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Embracing Dynamic Models for Gene Drive Management

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Robust methods of predicting how gene drive systems will interact with ecosystems is essential for safe deployment of gene drive technology. We describe how quantitative tools can reduce risk uncertainty, streamline empirical research, guide risk management, and promote cross-sector collaboration throughout the process of gene drive technology development and implementation.

Management under Uncertainty

Gene drive technologies, although diverse in design and mode of action, are molecular architectures that promote the transmission of genetic information between generations. In theory, the release of one gene-drive-modified organism (GDMO) has the potential to irreversibly alter species, ecosystems, and environmental processes at a global scale (although in practice numerous mechanisms can limit invasiveness) [1]. This alarming and tremendous potential is an unprecedented challenge to biotechnology management that demands a different scope of oversight and coordination between public stakeholders, developers, and regulators [2,3]. Responsible management of GDMOs needs robust methods of risk assessment that account for and reduce uncertainties across different geographic and ecological contexts [1–3].

Dynamic Models for Guidance

Models are important tools for understanding how complex systems work and are widely utilized to inform regulatory decisions [4]. They provide a framework for integrating multiple data inputs to discover patterns and processes that are difficult to intuit. Their accuracy can be improved through an iterative process of model-driven data collection and data-driven model prediction, a practice that identifies and actively reduces important sources of uncertainty [5]. With the capacity to explore large regions of parameter space, models can help elucidate system drivers and behaviors that could take decades to reveal through empirical research, thus accelerating the cycle of hypothesis generation and testing during product development phases and for product evaluation prior to and during release phases. There are many different types of models that can be used to predict outcomes from data, but process-based models (e.g., how populations and allele frequencies change over time) are particularly useful for evaluating our understanding of the role of different processes (e.g., birth rates, homing rates, etc.) in predicting outcomes (e.g., invasion rates, and risk to non-target populations) [5–7]. Dynamic population genetic models (DPGMs) incorporate both the processes that lead to changes in population abundance and distribution over time (demography) and those that determine changes in allele frequencies (population genetics), allowing for prediction of GDMO propagation in space and time (Box 1). By specifying how GDMOs interact with complex ecological factors, DPGMs provide a tool for investigating the impact of GDMOs at population and ecosystem-scales that can be too uncertain or logistically challenging to safely study empirically.

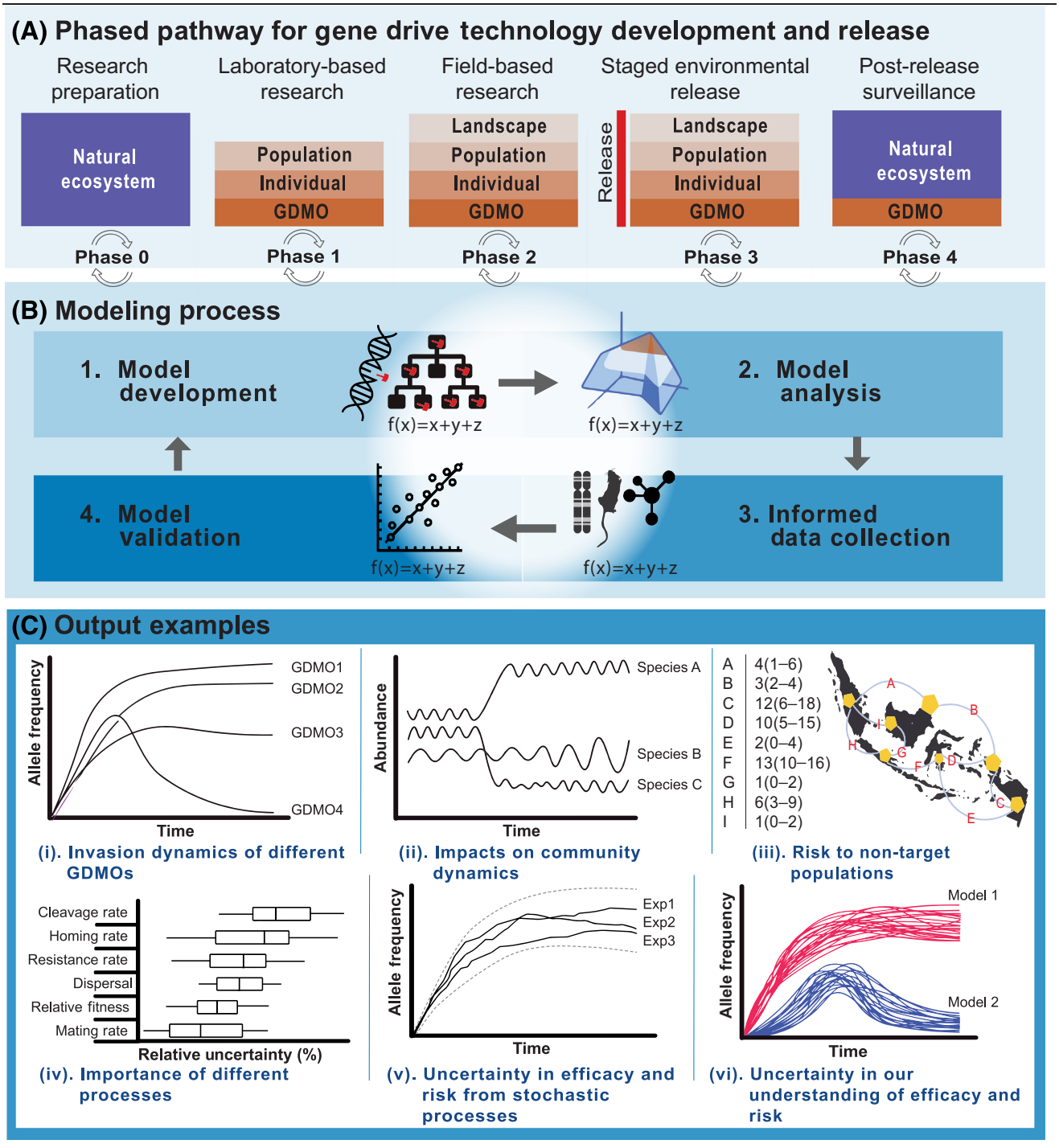
Challenges of Model-Guided Regulation

Integrating new methods of quantitative analysis, such as DPGMs, into the regulation of biotechnology faces logistical and institutional challenges. Considering models are an imperfect reflection of reality and can be difficult to communicate, concerns that they misrepresent system properties or bias outcomes of interest can make new methods of modeling difficult to trust. Furthermore, regulatory structures are frequently criticized as an encumbrance to innovation, and therefore, any alteration to the status quo may elicit resistance from regulators and developers that are not equipped with the technical knowledge to engage in new methods of analysis or the resource capacity to implement new procedures [8].

To implement quantitative tools, regulatory agencies generally depend on standardized modeling practices to streamline the potentially challenging and time-consuming task of continuously validating new evaluation approaches – an essential prerequisite for

Box 1. Model Structures throughout the Phased Pathway (Figure 1A)

DPGMs with parameters such as drive efficiency, resistance, and relative fitness can help inform GDMO design and evaluation at phase 1. For example, Nash and colleagues compare different molecular architectures and specifically outline individual traits that could be engineered into a GDMO during phase 1 [6]. DPGMs that integrate additional factors, such as age, sex, density, carrying capacity, genetic structure, and reproductive strategies can help understand how engineered GDMOs spread and impact population-level processes during phase 1 research (e.g., invasion thresholds, allele fixation, resistance dynamics, and demographic structure). For example, Walker and colleagues fit an age-structured DPGM to cage trial data to evaluate the performance of a dengue-blocking *Wolbachia* strain in populations of *A. aegypti* [13]. Research at phases 2 and 3 benefit from additional landscape-level extensions, such as social structure, spatial structure, habitat heterogeneity, and dispersal which help inform how GDMOs function over space and time (e.g., invasion kinetics, persistence, and nontarget impacts). Facchinelli and colleagues demonstrate how population-level DPGMs can be integrated into large-cage trials to validate that transgenic mosquito behaviors can be predicted in semirealistic conditions [14]. These extensions highlight the impact different ecological contexts might have on the rate that a particular GDMO spreads in a population. Validated model structures from phase 2 and 3 can then be leveraged to optimize and assess deployment, monitoring, and remediation strategies at phase 4 – like the DPGM Hancock and colleagues used to capture the metapopulation dynamics of *Wolbachia* spread in *A. aegypti* [15].



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appropriate model application and interpretation. Typically, the risk assessment process for genetically modified organisms (GMOs) relies on empirical data obtained from one or several standardized experimental protocols, depending on the pathway to risk. Regulatory agencies then compare empirical results to similar products of known risks to streamline decisions based on precedence, or integrate the data into agency-vetted models to quantitatively characterize risks [9]. Current agency-vetted models are designed to evaluate risks from a given dataset and are not designed to make predictions in other settings or to predict the dynamics of ecological systems. Fundamentally, gene drive products may challenge this process because they could impact socioecological endpoints at scales that are unrealistic to study empirically, and because uncertainty about their risks to ecosystems remains too great currently for data collection that would enable risk assessment by agency-vetted models.

Embracing DPGMs throughout the risk assessment process will enhance GDMO risk management by helping scientists and regulators account for uncertainties and outcomes that are difficult to study or verify empirically [4,7]. However, the integration of new quantitative tools, such as DPGMs, throughout the regulatory process will require two key developments: first, establishing a protocol that outlines how to evaluate and use novel quantitative tools for GDMO regulation, and second, increasing quantitative expertise in regulatory agencies, especially within multinational organizations, such as the Organization for Economic Co-operation and Development (OECD), which can provide support to nations that are first time users or lack regulatory infrastructures [1,3]. Together, these developments will ease institutional and logistical challenges that may prevent the adoption and effective implementation of novel quantitative tools by providing regulators with opportunities to learn and participate in the discussion of best practices [10]. In the following sections we expand upon model-guided development and regulation of GDMOs with recommendations and a discussion of benefits.

Model-Guided Advancement of Gene Drive Technology

A conditional approach to discovery research and product evaluation (phased pathway) that builds from our baseline understanding of a target organism, and their role in the ecosystem, towards the strategic deployment of a GDMO is frequently cited as a practical method for managing gene drive technology (Figure 1A) [1,2]. In Figure 1A, we present a five-phased process previously outlined by NASEM 2016 modified to emphasize how the biological scope of research increases in successive phases to simulate realistic ecological systems while biocontainment decreases. Should the GDMO fail to meet predefined safety and efficacy standards sufficient to graduate into the next phase, such as cage trials, field-based research, or staged environmental release (i.e., deemed too high risk), the product is terminated. By integrating a four-step modeling process throughout the phased pathway we can strategically improve our understanding of gene drive systems (Figure 1B).

Prior to initiating the modeling process, it is important to define goals and metrics of success with input from stakeholders [11]. At each phase, the first action of the modeling process is to formulate a mathematical model that mechanistically defines how gene drive systems propagate in populations (Figure 1B). The second action is to explore model input and output over a range of values to understand the role of different processes in driving outcomes of interest (i.e., sensitivity analyses) [5]. The third action is to design studies that collect data that will inform the most important sources of uncertainty [5]. The fourth action is to evaluate how well the model predicts outcomes using the newly collected data and to refine the model to reduce its predictive uncertainty. Models can generate a range of outputs (Figure 1C) that help define and communicate desired products, optimize data collection, evaluate efficacy and risk, and optimize GDMO remediation, deployment, and surveillance strategies [1–3]. Although there are no prescriptive criteria to determine when a GDMO product can move between research phases, models with increasing levels of complexity can be used to assess efficacy and risk as product evaluations successively build towards realistic ecological arenas (Box 1).

Benefit to Public and Private Interests

The release of GDMOs into the environment will require input from public stakeholders,

Figure 1. A Schematic Outlining How DPGMs Inform the GDMO Phased Pathway. (A) At phase 0, ecological and genetic knowledge of the target organism informs management objectives and GDMO design. Phases 1–3 are characterized by research of increasing biological scope (individual, population, and landscape) and decreasing containment (laboratory, field-based research, or staged environmental release). At stage 4, GDMOs are intentionally released into the environment, monitored, and managed to improve ongoing and future applications of gene drive technology. (B) Research throughout the phased pathway can benefit from an iterative, four-step modeling process. The first action is to establish a well-defined modeling structure. The second action is to explore how the model behaves under a wide range of parameter values and assumptions that are checked against data, expert opinion, and intuitive plausibility. The third action is to inform study design by ensuring data collection focuses on key parameters that drive model output. The fourth action is to evaluate the predictive value of the model with goodness-of-fit metrics (such as r^2 or root-mean-square error metrics) and update model performance with newly collected data, which starts a new iteration. (C). DPGMs can be used throughout the phased pathway to (i) predict invasion dynamics of different GDMOs; (ii) estimate impacts on community dynamics; (iii) assess risk to nontarget populations; (iv) estimate the importance of different ecological and genetic processes in determining invasion dynamics; (v) quantify uncertainty in invasion dynamics due to chance events; and (vi) quantify uncertainty in system dynamics due to data and knowledge limitations. Abbreviations: DPGM, dynamic population genetic model; GDMO, gene-drive-modified organism.

developers, and regulators [1–3]. Each group will have distinct criteria for success. The public will want assurances that GDMO release strategies will not adversely impact health or environmental services. Developers will want to know how efficiently the drive will function and whether resistance will emerge quickly. Regulators will want to ensure that the release of a GDMO complies with all applicable laws and the amount of uncertainty in their evaluation is acceptable. Outputs from DPGMs can inform all three groups in a consistent manner and provide real time projections of ongoing GDMO management strategies. With an iterative process of stakeholder input and model-guided inference throughout the phased pathway, we can ensure transparency and that the diverse concerns of public stakeholders, developers, and regulators are integrated into GDMO management.

Recommendations

Quantitative tools can help public stakeholders, developers, and regulators understand, predict, and manage GDMO development and release [4,7]. However, in the absence of widespread training, quantitative tools are likely underutilized and sometimes resisted throughout the process of biotechnology development and regulation [5]. To maximize their use within regulatory infrastructures there is a need to invest in specialized personnel that can evaluate models and facilitate their full potential within regulatory agencies. This type of expertise can also help optimize data collection designs that reduce decision risk. Additionally, there is a need to establish guidelines on how to utilize quantitative tools, such as DPGMs, to characterize the risk and efficacy of GDMOs [1,2]. Transparent standards can communicate to developers, consumers, and public stakeholders how regulators are characterizing risk and clarify what theoretical and empirical research is necessary to demonstrate product safety [4,12]. Using DPGMs to help reduce uncertainty in our understanding of GDMO risk and efficacy is an important step towards the cross-sector management of gene drive technology.

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