Journal of Responsible Innovation

ISSN: 2329-9460 (Print) 2329-9037 (Online) Journal homepage: http://www.tandfonline.com/loi/tjri20

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To cite this article: J. Kuzma, F. Gould, Z. Brown, J. Collins, J. Delborne, E. Frow, K. Esvelt, D. Guston, C. Leitschuh, K. Oye & S. Stauffer (2017): A roadmap for gene drives: using institutional analysis and development to frame research needs and governance in a systems context, Journal of Responsible Innovation, DOI: 10.1080/23299460.2017.1410344

To link to this article: https://doi.org/10.1080/23299460.2017.1410344

Published online: 21 Dec 2017.

JOURNAL OF RESPONSIBLE INNOVATION, 2017
https://doi.org/10.1080/23299460.2017.1410344

RESEARCH ARTICLE

A roadmap for gene drives: using institutional analysis and development to frame research needs and governance in a systems context

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ABSTRACT
The deployment of gene drives is emerging as an alternative for protecting endangered species, controlling agricultural pests, and reducing vector-borne diseases. This paper reports on a workshop held in February 2016 to explore the complex intersection of political, economic, ethical, and ecological risk issues associated with gene drives. Workshop participants were encouraged to use systems thinking and mapping to describe the connections among social, policy, economic, and ecological variables as they intersect within governance systems. In this paper, we analyze the workshop transcripts and maps using the Institutional Analysis and Development (IAD) framework to categorize variables associated with gene drive governance and account for the complexities of socio-ecological systems. We discuss how the IAD framework can be used in the future to test hypotheses about how features of governance systems might lead to certain outcomes and inform the design of research programs, public engagement, and anticipatory governance of gene drives.

ARTICLE HISTORY
Received 23 June 2017
Accepted 24 November 2017

KEYWORDS
Gene drive; governance; risk; systems; IAD; genetic engineering

Introduction

Gene drive systems constructed using genetic engineering can theoretically spread genes through populations. The DNA of animals, including humans, typically has two copies

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of each gene. The copies often differ slightly in form from each other and are called 'alleles'. Offspring produced by sexual reproduction normally have a 50% chance of inheriting each of the two alleles carried by each parent. If the frequency of one allele in a population is 10%, it will remain at about 10% unless it has a positive or negative effect on fitness, for example, due to disaster, disease, or outside selection by a predator or human. If a gene drive mechanism is linked to one of the alleles, that allele will be inherited much more frequently than expected by chance. Even if that allelic form of the gene decreases the fitness of the organism, its frequency in the population can increase. A recent type of gene drive system, based on clustered regularly interspaced short palindromic repeats (CRISPR), can copy itself into both chromosomes of a pair during sex-cell division (Esvelt et al. 2014). This means that, if linked to a genetic allele of interest, a CRISPR-Cas9-based drive can result in that allele being inherited by almost 100% of the offspring. Under idealized conditions, this can drive the gene into each successive generation until the entire population contains it.

Scientists have proposed several reasons to use gene drives to engineer populations in the wild (Gould 2008; Esvelt et al. 2014). For example, they could spread synthetic alleles that inhibit female reproduction in unwanted pest populations, invasive species, or disease-carrying organisms. They could also spread synthetic alleles that prevent insects from transmitting pathogens. Editing systems like CRISPR-Cas9 could carry cargo genes with them to immunize an endangered species against disease or protect it from particular environmental conditions.

Gene drives have not yet been released into the wild, but they have been demonstrated in laboratory-cage experiments with fruit flies, yeast, and mosquitoes (Dicarlo et al. 2015; Gantz and Bier 2015; Gantz et al. 2015; Hammond et al. 2016). They are also being developed in mice for rodent control on islands (Leitschuh et al. 2017, this volume). However, recent modeling studies suggest that getting gene drives to work in complicated ecological and social systems is tricky and will depend upon many factors, including the migration pattern of the wild-type population, mating behavior, the fitness cost of the genes introduced, and the potential for resistance to the drive to emerge (Gould and Schliekelman 2004; Champer, Buchman, and Akbari 2016; Champer et al. 2017; Dhole et al. 2017; Manser et al. 2017).

Furthermore, gene drives are being developed within complicated innovation, political, and social systems – and, if released, deployed into even more intricate social and ecological systems. Although there are growing literatures surrounding gene drives and ecological risk (Oye et al. 2014; NASEM 2016), governance (Charo and Greely 2015; Carter and Friedman 2016; Kuzma and Rawls 2016; NASEM 2016), and biosafety (Esvelt et al. 2014; NASEM 2016), systems thinking has not been at the forefront of analysis to date. Recommendations in these areas have been presented as lists, or linear, staged models of decision-making. As such, we hosted a workshop to put systems thinking at the forefront of discussions and to embrace complexities of the various systems and subsystems into which gene drives would operate (more on this below).

Systems thinking grew in popularity in the mid-twentieth century as a counterpoint to reductionism. It recognizes that phenomena arise from the linkages, feedback, and interrelatedness of multiple parts of a system, and that from the 'whole', there are emergent properties that cannot be understood with knowledge of only the constituent parts (Flood 2010). In the mid-1990s, the concept was extended to the emergent properties when social and ecological systems interact. The social–ecological systems (SES) concept upholds the view that neither social nor ecological systems can be understood in isolation, as humans shape the natural world and vice versa (Cote and Nightingale 2011). It also acknowledges the importance of a diversity of scholarly disciplines to achieve a more holistic understanding of these interactions and embraces feedback relationships.

This paper reports on a workshop that took an SES and systems thinking approach to explore the intersections of the political, social, economic, ecological, and ethical facets of gene drive deployment. We believed that through a systems lens, we would uncover emergent themes that could advance scholarship on gene drive governance and call attention to research and policy needs that might otherwise go unnoticed. Below, we first describe how the workshop was structured and analyzed, and then we present the results from our effort to incorporate systems mapping as a tool to facilitate systems thinking at the workshop. We then draw on the Institutional Analysis and Development (IAD) policy framework (Ostrom 2009) to structure the workshop themes in a way that system interactions can be explored in future governance studies. We discuss how the IAD framework can be used in the future to test hypotheses about how features of governance systems (actors, rules, social, and biophysical environments) might lead to certain outcomes. This paper thus sets the stage for the careful design of research, public engagement, and oversight systems for anticipatory governance of gene drives.

Workshop structure and analysis

In order to examine core governance issues and research needs in an anticipatory way (Guston 2014), the 'Roadmap for Gene Drives' workshop brought together over 70 subject matter experts from academe, business, government, and non-profit organizations from 10 different countries in Europe, Australia, and North and South America (see list of participants in Appendix). There were participants from the natural sciences ($n = 33$ including ecology, genetics, and molecular biology), social science ($n = 31$ including policy sciences, economics, science and technology studies, and sociology), and humanities ($n = 8$ including law, history, and philosophy). The workshop also included a significant number of participants at early career stages (17 students and 4 postdocs).

This three-day meeting was funded by the US National Science Foundation (NSF) and held on 24–26 February 2016, prior to the release of the National Academy of Sciences, Engineering, and Medicine report on gene drives (NASEM 2016). The workshop was designed to frame core governance issues and research needs for gene drives within a systems context and focused primarily on the intersection of risk analysis, ethics, policy, and governance. In these ways, it differed from previous workshops on gene drives that have been designed to identify ecological research needs or offer practical policy advice to researchers and regulators (Oye et al. 2014; Carter and Friedman 2016). The meeting was held on 24–26 February 2016, prior to the release of the National Academy of Sciences, Engineering, and Medicine report on gene drives that also makes recommendations about ethics and risk governance (NASEM 2016).

The workshop made use of both top-down and bottom-up methodologies (Figure 1) to elicit research and governance needs. Specific prompts were used to encourage participants to think about intersectional issues (like ethics and ecological risk), and collaborative systems modeling (CSM) was used as a tool to map relationships among variables in governance systems and feedback loops (Cockerill, Malczynski, and Tidwell 2009). On the

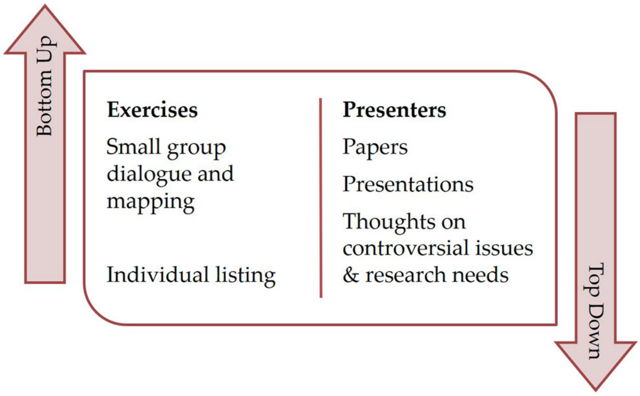

Figure 1. Top-down and bottom-up methods for eliciting subject matter experts input.

first morning, presentations focused on three case studies of gene drives, which are described in detail elsewhere in this volume (ie vectors of human disease, ecological pests, and agricultural pests), and proposed a framework for considering ethical issues posed by gene drives (Thompson 2017). These presentations were followed by parallel, small-group discussions to identify ethical issues specific to each of the case studies or the different molecular mechanisms of gene drives (Figure 2). Each group had 6–10 participants and was designed to represent a mix of sectors and disciplines.

On day 2, morning presentations in the thematic areas of risk analysis, public policy, environmental studies, science and technology studies, and economics were followed by small-group exercises using CSM to map the governance system in the context of a case study while integrating concepts from these thematic areas. From these maps (Figure 3), governance variables and relationships were identified at the intersection of

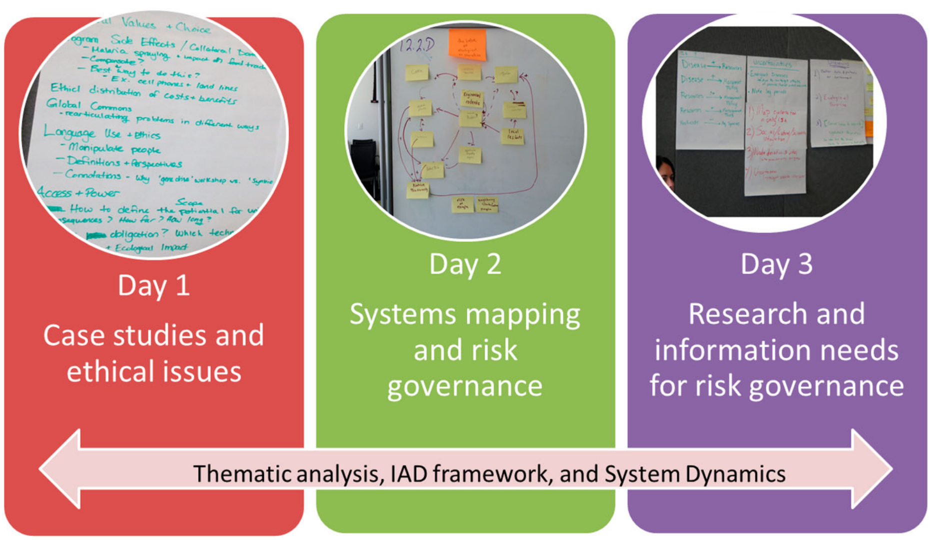

Figure 2. Workshop structure.

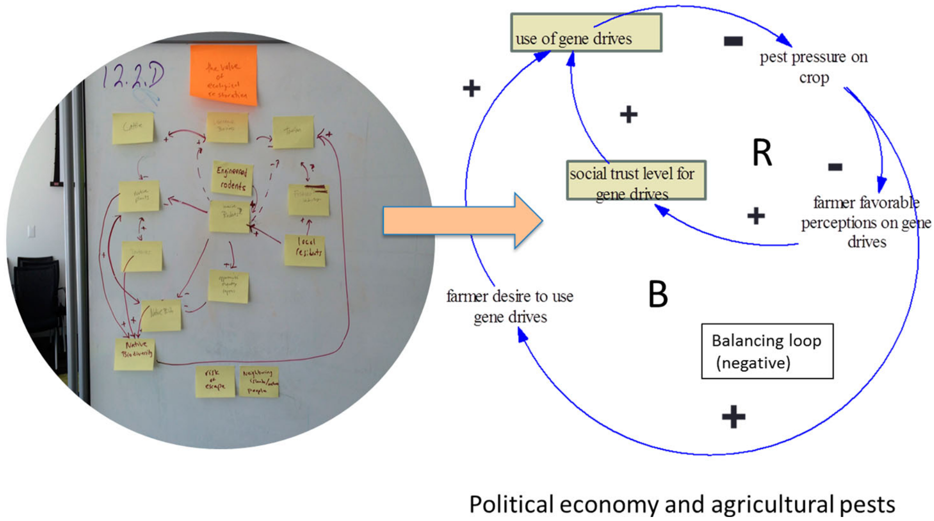

Figure 3. Example systems map from workshop: case study of agricultural pests.

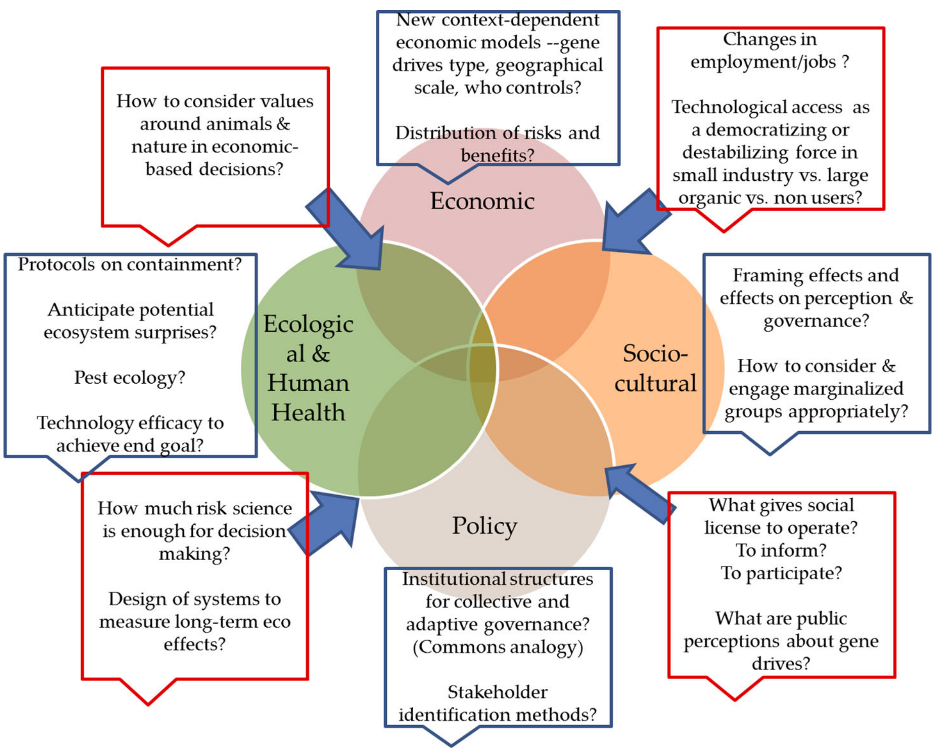

Figure 4. Important research and information needs from systems mapping.

disciplines. On day 3, further observations from the maps and a list of ethical issues were used to develop a list of information and research needs needed for understanding governance and how social, economic, political, and ecological systems interact (Figure 4).

Throughout the workshop, key findings of the small-group dialogues were reported back to the full group in voice-recorded sessions. For the small-group dialogues, note takers were present. Transcripts from the large group meetings and notes from the small-group dialogues were combined and consulted in the preparation of this manuscript to identify major themes arising from the discussions and to place them into system frameworks. Although we do not claim to have achieved consensus on the points raised in this article, they represent key themes expressed by the workshop participants. We note points where participants verbally disagreed. In several places in this manuscript, we also note where there seemed to be support from more than one participant (some, several, many, etc.) and when there was no verbal disagreement recorded. However, we do not claim that the group agreed or came to consensus on these points, as participants with dissenting views may not have spoken up. We used the workshop transcripts to identify important themes that in at least some of the participants' view should be considered in governance of gene drives. We also add context and meaning to these points, for example, through our development of the IAD framework for gene drives. Therefore, like any qualitative analysis of interviews or focus group research, this paper is a combination of the participant views and the authors' own views. Ten of the 11 authors attended the workshop, and all authors represent the steering committee planning the workshop. Therefore, the analysis in this paper has been validated by several participants (ie the authors, constituting about 15% of the participants) for its reflection of the workshop themes.

Given the breadth of discussions at the workshop, we cannot comprehensively report on all of the rich and diverse ideas explored. Instead, this paper serves to theorize and identify governance issues for gene drives within complex social and ecological systems. It also identifies research needs at the intersection of disciplines. We began the analysis with a close reading of the transcripts and examination of the system maps and issue lists generated by the participants. From there, emerging themes were identified. During this process, we found that the IAD framework developed by Ostrom (2009, 2011) provided a good fit for organizing the complexities associated with gene drives that were raised at the workshop. Transcripts, maps, and lists were then re-examined with IAD in mind to identify variables and place them into the framework so that it could be used in future research to explore how attributes of governance systems affect outcomes.

Below we first describe how CSM was used to evoke systems thinking and then move to a discussion of the elements of IAD identified from the workshop.

System dynamics framework

To encourage thinking about complex relationships, workshop participants were asked to create systems maps that integrate social, policy, economic, and ecological variables. The method used at the workshop was adapted from CSM (Cockerill, Malczynski, and Tidwell 2009), which is based on system dynamics in its use of causal loop diagrams to depict feedback loops, and positive or negative correlations among variables within systems (Sterman 2000). Small breakout groups using CSM focused on the three meso-level case studies discussed at the workshop, gene drives for: reducing mosquito-borne disease, eradicating invasive species or rodents on islands, and controlling agricultural pests. The groups first considered their case study according to one of the following issues as a central point of their map: governance policies, economics, or ecological risks and benefits. Then they were asked to include all types of issues as variables, connecting them to the central node. For example, one group considered the case study of invasive rodent eradication on islands with the central node (main stock) of bird populations. They then connected variables associated with the economics, politics, public perception, and ecological systems connected to the release of rodents for bird protection.

Through their mental models of the case studies and the systems into which gene drives would be deployed, the groups identified key feedback loops that would affect the variables of concern (eg bird populations) and determined their polarity (reinforcing, positively correlated loops which can get out of control or balancing, negatively correlated loops, which tend to stabilize systems) (Figure 3). Participants were then asked to make qualitative observations from their maps, with an eye toward where information or data are lacking. This method helped the groups to identify intersectional research needs between disciplines and of relevance to governance (Figure 4).

As an example, the system map for the case study of agricultural pest eradication and political economy issues is shown in Figure 3. It was through this exercise that this group recognized two important things: (1) if successful, farmers may utilize gene drive technology to the point where the need for them becomes at least temporarily obsolete (ie if gene drives work as intended, the population should rapidly and completely change, diminishing the need for gene drives in the future) and (2) social trust is a key intersecting variable for use of gene drives by farmers. The participants saw that public and stakeholder attitudes form key linkages in the systems map (Figure 3) which underscores the importance of prioritizing research on them. These observations have since prompted a few of the group members to write a research proposal on assessing farmer and public attitudes toward gene drives, which are currently unknown.

Despite the success in helping groups identify possible connections and research needs, the systems mapping exercise was frustrating for some participants not accustomed to CSM or system dynamics. Facilitators and the hosts noticed difficulties in several of the groups with getting started on the mapping. Also, in the post-workshop evaluation survey, 47% agreed that the CSM small-group exercise was useful for identifying research needs, and 22% disagreed. In contrast, all but two participants agreed that the small-group exercises in general were a good use of time (96% of survey respondents) and all 74 survey respondents agreed that the overall workshop was a good use of their time. Regardless, we did find that the CSM maps produced by the groups helped to bring to light important interactions and issues that in turn pointed to key variables in the systems. Here we draw on the maps, together with the workshop transcripts and lists of research and governance needs to place the variables into the IAD framework as described below.

IAD framework

The IAD Framework was developed by Ostrom (2009, 2011) to help identify and explain relationships in policy processes by using a general set of variables to analyze SES. This framework helps to organize information about variables exogenous to and within a policy 'action arena' (Figure 5) so that they might be connected to certain outcomes and hypotheses can be generated. Ostrom applied the IAD Framework to common-pool resources such as irrigation water and forests. Common-pool resources are

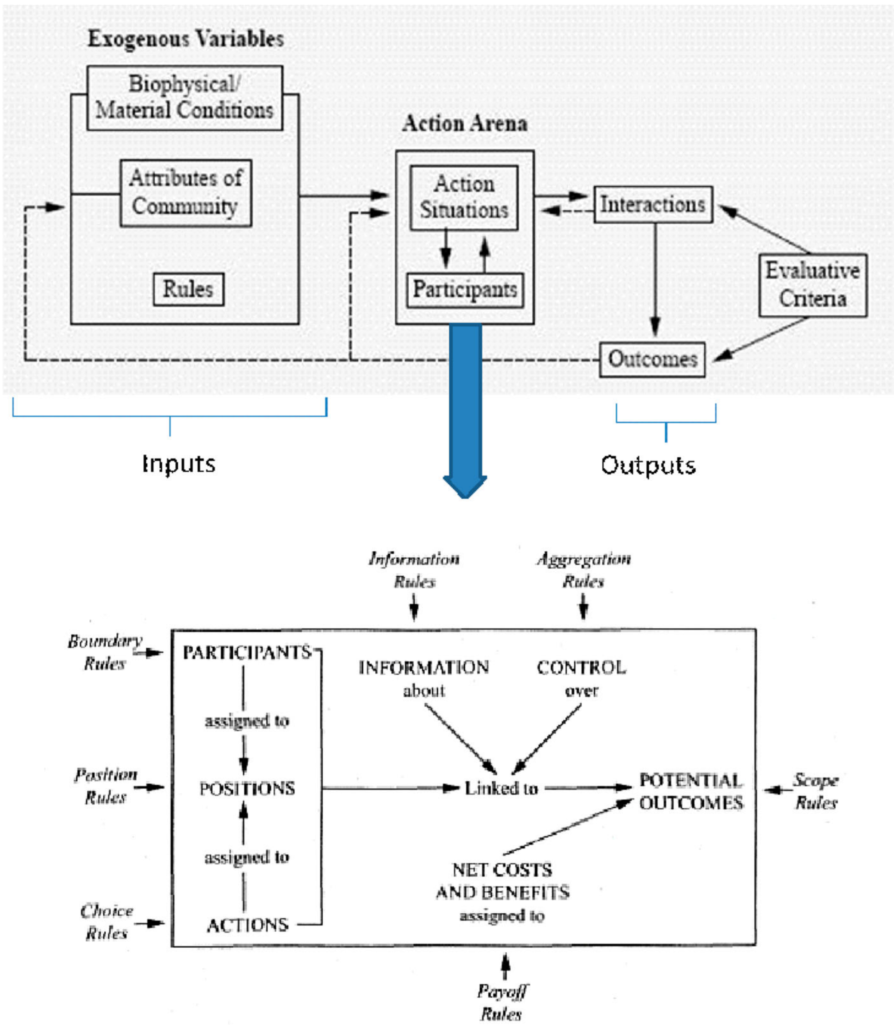

Figure 5. The IAD framework (adapted from Ostrom 2011).

considered nonexcludable goods, as many people can share the benefits (and risks) and it is difficult to restrict access to their use. Through research using IAD as an organizing framework, Ostrom found that isolated individuals will often overconsume common-pool resources; but when people in a resource system communicate, they tend to work together to limit overuse. Ostrom concluded that cooperative networks of users can often protect and govern common-pool resources better than top-down government regulation (Ostrom 2011).

We posited that the IAD could be useful to organize the workshop themes given that, like common-pool resource, gene drives will be embedded in SES, and given that gene drives have some 'public good' characteristics. Public goods (such as fire protection or national security) are both nonexcludable and of low subtractability. In other words, one's consumption of the good does not necessarily subtract from the possibility of use by others (Ostrom 2010, 2011). The conditions that gene drives aspire to create, such as benefits to human health and ecological conservation, share some features of local (in the case of self-limiting gene drives), or global (in the case of successful self-sustaining gene drives) public goods. For example, the benefits are likely to be widely shared and non-exclusionary, as they spread across landscapes to reduce disease or conserve species across large geographic areas.

Gene drive systems also match other uses of the IAD Framework according to several criteria (Ostrom 2009): they (1) involve institutional arrangements in *collective action* settings, and for intentional release, gene drives will require ongoing cooperation between different sectors and geographic regions to plan for, execute, and monitor gene drive releases and their impacts; (2) exhibit the nonexcludability property described above; (3) utilize institutions that are not necessarily formal but rather defined by organization and rules that guide interactions, such as farming communities or conservation groups; and (4) start with a shared problem that people are trying to solve, such as species loss or invasive pest destruction in ecosystems. The goals of most current gene drive projects focus on widely shared social goals such as protecting endangered species or combating insect-borne diseases. With first-generation genetically engineered organisms (GEOs), motives were more profit-focused (eg to sell more agricultural seeds and chemicals). Gene drives are so far being developed for wider social and ecological problems, like aiming to ameliorate mosquito-borne disease, decrease ecosystem harm from invasive species, or protect endangered species.

Through the IAD framework, we organized variables important for gene drive governance that were identified by the workshop discussions. We set out to develop a gene drive-specific IAD framework that could set the stage for future research in understanding how features of governance affect outcomes. Below we place the predominant themes from the workshop into the IAD framework so that future work can interrogate these relationships for hypothesis- and theory-building (eg Smythe, Kerr, and Phillips 2013). Key components of the framework involve exogenous variables such as biophysical and community attributes, and endogenous variables such as 'rules for use' and actors in the 'action arena', and how they interact to lead to outcomes of the system (Figure 5). Below we begin with the exogenous variables of the IAD and gene drives.

Exogenous variables: *biophysical and community attributes*

A major research need identified by the workshop participants related to the need for a greater understanding of the *biophysical attributes* of species that are targeted by gene drives and their surrounding ecosystems. Roles of species in the environment and their population dynamics are important to understand for environmental risk assessment prior to release of gene drives. Predators might depend on a species carrying a self-killing gene drive as a food source. If the prey with the gene drive declines, so might the predator. Other risks might involve the gene drive's negative effect on to non-target species should horizontal gene flow occur. These risks are hard to quantify and their pathways are often illusive. The probability of escapees also comes with significant uncertainty. Even if there is a low probability of escapes outside of the target area, for self-sustaining gene drives, they still might have significant impacts on ecosystems should they occur. Thus, understanding the role of a gene drive-containing organism in the ecosystem is crucial to understanding the potential risks.

Generally, there is great uncertainty associated with the role of pests in the environment. Although some might be non-native to an ecosystem, they might have established themselves for decades and other species may have come to rely on them. Furthermore, a species that is a pest in one geographic area might be desirable in others, especially across large areas that could be reached by gene drives. Much more research is needed to predict the effects of gene drives on off-target species. A significant challenge is that field trials are the best way to study such interactions, yet gene drives are not likely to be confined to the field trial area (especially for self-sustaining drives), so essentially one must assume 'release' without field trial information (more on this problem in 'Outcomes and Evaluative Criteria' section). This problem might mean that sufficient information for risk assessment may never exist prior to use or release of gene drives.

Not only do population and genetic characteristics matter for the impacts of gene drives, but so do biophysical attributes of weather and climate, geographies, and surrounding ecosystems. A significant challenge involves complexity in weather and climate and their effects on the spread of gene drives, reproduction of the host, and distribution of the host. Even if a field trial can be confined, it is unlikely to capture the range of physical conditions under which gene drives will be deployed and spread. These conditions will impact interactions with and potential risks to other species, such as predators and prey. Several participants highlighted the need for better ecosystem and population models that account for uncertainty and variability in biophysical parameters across temporal and geographic scales.

Community attributes will also influence the effectiveness and spread of gene drives in passive and active ways, as well as mediate the risks associated with gene drives within political and economic systems. For example, patterns and behaviors of human movement may carry gene drive organisms into unwanted areas, even across national borders through trade or travel. At the workshop, several participants voiced support for first deploying gene drive technologies in countries that are more developed, educated, and highly regulated; otherwise, less well-resourced countries could become testing grounds, creating at least the appearance of using marginalized peoples (and their ecosystems) as 'guinea pigs'. In contrast, other participants expressed the view that holding back tools that could decrease diseases like malaria in developing countries would be unethical. Both of these perspective abstract from the possibility that researchers and communities in developing regions might be partners in the development of gene drive systems and help make decisions for their own communities or regions. Several workshop participants were of the opinion that the first open releases of gene drive systems should be on isolated islands with no-to-low human populations, but some participants were skeptical that self-sustaining drive systems could ever be safely released or even tested in field trials.

In IAD, behavioral and value systems of communities are important for managing natural resources and for shared governance. Communities that share common values and interact with each other are more likely to develop adequate rules and norms for governance of common-pool resources (Ostrom 2011). In limited geographic areas, such development is more likely given the probability of greater homogeneity in nationality and culture. As self-sustaining gene drives are designed for greater geographic areas and even for crossing national borders, the potential for shared values and norms is lower.

In addition to embedded norms and values, human activities influence the biology of species and their spread. For example, passive transport of *Aedes aegypti* on humans via motorized travel is thought to have resulted in the distribution of the mosquito in Florida and California in the United States (Oxitec 2016). These attributes of community systems, such as transportation and trade patterns, also need to be understood for the best assessment of environmental benefits and risks.

Action arena: action situations

The IAD action situation involves the portions of the community involved in the decision or governance system, and their positions. 'Rules in use' impact how action arenas are structured and operate. The six types of 'rules in use' in the IAD framework provided a typology for organizing and understanding the issues raised during workshop discussions regarding gene drive governance systems.

Position Rules specify a set of positions and how many actors hold each one (Ostrom 2010). Key actors in gene drive governance are those groups that research the gene drive, release the gene drive, are affected by the gene drive, and have regulatory authority over its use. As mentioned above, the landscape of those actors differs from actors in first-generation GEOs. Those currently investing in gene drive release include non-profits, such as Gates Foundation and Island Conservation, and not typically, not multi-national companies. Generally, most gene drive research is occurring in academe, and collaborative partnerships between non-profits and academics seem to be the key institutional actors (with institutions loosely defined as in Ostrom 2009, 2011). Collaborative networks of governance between these organizations are forming (Target Malaria 2017). However, they are also impacted by formal rules and regulations overseeing the release of first-generation GEOs, as most gene drives will fit the statutory definition of GEOs given the introduction of engineered genes that accomplish the drive function. In the US, federal agencies such as the Food and Drug Administration (FDA), US Department of Agriculture (USDA), and Environmental Protection Agency (EPA) are likely to be involved depending on the product and purpose of gene drive technologies (more on this below). Significant authority lies within the federal agencies; however, they have been known to work closely with developers of GEOs and are starting to work with gene drive researchers and non-profit coalitions, as noted by some workshop participants.

Several workshop attendees emphasized the need to include some members of the general public(s) in the action arena. Other groups have since made this point: that participants within the action arena should include members of the communities in and surrounding gene drive deployment, not just outside parties such as government, academic, or industry representatives that are releasing organisms with gene drives (NASEM 2016). Public involvement and engagement can come in many forms, including education campaigns, direct voting, public comment periods, town hall meetings, focus groups, consensus conferences, and widespread national dialogues (Rowe and Frewer 2000). Goals include educating the public, incorporating local knowledge into expert decision-making, increasing legitimacy and trust, respecting procedural ethics in line with a democratic decision-making, building capacity for future engagement in science and technology, and improving the quality of decisions (NASEM 2016). There are also choices related to which public(s) to engage, when to engage them, and how to consider the roles of stakeholders and communities (NASEM 2016).

Several workshop participants were supportive of involving people in the geographic areas affected by gene drives, although they differed in their preferences for the extent, depth, goals, and format of public involvement. Some participants operated under the premise that the main goal should be to educate the public, as they perceived a current lack of public knowledge about gene drives and, thus, were hesitant to include the public as full partners in decision-making for fear that this lack of understanding would lead to fear of anything that is genetically engineered (GE). These views were in line with the 'deficit model' of risk communication, which espouses that with more education, laypersons will be convinced of the lower risk of the technology in comparison to alternatives (eg Ahteensuu 2012).

In contrast, other participants supported the view that some public(s), especially those in geographic areas of release, should be involved as decision makers in the action arena and should also have veto power over gene drives in areas where they reside (i.e. ability to stop the advancement of gene drives if the community desires). However, questions at the workshop were raised about how wide to cast the participation net beyond the immediate area of release, given uncertain probabilities about our ability to confine or reverse gene drives should they spread outside of these areas. Some felt that widespread public engagement was difficult and costly, yet others noted that previous examples of wide-scale engagement for emerging technologies were successful and could serve as models (Hamlett, Cobb, and Guston 2013). Some participants expressed the view that representative members of all interested and affected parties (NRC 1996) have a right to participate in decision-making in the action arena.

Related to position rules are *Aggregation Rules*, which affect the level of control that a participant in a position exercises (Ostrom 2010). Aggregation rules intersect with position rules in that power and control are often tied to position, as seen above in who is allowed into the action arena and has a choice in decisions made. In addition to the need for community involvement and their control through veto power, some participants felt the need for gene drive research to be open not only at deployment, but also at early stages of research and onwards (Esvelt 2016, 2017). Such openness was also seen as a way to facilitate community understanding and awareness. There is at least one notable case in which the alteration that could one day be spread using a CRISPR-based gene drive was publicly discussed prior to any experimental testing in the laboratory, explicitly intended to set a precedent for future research and community input (Harmon 2016).

Given issues like the tight coupling between technological choice and ethical parameters and the increasingly accessible techniques of genetic engineering, synthetic biology and, prospectively, gene drives, many social science scholars promote public engagement to confront issues of the collaborative setting of research agendas and the co-creation of gene drive technologies, either through public participation directly in laboratory-based decisions, public concerns channeled or moderated by collaborations between laboratories and social scientists and ethicists, or through public development of techniques and technologies through do-it-yourself activities (eg Guston and Sarewitz 2002; Stilgoe, Owen, and Macnaghten 2013). Although this possibility was raised, generally, the workshop discussions focused primarily on public engagement activities relating to questions of governance and decision-making about deployment, which are at least analytically distinct from questions of soliciting public input into research agendas and technology development.

Some workshop participants also argued for the public to be engaged in the interpretation and guidance of risk and regulatory assessments for GEOs, as risk analysis has many normative dimensions (Thompson 2007; Meghani and Kuzma 2011; Kuzma 2016). Others at the workshop preferred to leave technical risk assessment to 'the experts' while having the public consider the ethical and social issues. Among some of the participants, public involvement was viewed as a way to get 'buy-in' and 'convince' the public of gene drive benefits and safety. This view is pragmatic and aligned with common practices in commercial product development but runs counter to current thinking in the field of public engagement that it should provide an opportunity for meaningful input (NASEM 2016). It also conflicts with the elements of responsible innovation in that scientists should be responsive to public concerns and desires (Stilgoe, Owen, and Macnaghten 2013).

In the IAD framework, *Scope Rules* involve the outcomes that could be affected by the action situation. In other words, they help define what topics are within the purview of decision-making in the action arena (Ostrom 2010). For gene drives governance, an important set of scope rules includes the type of information that can or should be considered in regulatory assessment. In current US regulatory decision-making about GEOs, direct harms are a primary (and often sole) focus of decision-making (Kuzma 2016), and often the scope of the rules under which GEOs are approved limits which harms are considered (Thompson 2007; Meghani and Kuzma 2011).

For example, many GE animals are (and will be) subject to regulation by FDA under the New Animal Drug (NAD) provisions of the Federal Drug and Cosmetic Act. With the exceptions of plant pests and organisms that act as pesticides, GE animals will fall under the FDA (as of September 2017). For example, FDA's new guidance #236 from October 2017 splits transgenic mosquitos: those designed to treat disease would fall under FDA's authority for NADs and those designed for general pest reduction (including population suppression for disease control) under EPA's pesticide regulations. Gene drive animals that come under FDA as 'animal drugs' would be formally reviewed for the safety of the gene construct to the animal and the efficacy of the gene for population suppression (see Meghani and Kuzma 2017, this volume). Broader ecosystem risks, like loss of prey for predators, or public health harms, like temporary rises in mosquito populations, are not technically part of the legal authority of FDA's NAD review, although they are procedurally considered under the National Environmental Policy Act. This example shows how a scope rule limits the actors in the action arena to certain decisions. However, non-governmental actors, such as the non-profits and academics developing gene drives, would not be limited to this scope. Several times, workshop participants stressed the need to consider not only direct environmental and health risks, but also indirect ecosystem effects, socio-economic impacts, and cultural impacts. Projects underway on gene drives are broadening the scope of governance questions beyond formal regulatory authority (Target Malaria 2017; Leitschuh et al. 2017, this volume); thus adding to the scope rules of the action arena.

Related to the scope of regulations, federal agencies profess that assessments used in regulation are 'science based'; they do not explicitly consider value judgments in risk analysis, and assessments often mask normative assumptions behind the interpretation of data and information (Meghani and Kuzma 2011). Cote and Nightingale (2011) argue that 'knowledge at the intersections between social and environmental dynamics helps to address normative questions and capture how power and competing value systems are not external to, but rather integral to the development and functioning of socio-ecological systems'. In one exercise at the workshop, participants were asked to consider ethical issues in the context of ecological risk analysis and governance systems. The results led to a unique list of normative issues to consider in the typical framework of risk analysis (Figure 6). Participants expressed a range of other values associated with decision-making: (1) precautionary versus promotional worldviews in the face of uncertainty about environmental risk, (2) the role of technology as a problem versus a solution to conservation biology, human health, or agriculture, (3) the role of ecosystems in general as providing services to humans versus having intrinsic value, and (4) positive versus negative attitudes toward experiences with first-generation GEOs in the environment. These worldviews will color the judgment of stakeholders, publics, and federal agencies. Several participants expressed the need to include discussions of values and worldviews in the scope of both public engagement and decision-making about gene drives.

Overlapping with Scope Rules are *Choice Rules* that specify which actions are assigned to an actor in a position and, in essence, set forth the options considered for decision-making. Although most of the workshop discussed downstream decisions about gene drive deployment, some participants expressed the need to move further upstream in the decision context, before the question of whether to use gene drives even arises. They suggested that risk governance questions should start with 'what problem is to be addressed and what are a range of alternatives for addressing that problem?' In other words, the choice is not just gene drives or not, but whether gene drive deployment is appropriate to maintain and repair ecosystems in comparison to other existing and more conventional alternatives. Several participants expressed diverse views on the imperative to deploy gene drives for the three cases considered vis-à-vis other options

Figure 6. Interactions among risk governance and ethics prompted by systemic thinking at workshop.

like chemical pesticides, traditional biological control, vaccines, or changing human behavior (eg reducing standing water around homes for mosquito control). Several participants thought that alternatives assessment, comparing the pros and cons of options for addressing the problem, should be part of decision-making for deployment, not just the risk assessment of deployment.

Another question that occurs upstream in the action arena for gene drives governance is whether even to pursue gene drives in *research* laboratories at this time. While the workshop did not extensively examine this question (perhaps because of the high number of gene drive developers who were participants), it is a logically necessary choice. The NASEM committee on gene drives did not suggest any ban or moratorium on gene drive research, but rather suggested that a cautious, step-wise approach to research is warranted at this time (NASEM 2016).

When gene drives are pursued in research contexts, subsequent choices include which technological approaches to use for a particular health, agricultural, or environmental application. In this volume, Min et al. (2017) describe a technical typology of gene drives and their risks and benefits, extending that of Champer, Buchman, and Akbari (2016) and Sinkins and Gould (2006 with a particular focus on localization and public perception). As described by Champer, Buchman, and Akbari (2016), technological choices include (1) whether the gene drive is designed to suppress the target population or to replace it; (2) the rate of its spread; (3) whether it is locally confined or not; (4) whether it has a fitness cost; (5) the rate of resistance allele generation; (6) whether it is reversible; and (7) whether it can be removed and replaced with the original wild-type individuals. Other key choices among gene drives were discussed and included whether a given drive system was anticipated to spread to all members of the target population (self-sustaining); whether it was intended to enhance, replace, suppress, or eliminate the population (control system or cargo carried); whether it could be actively eliminated by subsequent releases (reversibility); and whether the drive system required an exogenous factor in order to act (inducibility).

Each of these technological choices will have implications on value-based choices such as environmental restoration or preservation, human health improvement or decline, and cultural respect. Workshop participants also recognized, beyond human concerns, the existence of the inherent rights of species (Samdler 2012). An anticipatory governance approach, which was supported by several workshop participants, suggests that the relationships between these technological choices and ethical parameters be explored (through foresight, participation, and integration) even if they cannot be predicted (Barben et al. 2008).

Choice rules also include whether active forms of monitoring take place after release and how rule breakers are sanctioned. Several participants argued that local communities should be able to frame certain choices for deployment of gene drives, for example, requiring post-release monitoring even if regulations do not. This framing could broaden the scope of the outcomes considered in gene drive governance action arenas.

Boundary rules relate to how groups move in and out of certain positions in an action arena, the number of participants, and their attributes and resources. For example, during the workshop, issues were raised concerning the insufficient resources available for federal agencies to keep up with the pace of gene drive development in order to govern, for researchers to conduct risk science and risk assessment research, and for formal organizations in the action arena to conduct public engagement. Also, significant resources would be needed for widespread public engagement, as people outside of the action arena would need to be invited and willing to come into it. Even if engagement is a goal and shared power is desired, identifying and selecting participants is challenging, and there are tradeoffs between the depth of public engagement and the breadth of reaching all interested and affected parties (NRC 1996). The participants also discussed the challenge of reaching initially inattentive or apathetic people within areas of deployment, as well as those outside deployment areas if desired, with the typically few resources available for engagement. In turn, people who have limited time and financial resources might need incentives for engaging in dialogue in order to take time away from their jobs or families. The workshop participants also raised the challenge of reaching disenfranchised or marginalized groups who often distrust those in control of new technologies.

Geographic boundaries may be crossed by organisms with gene drives, thus changing the actors in the action arena and their positions. With self-sustaining gene drive systems in particular, a neighboring country's communities or federal regulators might be pulled into the action arena. Even with a low likelihood of travel across countries, gene drives might trigger the Cartagena Protocol on Biosafety (BSP) and the advanced informed consent agreements necessary for the transboundary movement of GEOs between participating nations. The workshop participants discussed whether there would be a threshold probability of spread that would trigger engagement with a neighboring community or country. Few, if any, countries are geographically isolated and even then, biological isolation is not ensured given that humans can assist movement. The workshop participants considered whether a gene drive released in one country should be assumed eventually to spread to neighboring countries. Several noted that this likelihood will depend on the geographic range and habitat of the target species, while others argued that history has shown that surprises occur in this regard, particularly through human activity. The group discussed that entry through trade or passive transport on vehicles will need to be seriously considered, especially for self-sustaining gene drive systems.

Boundary rules associated with formal international governance for gene drives have yet to be decided, although they are being actively debated under the Convention on Biological Diversity (CBD), Biosafety Protocol (BSP) (Callaway 2016). However, some key countries – eg the United States, a leader in gene drive research – are not parties to the CBD and BSP. Furthermore, if an organism is to cross a border, that country's specific biosafety laws will likely be triggered in addition to the CBD. Several workshop participants described how the complexities of international governance will be difficult to manage in advance of release and if spread occurs across geopolitical borders. Gene drives designed for limited spatial and temporal spread may decrease these concerns. However, even in these cases, if individuals or groups see an advantage to using a gene drive, it might be feasible for the gene drive strains to be intentionally moved across borders, presenting a problem even though the impact would be limited. Historically, GE soybean and cotton have been intentionally moved from countries where they were legally grown to countries in which they were not permitted (Scoones 2008).

Information Rules determine what information is available, made public, or is held secret. These rules are important for public trust and legitimacy, and several participants discussed the need for more public information about gene drives, in order to support public participation in the action arena.

Information is also important for the staged model of gene drive testing, which goes from lab to field tests, to deployment. NASEM (2016) suggests the need for great care and precaution (Kaebnick et al. 2016) in moving from almost 100% contained laboratory studies to mostly contained field cage experiments, to confined but geographically limited releases, and finally to wholly unconfined releases. The model allows for the process to be stopped at any point; however, the momentum of the projects (eg through supporters who have invested time and money into them) would make this difficult. Unfortunately, there are currently no good decision protocols (i.e. specific criteria and guidelines for the types of information and data needed in specific cases of gene drives) for moving from contained lab experiments to release into mostly contained field cages or isolated areas. This juncture is key analytically for gene drives, especially self-sustaining ones, as one escapee from a field cage could really turn it into full-scale release. A few other emerging technologies that are accompanied by significant uncertainties have this problem (eg geoengineering, where there may not be any field trial that would be both helpful and easily distinguishable from an actual intervention).

Participants at the workshop also considered the fundamental question of how much information is enough to let loose the first organism with a self-sustaining gene drive system, even if the intended release is apparently confined to an isolated island. Throughout history, species and populations have frequently traversed natural barriers, often thanks to humans with economic incentives to defy established laws (see O'Hara 2006 on the illegal introduction of rabbit hemorrhagic disease virus to New Zealand). Because the use of locally confined gene drive systems was widely viewed to avoid these problems, several workshop participants agreed that their development and use was preferable whenever possible (ie. stated verbally by several participants with no vocal opposition). Absent the use of laboratory safeguards as recommended by numerous scientists (Akbari et al. 2015), a simple laboratory accident involving a self-sustaining gene drive system – let alone a deliberate break-in and release as has occurred for other animal research – could have wide impact on people and ecosystems outside the laboratory.

Information rules also establish channels of communication among participants. Meghani and Kuzma (2017, this volume) discuss the current regulatory framework for GE animals, which at this time would also apply for some categories of animals with gene drives. The NAD provisions of the Food, Drug, and Cosmetic Act (FDCA), used for regulatory approval of the Oxitec GE mosquito and other GE animals, allow for most information to be kept secret during regulatory review. However, many participants felt that community action arenas, shared decision-making, and two-way public communication and engagement models will not be seen as legitimate if information is withheld during the decision-making process. Some participants at the workshop, including many of the technology developers, were committed to open access to the results of research and risk analyses prior to decisions about deployment. However, traditional regulatory regimes for GEOs allow for the providers of data to claim confidential business information, often even in safety studies. A few workshop participants noted that public efforts to deploy gene drives have thus far been more transparent than regulatory efforts with GEOs, and that transparency is an important cornerstone for maintaining public trust and respecting local values.

Some participants also mentioned, however, that even if experts can provide information in transparent ways, it is difficult to understand the nuances among gene drives, other genetic engineering technologies, and biocontrol. 'Apparency' is a term that has been used to combine transparency with the idea that the information should be not only available but understandable. Workshop participants noted that it will take significant research in science communication to assess the best ways to communicate openly and honestly about gene drives and allow people to make informed decisions without leading them to certain conclusions about risks and benefits.

Finally, *Payoff Rules* in the IAD framework determine how to impose sanctions or rewards for actors in the action arena. They also specify how benefits and costs are to be distributed to actors in particular positions. Payoff rules can be written into regulations, laws, or procedures, or unwritten as governed by cultural or social norms. Ex ante theory about whether technology developers will find it in their interest to release a gene drive often relies on considering incentives (economic and otherwise) facing these developers (Mitchell and Brown 2017 this volume; Brown 2017). These economic issues were discussed at the workshop. Gene drives share some features of local public goods, in that their impacts – both positive and negative – are likely to be *nonexcludable*: parties without direct agency over the deployment decision are likely to experience benefits or harm from the technology as it spreads across landscapes. Developers of gene drives might make riskier deployment decisions than would be socially prudent, since they may not directly bear the consequences of those risks. However, private sector technology developers may be less likely to deploy gene drives as the benefits are also nonexcludable. For example, a farmer in an area with a pest-controlling gene drive could free ride on neighboring farmers' investments in the deployment. Nonexcludabilty and this potential divergence between deployment choices of different stakeholders generate a number of areas of conflict to consider.

The political economy of developing and deploying gene drives was seen by several of the workshop participants as distinct from the first-generation of GEOs. Systems modeling exercises at the workshop highlighted the conflicts with current market-based technology development systems (eg Figure 3). In the first generation, GE crops based on herbicide tolerance and pest resistant traits were designed to spread through markets and require annual purchases from suppliers. Each year farmers bought GE seeds from companies involved in biotechnology and/or seed distribution, and there was a profit motive to technology development. If self-sustaining gene drives work well, they will no longer be needed in the future, and developers will eventually have no market for that gene drive system. Thus, self-sustaining gene drives may not have a viable business model, unlike first-generation GEOs. As a result, the workshop participants noted that the landscape of developers is currently weighted towards academic and non-profit groups, who have different motives. The benefits of gene drive systems will be more widely shared, and participants noted that the payoff rules are likely to stem from contributing to solutions to problems of agriculture, health, or ecosystem protection as well as professional recognition (and future funding). Local gene drive systems may represent a middle ground to reap some financial benefits.

Outcomes and evaluative criteria

The opportunity to derive hypotheses from the IAD rests on the measurement of desired outcomes as a dependent variable (with action arena and exogenous factors as independent variables). In IAD, evaluative criteria can take any form to reflect the values of the actors, but they are often derived from rational choice theory which professes that individuals are utility maximizing and goal oriented but have 'bounded rationality' relating to limited or imperfect information on which to base decisions. Problems with which utilities to maximize are always present given different worldviews and values.

Evaluative criteria are applied to assess outcomes of the action arena. As discussed above, the goal of making huge profits seems elusive in the case of most deployments of gene drives, especially those that are self-sustaining. One of the most important outcomes will be how well the gene drive solves the agricultural, health, or ecological problem it was intended to solve. This criterion, typical of policy analysis, is *effectiveness* and how it is measured becomes important. For example, does effective mean measuring the percentage of *A. aegypti* prevented from existing, or estimating the lives saved from reductions in disease? In policy analysis, this difference is often understood as that between outputs, which are intermediary but under greater control of those who intervene (eg reduction in mosquito populations), and outcomes, which are what is truly aimed at but are under less control (eg reduction in disease).

Different kinds of criteria can be weighted for multi-criteria evaluation of decision options, or once gene drives are deployed, for the results. Workshop participants argued for broader criteria to be considered in evaluating the success of gene drives, such as indirect human and environmental impacts, social system health, respect for community ethics, security, justice in distribution of benefits and risks, and economic prosperity. They also argued for procedural criteria to evaluate the process of deploying gene drives such as the 'care' ethos, public engagement, shared governance, and transparency and apparency (see discussions above). The International Risk Governance Council argues that with emerging technologies, such as gene drives, procedural criteria become as important as substantial criteria for evaluation of risk governance (IRGC 2015) as it is too difficult to predict outcomes prior to release and therefore the process becomes important for legitimacy.

Organisms with gene drives and their deployment raise some new or magnified procedural challenges for risk governance in comparison to the deployment of other genetic engineering technologies. At the workshop, discussions revealed some basic conflicts between deployment of gene drives and current governance systems for first-generation GEOs. The most notable is that gene drives are meant to spread through a wild population; whereas the goal for the deployment of other GEOs has typically been containment or confinement in managed settings (eg agriculture). First-generation GEOs were thought to be less fit than their wild-type counterparts and therefore, even if there were a few escapees, they would quickly die. As a result, regulations and standards designed for GEOs are unlikely to be appropriate for gene drives. For example, USDA-APHIS suggests isolation distances between field trials of GE crops and other fields of that crop. However, if the GE plant is designed to spread with a gene drive, like a weed designed to reduce its own wild population (NASEM 2016), basing regulatory standards on confinement becomes meaningless. The goal of spread also challenges field monitoring strategies and even field testing, as even impractically wide and costly boundaries may prove inadequate. A basic problem in this distinction is that the escape of one fertile female from a limited field trial could in some cases (depending on gene drive design, see Min et al. 2017, this volume) spread a gene throughout an entire population.

Furthermore, organisms have long been known to move across geographic barriers with and without human assistance, such as mice moving to islands (see Leitschuh et al. 2017, this volume) or viruses deliberately spread by farmers (O'Hara 2006). In other words, 100% containment or confinement is never guaranteed, and again, processes for making a decision (as measured by procedural criteria such as opportunities for stakeholders to have input, transparency, etc.) take on greater importance.

International governance of gene drives (discussed in Boundary Rules) will also influence the outcomes that are to be evaluated, particularly those related to values. Participants raised the following questions: What obligations are there to respect the cultural norms and values not only of the community in which the gene drive is released but also those of all potentially affected countries? What if communities disagree because of different priorities? Furthermore, an unwanted species in one country could be a treasure in another country (see eg the *Amaranthus* case study in NASEM 2016, 64, 151), and a gene drive designed to get rid of a pest in one country might cause problems in another. Therefore, applications of self-sustaining drive systems to conservation, where the goal is to remove invasive populations without impacting native populations, were viewed as particularly problematic for defining desired outcomes across shifting geographic areas.

Conflicts of values and how they influence desired outcomes also occur within communities. Conservation biologists are often split about desired outcomes of their work. Gene drives have been proposed to protect endangered populations; for example, a species threatened by disease could be replaced with a population that is immune to that disease due to the spread of a gene drive. The resulting species with an engineered gene in it would now be protected, but would it be of equal value to the original population? Some conservationists view it as a duty to preserve the original species for its own sake, whereas others see it as a duty to protect species because of the value they provide to humans directly or through ecosystem services. This disagreement is between 'preservation' in native forms and 'conservation' in the sense that it is still there, in whatever form, to fulfill a utility or function (NASEM 2016). The question of whether future generations will value the presence of species in the wild that are GE also came up at the workshop and has been discussed in the literature (Kuzma and Rawls 2016). Participants discussed this as another fundamental disagreement in the desired outcome of a gene drives for ecological restoration.

Conclusions

In this analysis, the Roadmap for Gene Drives workshop discussions were used to identify variables for the IAD framework, so that in the future, work to correlate features of gene drive governance systems to desired outcomes could begin. In doing so, we also identified governance issues that are likely to be magnified with self-sustaining gene drive systems, which are anticipated to cross geographic and national boundaries, in comparison to local drive systems that might be confined to certain communities. One of these issues involves the challenge of defining what outcomes are desired from gene drive governance. As outcomes to evaluate the success of governance systems are value-based, public and stakeholder involvement to define them seems warranted. Workshop participants stressed the importance of public engagement in gene drive research and decision-making, as did the NASEM (2016) report. The inclusion of communities in and surrounding the area for which gene drives are intended will be particularly important to bring into the action arena to help define desired outcomes, have a voice in decision-making about governance, and assist with evaluating the performance of gene drive governance systems. This would be in spirit with the networked, collaborative governance systems for common-pool resources that Ostrom found particularly effective through use of the IAD framework for analysis (Ostrom 2009, 2010, 2011). Our IAD analysis set the stage for further exploration of relationships among exogenous, action arena, and outcome variables in gene drive governance systems.

Future work should expand the list of IAD framework variables, specify them for certain SES contexts, and ultimately test them for desired outcomes. The workshop also identified several other important research questions at the nexus of disciplines (Figure 4) that will be important to inform the design of policies and programs for gene drive governance. However, a significant barrier to such a policy research and design approach is the limited funding for it (Kuzma 2015).

Regardless, the Roadmap for Gene Drives Workshop could be seen itself as the beginning of collaborative policy design for gene drive governance systems. It engaged a disciplinarily and geographically diverse group in the assessment of gene drive cases and made use of systems thinking and mapping to explore intersectional issues that fall in between disciplines and sectors (Cockerill, Malczynski, and Tidwell 2009; Flood 2010). It also embraced other principles of responsible innovation (Stilgoe, Owen, and Macnaghten 2013) by reflecting on the motivations and ethics of gene drive research; anticipating contingencies, uncertainties, and governance needs upstream of gene drive deployment (Wiek et al. 2012; Guston 2014); and calling for responsiveness to the concerns of public(s) and stakeholders early in gene drive research and deployment. We hope the workshop and this analysis serve as a resource for the practice of collaborative policy design, as well as future policy research to determine whether that design leads to desired social and ecological outcomes from gene drive governance.

Acknowledgments

The authors would like to thank Sharon Stauffer, Project Manager at GES-NCSU for her dedication to making the workshop happen, as well as Maurizo Lewis-Streit, Communications Assistant at GES-NCSU, Alison Wynn, former Deputy Director of GES-NCSU, and Jayce Sudweeks, PhD student in Public Administration and GES for additional assistance and planning. The authors appreciate the valuable input of the workshop participants (Appendix), including the ones who co-authored papers for this volume; and the NSF-IGERT students from NCSU's Genetic Pest Management graduate program for moderating and taking notes during the small-group exercises.

Funding

The workshop was funded by the Directorate for Social, Behavioral and Economic Sciences, National Science Foundation–Science in Society Program [grant number 1533990] with additional co-funding by the Genetic Engineering and Society Center (GES) at North Carolina State University (NCSU) and the Center for Nanotechnology in Society at Arizona State University. The views, however, are those of the authors and not these institutions.

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