

A Decision Analytic Model to Guide Early-Stage Government Regulatory Action: Applications for Synthetic Biology

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ABSTRACT

Synthetic biology (SB) involves the alteration of living cells and biomolecules for specific purposes. Products developed using these approaches could have significant societal benefits, but also pose uncertain risks to human and environmental health. Policymakers currently face decisions regarding how stringently to regulate and monitor various SB applications. This is a complex task, where policymakers must balance uncertain economic, political, social, and health-related decision factors associated with SB's use. We argue that formal, decision-analytical tools could serve as a method to integrate available evidence-based information and expert judgment on the impacts associated with SB innovations, synthesize that information into quantitative indicators, and serve as the first step towards guiding governance of these emerging technologies. For this paper, we apply Multi-Criteria Decision Analysis (MCDA) to a specific case of SB, a micro-robot based on biological cells called cyberplasm. We use data from a Delphi study to assess cyberplasm governance options and demonstrate how such decision tools may be used for assessments of SB oversight.

Keywords: Emerging Technology, Risk Governance, Synthetic Biology, Technology Governance, Uncertainty

Introduction

Synthetic biology (SB) seeks to apply the principles of biological systems engineering through the design and assembly of biologically-inspired parts and systems that do not exist in nature in order to rewrite natural biological systems for useful purposes. SB comes in many forms from the genetic engineering of metabolic pathways into existing organisms to the bottom-up construction of biological systems from macromolecule components to living systems based on amino acids or genetic material that are synthesized (deLorenzo 2010). One key example of SB was demonstrated by the J Craig Venter Institute in 2010 when they developed a synthetic genome for the bacterium *Mycoplasma mycoides* and implanted it within a bacterial shell that had its own genome removed (Gibson et al 2010; Hutchison et al 2016). Since then, visions of SB are that it will provide benefits to society across multiple sectors and improve a variety of processes, ranging from environmental remediation, to vaccine development, to biofuel production among others. However, SB is also expected to be controversial for many reasons including value-based objections about human interactions with nature, to concerns of potential human health, environmental, and socioeconomic risks (Kuzma & Tanji 2010; Church et al 2014).

For example, one SB application currently under development, “cyberplasm” converges synthetic biology, biomimicry, nanotechnology, and robotics to construct a micro-scale robot designed to be capable of sensing environmental chemicals for remediating purposes (Voigt 2012). It has been proposed for use in detecting and treating pathogens within plants and animals *in situ*. Cyberplasm is a biohybrid that integrates engineered bacteria, yeast, and mammalian

cells to undertake device-like functions modeled after the sea lamprey. It is expected to be in full development with a functional prototype by 2017.

As engineered microorganisms like cyberplasm are envisioned to be biohybrids, it is likely that such technologies will “belong in a different risk category than toxic chemicals or radioactive materials” and will not fit risk assessment approaches for living, genetically engineered or other organisms where risks associated with gene flow and invasiveness are of concern (Tucker & Zilinskas 2006). Appropriate governance mechanisms have the potential to diminish chances of serious harm and maximize the likelihood that benefits of SB can be shared across a broad spectrum of society while respecting a diverse array of societal values. Schmidt et al contend that SB requires “new methods of risk assessment to decide whether a new SB technique [...] is safe enough (for human health, animals and the environment) for the use in restricted and/or less restricted environments” (Schmidt et al 2009). Such distinction from established domains of risk characterization, assessment, and governance make any traditional risk assessment potentially irrelevant to SB products due to the potentially unique risks and uncertainties posed by the use of self-replicating microorganisms. While many effective governance structures for managing technological developments are currently in place around the world, there may be need to evolve and forecast governance actions due to the revolutionary nature of SB technologies like cyberplasm. Where SB requires potentially new and unique measures to govern the risks associated with human and environmental health, policymakers for national governments are already being forced to make decisions regarding how stringently to regulate, litigate, and monitor various emerging technologies that are in development or coming to market (Mohan et al 2012).

This is a complex task due to the inclusion of various stakeholders amidst a dearth of objective information. Further complicating matters includes the various factors that must be considered with any policy decision on this matter, where policymakers are required to balance economic, political, social, and scientific risks and benefits associated with the technology's use.

Such high stakes decisions must be undertaken often in the absence of robust quantitative data or extensive field research, making it more difficult for policymakers to identify optimal response options for governing SB applications as they develop. To better understand these issues, some have suggested that researchers make use of social scientific methods to demystify potential risk management strategies that could be employed given the technology's early stage development and use (Calvert & Martin 2009). Others have categorized SB products according to sector and technologies involved (e.g. kinds of parts or methods) in order to identify risk categories of most concern to develop scales of "precaution to promotion" that may be warranted (Kuzma & Tanji 2010).

Risk governance for emerging technologies has been given special attention in the literature due to the lack of knowledge and experience with potential hazards, their interactions with systems in which they are embedded, and their impacts. Emerging risks are characterized by uncertainty about potential consequences and probabilities of occurrence. The International Risk Governance Council (IRGC) has recommended that when risk problems involve high uncertainty and ambiguity, processes limited to traditional agency and expert-driven risk analysis based on quantitative data will not suffice (IRGC 2006, IRGC 2015). If there is a high degree of uncertainty, hazard criteria of reversibility, persistence, and ubiquity should be considered. Also, risk management should include more cautionary approaches such as close monitoring, small steps in introducing the hazard, strict containment, and systems that can absorb or tolerate surprises and that are resilient, flexible, and adaptive (IRGC 2006). In situations of high ambiguity, there is not agreement among stakeholders and experts as to the questions of most importance for analyzing or mitigating risk, and there are conflicting values about what is to be protected or what risks should be reduced. Under high ambiguity and uncertainty, broader societal discourse is most appropriate to frame problems and management options with participation from a wide-range of stakeholders and citizens (IRGC 2006).

In this paper, we propose a decision tool to aid policymakers, stakeholders, and societies with the task of assessing governance options for various applications of SB innovation. While such applications of SB may or may not come to commercial fruition, this decision aid affords regulators, policymakers, and stakeholders the opportunity to assess various tools of governance at their disposal for a variety of SB applications. This decision aid also may help to make appropriate policy judgments based upon qualitative expert-derived information in lieu of unavailable quantitative experimental data. This tool can also be integrated into wider deliberative processes suggested by the IRGC to help stakeholders and experts develop scenarios and frame management options together (IRGC 2015). In this way, such a tool systematically quantifies and makes use of expert and stakeholder opinion that may not always be reflected in the traditional regulatory policymaking process. We sought to identify answers to the following research questions:

1. What governance options could be proposed regarding the potential applications of cyberplasm?
2. What is a good process for distilling expert derived data to recommend policy options for synthetic biology products such as with cyberplasm?

Answering both of these questions requires methodological approaches to (i) acquire and interpret information pertinent to cyberplasm's risks and benefits, and (ii) analyze and rank decision alternatives based upon these risks and benefits. To accomplish these aims, we make collective use of the Delphi methods to generate qualitative expert interviews as well as Multi-Criteria Decision Analysis to assess value judgements and rank governance alternatives for cyberplasm based upon expert input and discussion within scholarly literature (Bates et al 2015; Linkov et al 2013). Specifically, Question 1 is addressed through the use of the Delphi method, where individual and collective opinion is assessed from subject experts to identify cyberplasm governance in the technology's early stage of development (Berube et al 2011; Linstone & Turoff 2002). Likewise, Question 2 is addressed through the use of MCDA, which integrates

qualitative findings from subject experts into a decision model that ranks governance options by their degree of perceived optimality (Bates et al 2015; Linkov et al 2013).

Where applications of emerging technologies such as with SB are generally lacking of substantial objective data, the use of subject expert opinions beliefs regarding the potential risks and benefits is required in order to inform policy decisions related to how the technology should be regulated and governed. Transparent decision analytical tools such as Multi-Criteria Decision Analysis (MCDA) make this task possible in the immediate term. Using MCDA, expert opinion and judgment may be aggregated in a formal and quantitative manner, ultimately affording its user the potential to make value judgments and tradeoffs based upon the perceived risks and benefits of the technology. Collectively, the use of the Delphi method (Linstone & Turoff, 2002; Berube et a 2011) and MCDA (Bates et al 2015; Linkov et al 2013) have been discussed as approaches that can inform governance of emerging technologies within an environment of high uncertainty. Such an approach may be helpful for regulators and other stakeholders seeking to drive the risk governance of synthetic biology products, where this paper demonstrates how this process would work for the case of cyberplasm governance.

Case Study

Modeled after the sea lamprey, cyberplasm is a biohybrid that integrates engineered mammalian cells and sensory neurons to undertake device-like functions (Voigt 2012). The sea lamprey serves as the biological model for cyberplasm's design. The animal swims by undulating its long tail in an uncomplicated wavelike motion and it also has a relatively primitive nervous system. These characteristics offer benefits for the ease of modeling that is easy to mimic. Biomimetic, synthetic muscles are being designed to initiate the undulatory movement that will propel the micro-robot through water while sensors derived from yeast cells report environmental signals (Grubišić & Parpura 2015). Such signals allow the micro-robot to move

towards their electronic stimulus to collect environmental data or deliver medical treatment on site. Such a framework requires a strong integration of biological sensory neurons with the artificial electrical ones, involving a level of interface scaffolding that facilitates the relay of signals throughout the nervous system. This is accomplished through the use of ultraviolet light on a silicon-derived organic polymer with a water coating. Through the additional integration of carbon nanotubes, the scaffold is constructed to be electrically conductive and react to predetermined stimuli (Szondy 2012).

Researchers have speculated that in the long-term, cyberplasm could eventually impact the healthcare industry by improving the biosensors and drug delivery systems through cellular machines after injection into the human body. Cyberplasm is currently being researched and developed by an international team of scientists and engineers in the USA and UK and is funded jointly by the National Science Foundation and the Physical Sciences Research Council, respectively (Cyberplasm.net 2010). Oversight and risk analysis for such a SB project is likely to be difficult given the convergent nature of the technologies used and the broad possibilities for deployment.

Methods

This study employs MCDA to data acquired from a Policy Delphi study to assess cyberplasm governance (Linstone & Turoff, 2002). Methodologically, the use of the multi-round Delphi study allows for a consideration of individual and collective discussion by identified subject experts on the subject of cyberplasm governance. This approach utilizes the strengths of such a qualitative approach by acquiring a context-rich assessment of a synthetic biology product whose risks and benefits would currently be impossible to quantitatively assess, while also mitigating the Delphi method's traditional weaknesses by acquiring individual opinions and insight into the technology's risks prior to group discussion (Linstone & Turoff). Likewise, MCDA serves as a

method to utilize information derived from subject expert interviews and rank decision alternatives via critical factors of consideration known as decision criteria (Bates et al 2015). MCDA may be of particular use to review governance options for emerging technologies like synthetic biology, the method offers some insight via expert elicitation regarding value tradeoffs and uncertainties that synthetic biology products may possess in their early stages of development (Bates et al 2015; Subramanian et al 2016; Linkov et al 2013).

The purposive sample of experts was chosen to provide “information rich” cases that can provide greater depth of insight into the potential policy impacts and issues of cyberplasm governance, where individuals in various professional disciplines are deliberately included to gain multiple perspectives on the technology and its proper governance (Patton 2005). The list of potential panel members list was compiled using a mixture of web database searches, literature reviews for relevant author names, and prior knowledge and experience by the research team. The initial listing contained 234 experts originating from a variety of groups including: attendance lists from research conferences and national and international professional association meetings, editorial review boards for SB research journals, and government listed panels of research, policy, and ethics review committees. Additional potential panel members were also added to the listing based on personal review from other SB researchers and analysts as well as the research team.

The initial panel members represented a wide range of disciplines (N=48) including chemistry, molecular biology, and bio-engineering (N=14, including those who working on biological parts like those used in cyberplasm – the presence of which gave firsthand accounts of risk and regulatory needs of the technology); policy, governance, and law (N=14); ecology, environmental science, and toxicology (N=6); and bioethics, philosophy, sociology, and STS (N=14). Thirty-five members completed the four rounds of the Delphi study (Table 1). Potential participation contacts are limited due to the novelty of synthetic biology, where countries with active research and development are limited to only a few dozen well-known scholars and

developers active in publication and conference presentations and such a respondent count is consistent with similar research efforts on synthetic biology governance (Bates et al 2015).

This Delphi study elicited expert judgments about the potential benefits and risks of cyberplasm, as well as judgments regarding the ethical, legal, and societal issues of the technology. Named after the oracle of Delphi, the Delphi method was designed to forecast decision-making under uncertain conditions when accurate information is unavailable for ethical or financial reasons, or when subjective information is all that is available for a decision or policy assessment. In a typical Delphi study, expert panel members respond to sets of open-ended and closed-ended questions individually, anonymously, and at their leisure, thus reducing group effect biases and allowing panel members to voice and change their opinions without fear of repercussion. This method also encourages equal flow of information between panel members and researchers and grants adequate time for experts to reflect on developing issues within the study itself. This project used a modified version of the Delphi study, called a Policy Delphi study where the primary goal is to “have an informed group present all the options and supporting evidence,” regarding the case of cyberplasm (Linstone & Turoff 2012). Given the uncertainties related to the risks and benefits posed by cyberplasm, a Policy Delphi study was chosen in order to generate individual context-rich insight into the technology across the included experts while also promoting group discussion and debate afterwards to discuss concerns or uncertainties related to the technology’s characteristics and development (Linstone & Turoff 2012; Berube et al 2011). Data presented forthwith in this study come from various phases throughout the Delphi study and the results are derived solely from qualitative and quantitative data collected during the project.

Information regarding the project’s four-round elicitation process, including the number of respondents at each stage, the type of elicitation conducted, and other general information are noted below in Table 1.

[TABLE 1]

MCDA Model

To integrate and analyze responses from Delphi participants, we utilized MCDA, which is a method of decision analysis that facilitates values tradeoffs of complex and uncertain issues with various sources of information (Linkov & Moberg 2011). Specifically, MCDA integrates qualitative and quantitative information alike, allowing experts to voice their beliefs and opinions on a subject with limited field data or formal scientific agreement (Linkov & Moberg 2011; Linkov et al 2013). Further, MCDA tools can be used to review any disagreements or uncertainties signaled by subject experts through the use of sensitivity analysis, making MCDA all the more helpful for regulators that have to address shifting political, economic, social, and environmental factors as more information about specific products becomes available (Linkov et al 2013; Saltelli et al 1999). Given these factors, MCDA serves as an appropriate method to analyze information derived from the Delphi process and rank governance options for cyberplasm based upon relevant decision criteria.

For this particular case, we make use of the DECERNS decision analytic software, which allows for a multi-method comparison of several decision analytical tools for a single dataset (Yatsalo et al 2015). Other MCDA models have been developed to assess the performance of oversight from a retrospective perspective, and have also been applied to case studies such as with genetically engineered organisms (Kuzma et al 2008; Kuzma et al 2009). This study also uses the case of technological product and multiple criteria for evaluation, but takes a prospective approach to help with future decisions about emerging technologies.

Specifically, this case will utilize Multi-Attribute Value Theory (MAVT), where expert perceptions of the technology's characteristics will be converted to values and evaluated alongside subjective weights and information. This may be represented mathematically as: $V(a) = F(V_1(a_1), \dots, V_m(a_m))$. The overall objective of this methodology is to represent the decision

maker's opinions and preferences in the value function $v(a)$, where a symbolizes the vector of criteria to be evaluated, w_m the weighted values, and $V_i(x)$ the partial value function for the criterion C_i (Yatsalo et al 2007). MAVT maintains underlying assumptions of stakeholder rationality and consistency in judgment, which we sought to assess throughout the interview process (Belton 1986). We illustrate the process of our model's creation below in Figure 1, and further explain below how decision criteria and alternatives were constructed and scored.

[FIGURE 1]

The first step behind the construction of our value hierarchy consisted of identifying the various criteria by which a decision maker would evaluate the risks and benefits of a cyberplasm product. This effort was driven primarily by assessment of qualitative interview transcripts and responses from Rounds 1 and 2. For additional argumentative validation behind a criteria's construction, suggestions from synthetic biology risk governance literature were reviewed for consistency with expert interview responses. This literature was constrained to those articles that discuss the implications as well as the governance of synthetic biology, including those articles that discuss the prospective risks and benefits that synthetic biology products (particularly cyberplasm) may offer to our decision criteria. With both sets of available information, the authors focused criteria construction on those elements that were mentioned by more than one expert, and were present for discussion as relevant in the consideration of risk and benefit by at least two articles published in peer-reviewed journals. This approach is similar to the one used by Bates et al (2015) and Linkov et al (2012), who utilized literature and expert insight alike to identify important factors for consideration that would influence MCDA output. Definitions for these criteria were derived in a rank-maximizing fashion to make results found later in MAVT calculation more intuitive to readers regarding cyberplasm risk and benefit.

Using information generated from expert interviews and confirmed by emerging literature, the second step included assessing the tradeoffs and optimality of six alternative sets of policies that could be pursued by a given nation's regulatory bodies. Similar to criteria and

sub-criteria formation in step one, alternatives construction was derived by reviewing comments made in interview transcripts in Interview Rounds 1 and 2 alongside governance responses from Round 3. Similarly, additional justification was derived from scholarly literature regarding the *possibility* that such a governance alternative could be deployed by a government agency for SB products in general. While these options are simplified due to the emerging nature of the field, they do cover a wide breadth of potential regulatory options, and could be easily modified in the future as SB applications for cyberplasm mature and commercialize. These options are arranged in order of restriction placed upon an individual researcher or scientist in the field, including:

- i) No Governance – no new or specific regulatory actions taken to govern or restrict SB research and development
- ii) IRB Pre Research – Research requires novel or technology-specific checkpoints which are monitored by within-organization review boards.
- iii) ERB Post Research – Research requires debrief with external government agency after completion or at certain checkpoints
- iv) ERB Pre Research – Research proposals require approval and oversight from an external government review board prior to research being conducted
- v) Secure Labs – Research is restricted to government-monitored laboratories only
- vi) Moratorium – Additional research and development is fully banned

Together, placeholders constructed for cyberplasm governance's decision criteria and policy alternatives enabled us to build the model's value hierarchy, or the general structure showing relationships between decision criteria and policy alternatives. Shown below in Figure 2, we detail the value hierarchy which breaks down the criteria and alternatives that must be considered in cyberplasm's multi-criteria decision framework.

[FIGURE 2]

After constructing the hierarchy above, we reviewed interview transcripts and surveys with subject experts to acquire weights for each criterion (in yellow), and scores for each subcriteria-alternative linkage (in gray). Criteria weights were derived from responses in Interview Rounds 2 and 4, while alternative scores were derived from survey responses and transcript comments from Rounds 2 and 3. Further, criteria weights were validated by question-specific ordinal scale survey questions, allowing for an indication of the relative importance that a criterion should have based upon existing knowledge for SB governance and decision making. Likewise, alternative scores were derived by a mixture of question-specific ordinal scale survey questions where available, or through indications of strength of statement made by respondents alongside the relative confidence expressed by respondents through qualitative interview transcripts and responses in discussing a particular risk or benefit related to cyberplasm governance options. In cases where respondents did not express confidence in their answers, or discussion for a particular policy alternative was limited, further consideration of SB governance literature related to efforts to mitigate risk and promote benefit was included in alternative scoring. This was minimized as much as possible, although general literature perusal was conducted for all decision alternatives to promote consistency in methodological approach for our model.

With regards to criteria weighting, survey questions asked specific queries about particular model criteria on a maximizing 1-10 scale, where each response signifies the general level of importance that a particular criteria factors into an overall SB policy decision. Individual criteria values were assessed as a simple arithmetic mean (see Equation 1 below). Any blank responses caused that particular respondent to be removed from average calculations for that given criteria. Later, all criteria values sharing a root source were scaled using unity-based normalization (also in Equation 2 below).

$$a = \frac{1}{n} \sum_{i=1}^n x_i \quad x' = \frac{a - \min(x)}{\max(x) - \min(x)}$$

Eq. 1 and 2. Equations for arithmetic mean calculation for individual criteria weights and unity-based normalization for a normalization of all shared criteria values.

Specific to alternative scoring, such quotes sought in transcript information include quotes such as “the environmental health impacts are not at all important in this case”, which contributed to a score of 0 to most alternatives’ environmental health score, or statements such as “I think that kind of less formal structures of governance that are less oriented around regulations but more thinking about the shaping of technologies [...] is actually something really important” generally favored alternative scores with less restrictive governance overall. As a coding rule, each scoring item required a minimum of two direct quotes to gauge the score, with separate coding passes taken and discrepancies reviewed by the investigators. Quantitatively, alternative scores were assessed on a rank-maximized integer scale ranging from 0-3, where each integer may be understood as:

- 0 – No improvement
- 1- Minor potential improvement
- 2 – significant potential improvement
- 3 – strong inevitable improvement

This encoding was accomplished by two reviewers, where both reviewers were instructed to review specific key phrases within interview text and score alternatives accordingly. Such key phrases centered on the degree of importance placed by the respondent upon the risk factors and regulatory needs of cyberplasm in a given context (i.e. economic or environmental). Further, the judges were told to base their scores on at least four specific comments within interview text, and were to contrast these phrases with any differing opinions noted by other experts. The two scoresheets were compared for consistency, and inconsistent scores were reviewed by both judges to arrive at a consistent result. It is important to note that no inconsistency between the

two reviewers was greater than 1 integer, indicating that no significant gap in respondent perception arose.

Results

Model calculation involved the aggregation of score and criteria weights, and a subsequent summation of these products across all criteria (or weighted sum). The resultant final score serves as an evaluation of each policy alternative's optimality, with a higher score being more favorable. This standard model was evaluated alongside a model detailing the level of confidence that each subject expert applied to their answer, or the level of surety that their answer was the correct one. This comparison allowed for a review of whether 'wild guesses' skewed the model significantly, or biased the results of a particular policy alternative.

For each of the six policy alternatives presented here, a net score was calculated as shown below in Figure 3. These calculations indicated small net performance optimality for the ERB-Pre Research alternative (Score of 0.76). However, the Secure Labs Only (0.64), IRB – Pre Research (0.61), and ERB – Post Research (0.59) alternatives also perform well. Below, we further discuss quantitative reasons why the alternatives score as they do, and also perform sensitivity analysis to determine which conditions the existing optimality may shift (Saltelli et al 1999). Such an assessment allows for an understanding of how resilient and dependable the selection of ERB- Pre Research is the highest scoring governance option for synthetic biology cyberplasm research and development (Saltelli et al 1999; Stewart 2005).

[FIGURE 3]

To gain an additional understanding of the uncertainty and relative strength of expert knowledge, we review the confidence scores (or the confidence expressed by subject experts

related to the perceived risks and benefits that a cyberplasm product poses for a given criteria) for the final raw results alongside the collective aggregation of the five major criteria and their relative subcriteria. Shown below in Figure 4, the results of this analysis demonstrate a general overall consistency in the overall ranked list of results ($\pm 2.5\%$ or less in each of the six policy alternatives). This indicates that despite some uncertainty in respondent answers, responses do not generally show any major outliers or points of concern that could shift optimality in the final results. Unpacking this by reviewing the confidence-weighted scores for the individual criteria weights is more distorted, particularly for the Social Criteria weight which maintained an overall lower level of confidence relative to the other criteria weights. Regardless, all but one individual data point falls below the 60% level of confidence, or roughly $\pm 5\%$ difference from the overall confidence-weighted final score.

[FIGURE 4]

Lastly, we sought to further test the magnitude of the difference in scores by conducting a sensitivity analysis on the primary criteria's weights (an example of the Economic criteria is shown below in Figure 5) (Saltelli et al 1999; Linkov et al 2013; Linkov et al 2012). Specifically, we reviewed the impact of increasing or reducing the degree of importance assigned to a given criterion, with the difference removed or added to the other five criteria distributed equally.

Our sensitivity analysis indicates at least one crossover point in each criteria's weight distribution, where the different alternative may achieve a top score based upon a shift in criteria weights. However, not all of these crossover points are reasonable, such as if Social were given a weight approaching 0 (meaning that stakeholders place virtually no value on Social criteria to SB policy and decision making) or Benefits were assigned a weight approaching 1 (meaning that stakeholders only care about Benefits as opposed to various concern for other criteria). While optimality may shift or reach a point of ambivalence at the ends of the spectrum for these criteria, these scenarios are highly unlikely and are generally unrealistic.

More realistically, the other three criteria (Risks, Political, Economic) each contain possible crossover points that, if weights on a given criterion moved from one side of the breakeven point to another, the model would call for a different approach to cyberplasm governance. Specifically, the top scoring option switches from ERB – Pre Research to Secure Labs and eventually even Full Moratorium once the criteria weight for Risk reaches 64% (assuming all other criteria weights are reduced proportionally). While this may currently seem distant from the current weight of 23.7%, it is within the realm of possibility that, should a strong paradigm shift take place where government officials and stakeholders place significantly more weight on avoiding risk of emerging technologies, the optimal policy alternative to cyberplasm development *should* be increasingly restricted commensurate with the government's appetite for hazard.

The remaining two criteria (Economic and Political) also contain crossover points that generate a sensible narrative based upon the driving factors that each criteria covers. For instance, the more a government decision maker cares for the Economic criteria driving cyberplasm development, the less stringent the optimal regulatory policy alternative would become (from ERB – Pre Research to IRB – Pre Research to No New Governance). Likewise for the Political Criteria, the more that decision makers value Political factors behind emerging technology, the more likely they are to restrict such technology development from taking place due to the potential negative outcomes that could accrue. While these individual inflection points may or may not be interesting and realistic in their own right, they do represent potential concern that, sometime in the future, the changing priorities amongst government stakeholders and the public may shift in such a way as to dramatically impact decision making in this field. Though any shift in the optimal governance alternative would require a substantial shift in priorities and risk/benefit tradeoffs by regulatory decision makers, the potential for such optimality to shift does warrant some discussion into the priorities that government stakeholders want to exhibit in the governance process.

[FIGURE 5]

Discussion

The use of MCDA, Delphi studies, and other analytic tools are geared toward improving identification of policy options and decision-making under situations of high complexity and uncertainty, as is the investigated case of cyberplasm. As the technology itself is further researched and developed, such decision analytic tools can help to focus investigations on oversight and policy choices “upstream” from final technological development and use (Linkov et al 2013; Kuzma et al 2008). Decisions about how best to prepare for governing emerging technologies like cyberplasm have often made use of multiple lines of quantitative and qualitative information (such as modeling and monitoring, risk analysis, cost-benefit analysis, and stakeholder preferences) which are typically combined in a subjective and unstructured manner (Linkov et al 2006). This ad hoc decision basis may ignore crucial factors to governance program success and is likely to yield suboptimal and regretted allocation of resources. Regulators, in partnership with stakeholders, can significantly benefit from new modes of decision analysis like the one presented here that allows them to acquire and analyze information about emerging technological applications in a manner that systematically incorporates qualitative and quantitative information regarding expert-derived risk and benefit data along with defined governance options. Tools such as the one described in this paper can also be integrated into stakeholder and public participation exercises to develop scenarios and help frame management options under conditions of high uncertainty and ambiguity (IRGC 2006, 2015).

Of the six policy options presented for the case of cyberplasm, the model calculated ERB-Pre Research as the most optimal governance option. This form of governance is characterized by a need for approval from external government review board prior to conducting

research. It supports the IRGC recommendation for wider participatory approaches (i.e. external review board) under areas of high uncertainty and ambiguity that include confinement and the step-wise introduction of emerging technologies into society (IRGC 2006). This conclusion was based out of expert-panel considerations of potential hazards associated with the development of the technology as well as its potential applications. This governance option demonstrated only slight net performance optimality compared to other governance options including secured laboratory study, IRB- pre-research, and ERB- post-research, respectively. Notably, the recommended governance option calculated by the MCDA system can be receptive to ranked weightings of its various criteria (Social, Risks, Political, and Economic). However, inaccurate weighting of criteria may unjustly skew calculations. A priori ranking of criteria importance must be considered carefully prior to calculation of recommended decision outputs and should reflect current environment and legislation schemes under which the technology being assessed will be governed. Criteria ranking could also be done in wider deliberative approaches to risk governance whereby stakeholders, interested and affected parties, and experts convene to explore risk management options and scenarios (IRGC 2015). Only then can these tools be used appropriately to guide decision making for cases like cyberplasm that are characterized by high complexity and uncertainty in order to highlight oversight and policy choices “upstream” from final technological development and use (Linkov et al 2013; Kuzma et al 2008).

Synthetic Biology decision-makers, stakeholders, and publics are likely to benefit from transparent, analytic approaches that identify and prioritize proactive governance options based on granular needs-assessments that incorporate expert-derived data and confidence estimates. As risk and benefit data analysis for emerging technologies continue to improve, analytic schema like the one portrayed here for cyberplasm, can be updated and evolved to incorporate new criteria or extinguish irrelevant factors from the analysis. Furthermore, this investigation of policy options for future governance of cyberplasm is just one example of the benefit of MCDA as an option to inform initiatives of early-stage governance of technologies while they are still in pre-production. SB technologies, nanotechnologies, and other revolutionary technological

applications are being developed at a frenetic pace. However, there is a dearth of proactive, rather than reactive, initiatives being undertaken to evolve governance structures. Forecasting policy options of emerging technologies will likely require greater governance involvement in early-stages of development due to the revolutionary nature of technologies like cyberplasm. Identifying and preparing for uses of hybrid and converging technologies increase the uncertainty of the potential impacts, and even uses of such technologies. In such cases of extreme uncertainty, the use of real data from expert studies like this one seems to be a most practical benchmark from which we can forecast governance needs prior to technological diffusion.

Overall, while this paper uses cyberplasm as a 'test case' for evaluating SB risks, benefits, and governance options, it could easily be applied to a whole host of emerging technology applications lacking objective data yet have clear and emerging governance needs to be met. There is no definitive guide to carrying out such research, but in general, using a transparent and robust interview and survey methodology while systematically selecting experts for inclusion would offer helpful and much needed early-stage policy and governance advice. This study also notes that governance decisions are likely to be influenced by the prioritized needs of governing bodies and stakeholders. For instance, should a governing body or stakeholders prioritize economic outcomes over others, the MCDA rubric and the DECERNS system provides calibrated flexibility to assist with such needs and prescribe alternate policy options may be calibrated to reflect such preferences and/or adopt new information about the technology's risk/benefit tradeoffs related to economics.

While we argue that this approach is a promising step forward in anticipatory governance and that tools like the one demonstrated here are likely to remain among the best viable options for guiding early-stage governance of technologies, we also note that certain limitations should be noted and recognized. Specifically, the Delphi method has the potential to suffer from drawbacks based on influence from highly influential group members during the face-to-face

workshop (Franklin and Hart 2007). To limit such effects, the Delphi study used here included multiple rounds of interviews, where each respondent was interviewed before and after workshop participation. Future work of this type may consider oversampling based on expected attrition, and may modify their use of the Delphi method to better reflect their programmatic aims (Linstone & Turoff, 2002).

While the decision analytic system described in this paper does not inherently advocate any particular policy options, and where its outputs are likely to change as the field continues to develop and expand into commercialization, this sort of investigation may serve as a heuristic to decision-making that prioritizes governance needs based on stakeholder and expert elicitation. Ideally, future inputs of the tool would be revised and ranked based on wider deliberation of experts, stakeholders, and policy makers, and outputs of the tool would be integrated into participatory processes to construct different governance scenarios and risk management options.

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Tables:

Round	Method	Description
One	Standardized open-ended interview protocol; n=45	Participants responded to a variety of questions about risk analysis, governance, and societal issues for cyberplasm as well as the other three cases (biomining, deextinction, and plant microbes for nitrogen-fixation). Interviews were approximately 75 minutes in length.
Two	Online quantitative survey; n=34	Designed from preliminary round one findings. Included various scaled items regarding risk governance issues associated with the case studies.
Three	Face-to-face workshop and	Focused on concept-mapping and mind-mapping exercises to generate lists of challenges and opportunities for SB governance. Also included

	ordinal ranking exercise; n=35	an ordinal ranking exercise of ideal governance characteristics.
<i>Four</i>	Online qualitative and quantitative survey; n= 35	Open- and closed-ended items and scales assessing factors that may influence future policy and governance options concerning the case studies.

Table 1: Delphi rounds and participants

Figure Legends:

Fig. 1. Flowchart of MCDA model creation using scholarly literature, qualitative interviews, and quantitative survey responses from 4 rounds of subject expert interviews.

Fig. 2. Value hierarchy of cyberplasm governance and decision making via product risk and benefit

Fig. 3. Cyberplasm Governance Alternatives: Ranked List

Fig. 4. Percentage Differences between Raw and Confidence-Weighted Scores

Fig. 5 Sensitivity Output: Economic Criteria Weighting Shift

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