the node-specific population dynamics produced by each MINLP policy with the outcome of the corresponding NLP.

The MINLP model includes a minimum constraint on daily deployments, D_{min}^{day}, that is not used in the NLP formulation. This was designed to help "make the case" for a mixed integer representation of the problem, hinging the choice to make an intervention at a given time and location on deployments that conform to at least one unit of transgenic organisms. For the RIDL simulations, $D_{min}^{day} = 1{,}000.0$ in accordance with the volume of the containing tube described in Garziera et al. [26]. The D_{min}^{day} value applied to the RIDL case was infeasible for the *Wolbachia* experiments because under the present problem specifications, the highly invasive population replacement technology demands deployments that are individually smaller than this minimum release size in all but one instance.

Figures 6(a) and 6(b) depict the schedule produced for the RIDL MINLP using heuristic "A" for nodes 4 and 5 of the network; Figures 6(c) and 6(d) show the same for heuristic "B." Both "A" and "B" criteria produced a policy of zero RIDL deployments for nodes 1–3. Figures 6(e) and 6(f) compare the population dynamics caused by these interventions to those driven by the NLP schedule; the result of "A" is essentially equivalent to that of the NLP, and "B," while less suppressive than the others, still succeeds in vector reduction. The objective values of each simulation $\left(NLP = 2.04304e^5, A = 2.04305e^5, B = 1.22399e^6\right)$ are in keeping with this qualitative assessment of comparative efficacy.

The panels of Figure 7 exhibit the outcomes of the *Wolbachia* experiment under each heuristic method; for the "A" as well as the "B" scenarios, releases were made in all nodes of the network. Notably, the *Wolbachia* MINLP did conclude with strictly binary values for the $R_{n,t}$ variable. Because the D_{min}^{day} used for RIDL was not applicable for this technology, heuristic "A" was conservatively based on $D_{min}^{day} = 1.0$, drawing on modeling and laboratory efforts that have found that introgression, pending contextual factors, is possible under even extremely stringent assumptions of *Wolbachia*-infected female escape or deployment [53, 66]. The release schedules and resulting population dynamics produced by both "A" and "B" postprocessing approaches are highly analogous across all nodes of the network; these similarities are supported by the objective values they generate in the model $\left(NLP = 5.6993975e^{6}, A = 5.7003275e^{6}, B = 5.7003277e^{6}\right)$.

4.3. Concluding remarks.

This paper explored applications of mathematical programming, including NLPs and MINLPs, to three genetic biocontrol technologies designed to manage populations of disease-transmitting mosquitoes. The formulations presented here enabled the inclusion of more detail than has been tractable to accommodate using the current state of the art for optimization in this domain, optimal control, while offering a greater degree of planning-relevant precision than can be expected of expert opinion or field trial-based guidance. Because it can be demonstrably tailored to account for the properties of diverse genetic tools, geographic realities, regional ecological conditions, and resource limitations, this work furnishes a potential analytical approach for defining the operational application of novel public health intervention techniques in myriad settings. From an epidemiological perspective, such flexibility can help to improve the effectiveness of a proposed deployment campaign. From an economic perspective, utilities include the option to calibrate interventions to save time, money, and materials in implementation. And from an environmental standpoint, it becomes feasible to scope plans such that the desired public health goals are achieved while the potential ecological consequences of excessive releases are mitigated.

Simulation results in section 3 showcase these advantages. For example, we can observe that NLP outcomes using (2.2) point to *Wolbachia* being the most epidemiologically and economically efficient, given experimental inputs, of the genetic tools assessed. However, in comparing the results produced by the NLP and MINLP, respectively, under (2.3), we also derive practical insight into the challenges of the latter class of mathematical programming problems. While MINLPs promise significant opportunity for the operational design of genetic biocontrol interventions as demonstrated by subsection 3.2 and discussed in subsection 4.2, developing the formulation of these problems to exploit them more fully demands further algorithmic improvement to their solution methods. This is left to future work. However, the present effort contributes two heuristic approaches with which to postprocess MINLP results, enabling the juxtaposition of NLP and MINLP case study outcomes and the assertion that, presently, the former furnishes robust insights to guide domain-relevant operational design that are nearly commensurate with MINLP outputs with the benefit of less computational cost.

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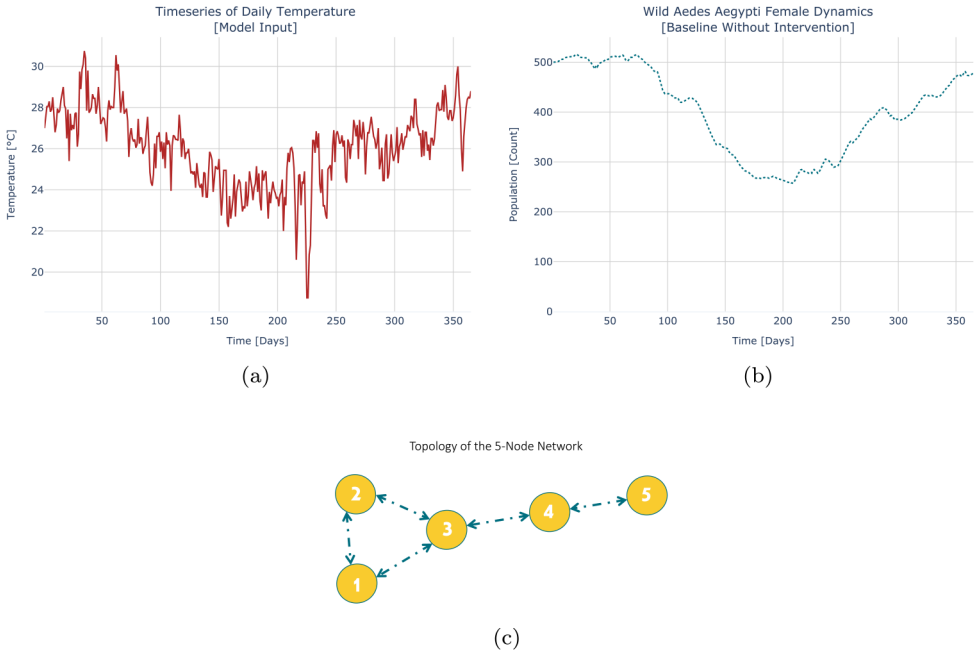

Fig. 1.

Panel (a) displays the annual time series of daily temperature used as model inputs for all experiments, while panel (b) shows the baseline, temperature-responsive population dynamics for Ae. aegypti females in the absence of any genetic biocontrol intervention. Panel (c) illustrates the structure of the geographic network across which all experiments are run.

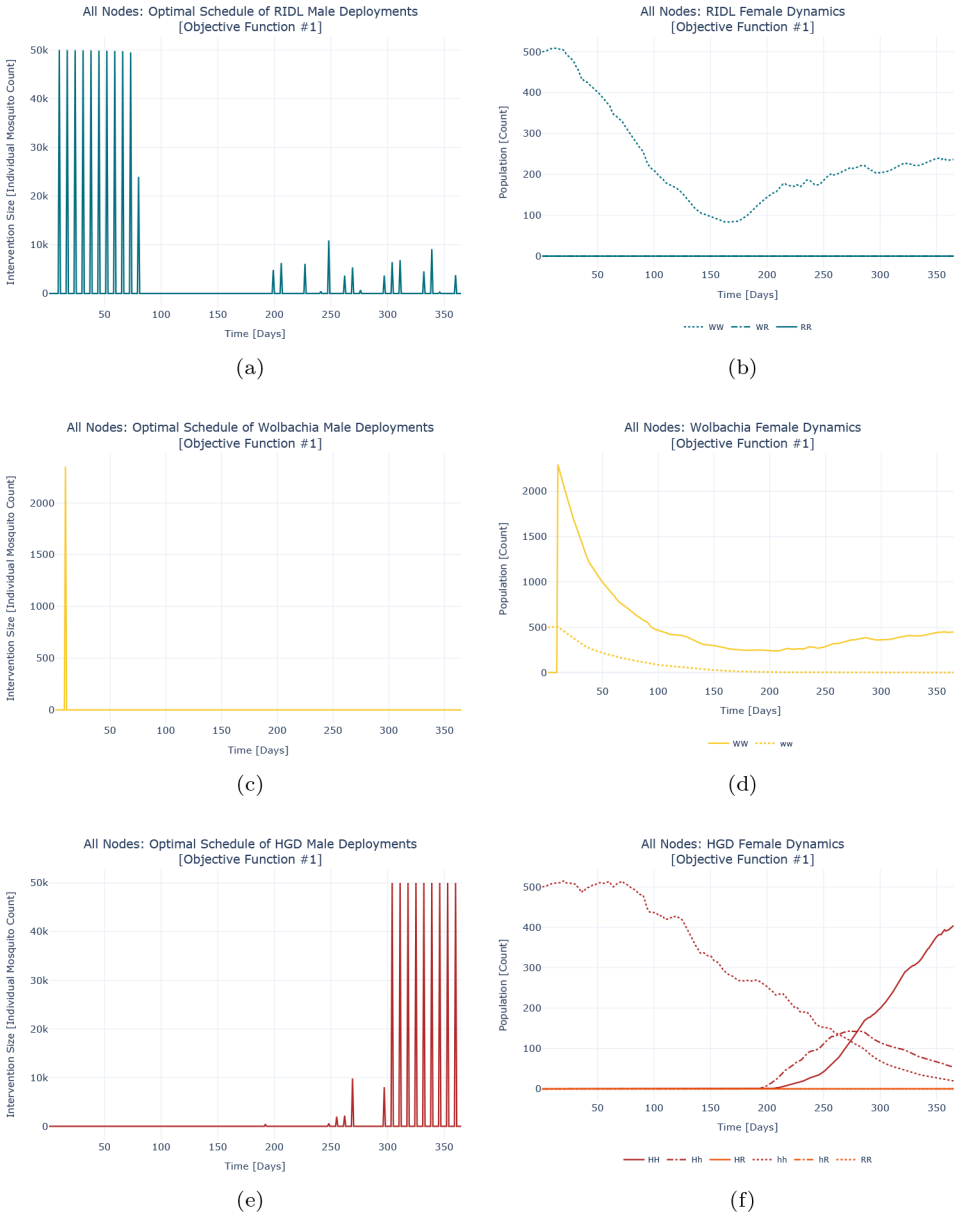

FiG. 2.

Left-hand column panels (a), (c), and (e) show the optimized decision policy for releases of genetically modified organisms across three distinct technologies. Right-hand column panels (b), (d), and (f) display the resulting dynamics of wild females (dotted lines) and, where applicable, the female mosquitoes that are heterozygous (dashed lines) and homozygous (solid lines) for the genetic modification. Colors denote the various technologies, with RIDL in green, Wolbachia in yellow, and HGD in red. In panel (f), the homozygous genotype is HH; the heterozygote is Hh.

FIG. 3.

Left-hand column panels (a), (c), and (e) show the optimal schedule of RIDL releases across each node of the network. Corresponding right-hand column panels (b), (d), and (f) display the resulting dynamics of wild females (dotted lines) in those nodes.

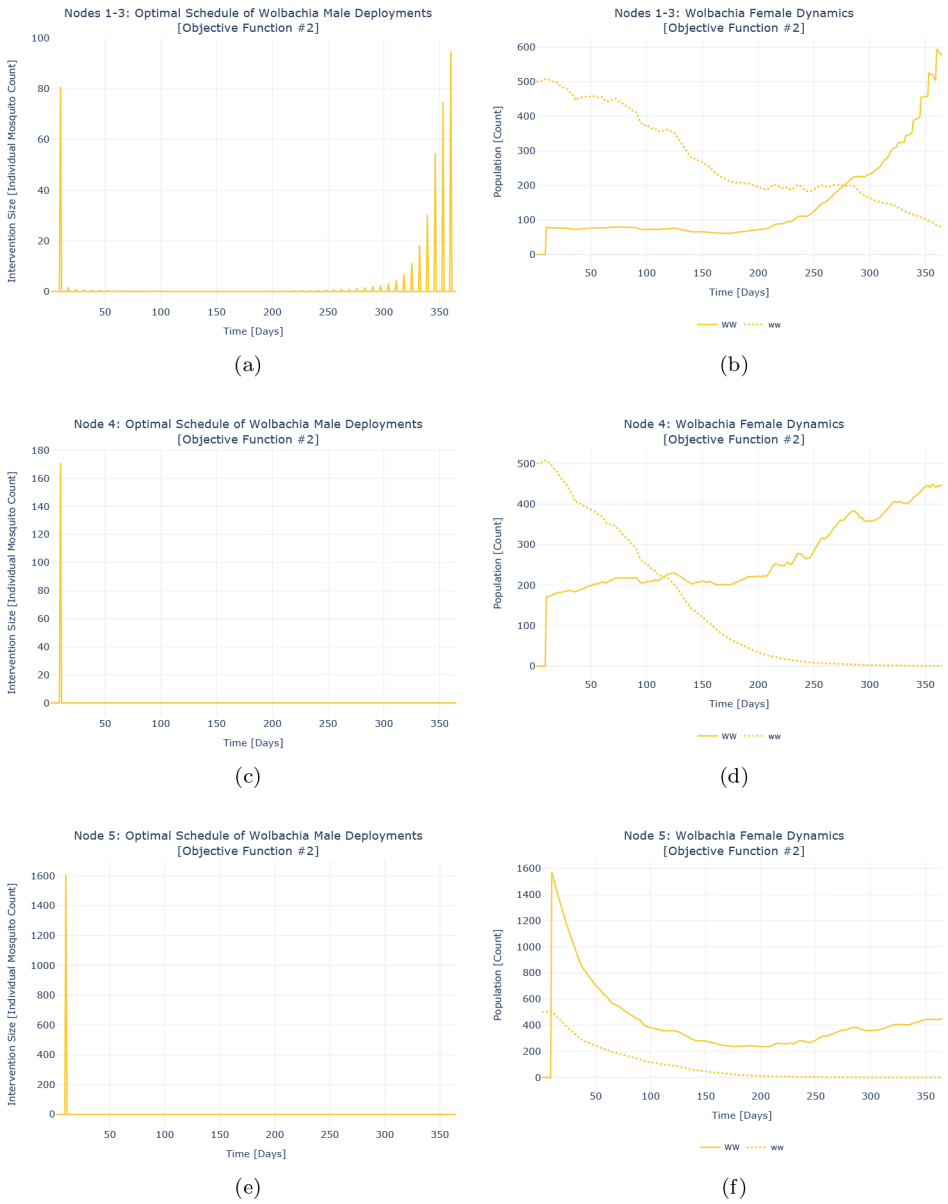

Fig. 4.

Left-hand column panels (a), (c), and (e) show the optimal schedule of Wolbachia male releases across each node of the network. Corresponding right-hand column panels (b), (d), and (f) display the resulting dynamics of wild females (dotted lines) and Wolbachia female carriers (solid lines) in those nodes.

FIG. 5.

Left-hand column panels (a), (c), and (e) show the optimal schedule of HGD male releases across each node of the network. Corresponding right-hand column panels (b), (d), and (f) display the resulting dynamics of wild females (dotted lines) as well as those females that are heterozygous (dashed lines) and homozygous (solid lines) for the HGD modification in those nodes.

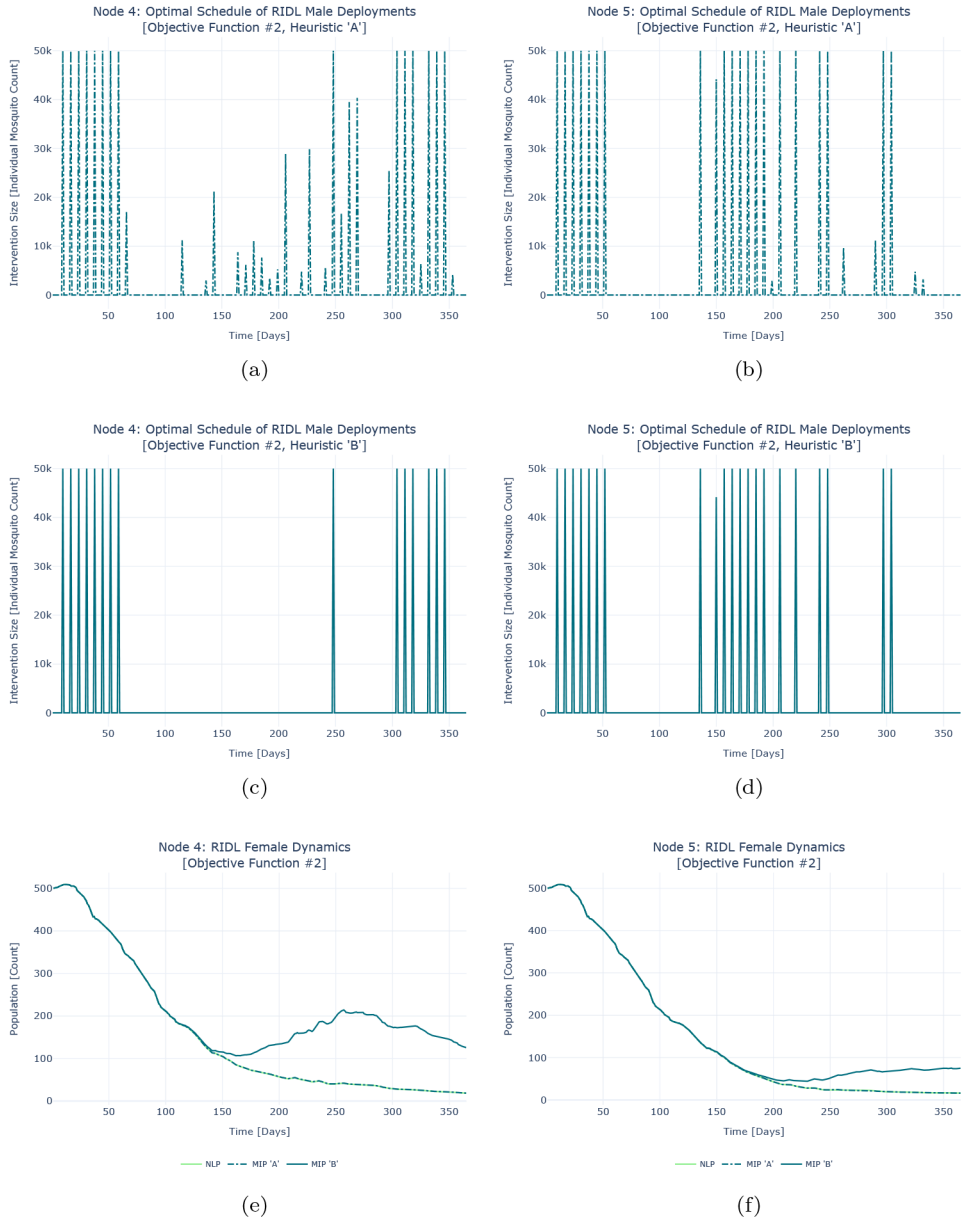

FIG. 6.

Left-hand column panels (a) and (c) show RIDL male releases for node 4 of the network when applying alternative postprocessing heuristics to the MINLP model results. Panel (e) plots the wild female population dynamics produced by these two schedules in node 4 alongside those generated by the NLP model under the same objective function (2.3). Right-hand panels (b), (d), and (f) show the same for node 5.

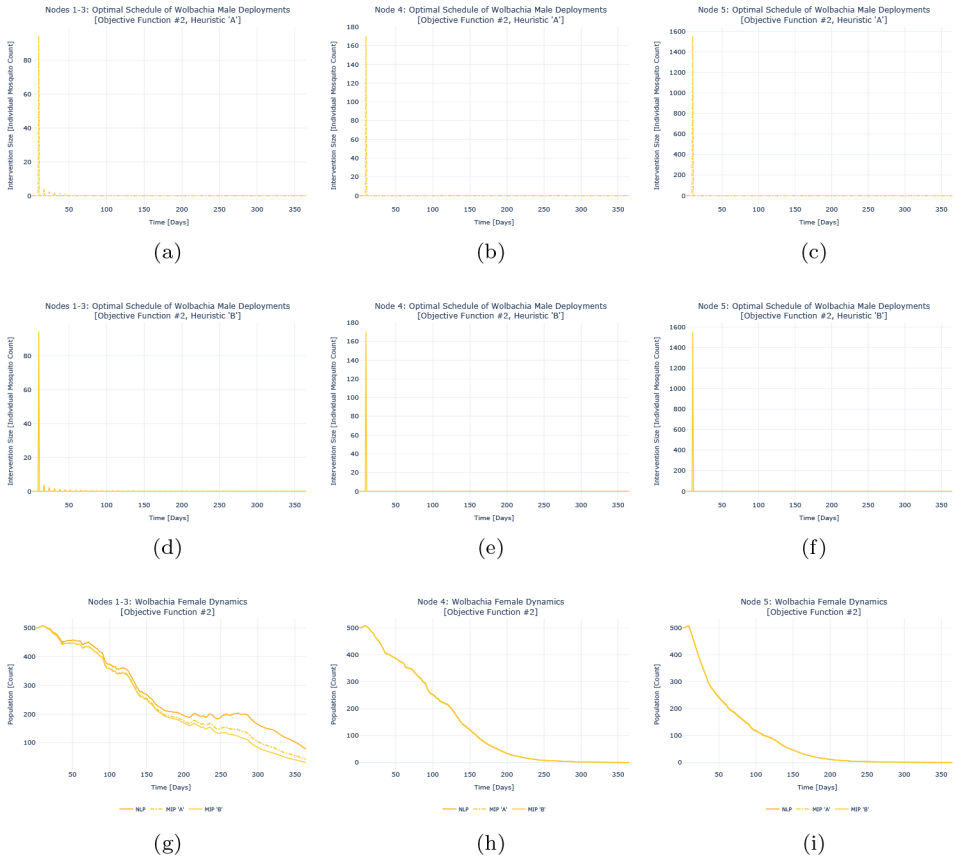

FiG. 7.

Left-hand column panels (a) and (d) show the optimal schedule of Wolbachia male releases for nodes 1–3 of the network. The wild female dynamics that result for each of the MINLP postprocessing routines are shown together with NLP-generated dynamics in g. Center column panels (b), (e), and (h) and right-hand column panels (c), (f), and (i) show the same series of information for nodes 4 and 5, respectively.