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Multi-Cellular Engineered Living Systems: Building a Community around Responsible Research on Emergence

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Abstract

Ranging from miniaturized biological robots to organoids, Multi-Cellular Engineered Living Systems (M-CELS) pose complex ethical and societal challenges. Some of these challenges, such as how to best distribute risks and benefits, are likely to arise in the development of any new technology. Other challenges arise specifically because of the particular characteristics of M-CELS. For example, as an engineered living system becomes increasingly complex, it may provoke societal debate about its moral considerability, perhaps necessitating protection from harm or recognition of positive moral and legal rights, particularly if derived from cells of human origin. The use of emergence-based principles in M-CELS development may also create unique challenges, making the technology difficult to fully control or predict in the laboratory as well as in applied medical or environmental settings. In response to these challenges, we argue that the M-CELS community has an obligation to systematically address the ethical and societal aspects of research and to seek input from and accountability to a broad range of stakeholders and

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publics. As a newly developing field, M-CELS has a significant opportunity to integrate ethically responsible norms and standards into its research and development practices from the start. With the aim of seizing this opportunity, we identify two general kinds of salient ethical issues arising from M-CELS research, and then present a set of commitments to and strategies for addressing these issues. If adopted, these commitments and strategies would help define M-CELS as not only an innovative field, but also as a model for responsible research and engineering.

1. Introduction: Designing for Biological Emergence

Researchers working at the intersection of biology and engineering are now able to design and build an array of unprecedented artificial living creations: stem cell-derived 3D structures that emulate organ-level functions (organoids) (Domansky et al. 2010, Quadrato et al. 2017) or model early embryo development (Rivron et al 2018); motile ‘biobots’ (i.e. robots developed from biological materials) that are propelled by the action of muscle tissues on a hydrogel frame (Cvetkovic et al. 2014, Raman et al. 2016); and even genetically programmed species and subpopulations (Moreno 2012). These provocative capabilities form part of a rapidly developing field of research, recently dubbed “multi-cellular engineered living systems” (M-CELS) (Kamm and Bashir 2013; Kamm et al. 2018; Raman and Bashir 2017). The primary goal of this field is the investigation and development of systems “composed of living cells and tissues organized in a way that produces novel functionalities by design” (Kamm et al. 2018, 1).

M-CELS researchers achieve this goal by working across disciplines and subfields, bringing together synthetic biology (Endy 2005), tissue engineering (Huh et al. 2010), stem cell research (Girgin et al. 2018), developmental biology (Lancaster et al. 2013), and cell-based bio-robotics (Cvetkovic, et al. 2014; Raman, et al. 2016). Researchers also depend on a shared set of diverse methodologies, including computational modeling and analysis (Morris et al. 2014; Glen, McDevitt, and Kemp 2018), micro-fabrication (Madou 2011), cell cultures (Spence et al. 2011, Sachs et al. 2018), reverse-engineering of complex systems (Csete and Doyle, 2002; Ingber et al. 2006; Narciso and Zartman, 2018), and genetically-encoded control systems (Basu et al. 2005, Tamsir et al. 2011).

Taken as a whole, M-CELS research is often characterized by its focus on understanding and harnessing *emergent* phenomena, loosely understood to mean macroscopic, system-level phenomena that arise from interactions between individual cells and between cells and their environment (Kamm et al. 2018). Although the precise definition of ‘emergence’ isn’t always clear -- the term sometimes denotes any properties that arise from complex systems, and other

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2 times refers only to those properties that are inherently unpredictable¹ -- it features heavily in
3 researchers' definitions of M-CELS research (e.g. see Kamm et al. 2018).
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6 This interest in emergence is about more than the pursuit of abstract scientific knowledge about
7 systems-level phenomena; it also arises from the field's focus on creating technology with
8 specific societal applications. The purposeful similarity of organoids to human organs, for
9 example, presents more than just an opportunity to understand organogenesis; organoids are
10 being developed with the aim of modelling and treating disease (Osaki et al. 2018; Raman et al.
11 2017), reducing the use of animals in research (Bredernoord 2017), and even creating
12 much-needed transplantable human tissues (Huch et al. 2015). Additionally, other researchers
13 have suggested that micro-scale biobots, due to their small size and customizable form, could
14 one day be used to conduct medical interventions in humans or assist in environmental clean-up
15 (Williams, et al. 2014, Raman et al. 2017, Pagan-Diaz et al. 2018).
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21 Although many of these applications are still highly speculative, the transformative aspirations
22 motivating M-CELS research demand careful, collective reflection. This was the purpose of a
23 National Science Foundation-funded interdisciplinary workshop held in August 2018, in which
24 72 M-CELS researchers gathered to discuss and formulate ethical principles to guide this new
25 field. The workshop participants, hailing from 38 universities and institutes, 7 countries (Canada,
26 China, France, Japan, South Korea, Spain, the United States), and a range of disciplines (i.e.,
27 STEM, bioethics, and history), discussed how research on organoids, embryoids, gastruloids, and
28 biobots is provoking difficult societal and ethical questions, some of which arise from the field's
29 focus on emergence. In this paper, we draw on discussions from this workshop, as well as on
30 literature in philosophy, sociology, and public policy, to report key societal and ethical issues
31 that could arise in the development and use of M-CELS. More practically, we then propose a set
32 of commitments and strategies by which these issues can be addressed. These recommendations
33 are tailored for an academic audience, but are designed to foster a conversation among diverse
34 *publics*, referring here to not only the general public but also researchers, university and funding
35 administrators, journal staff, industry representatives, policy makers, patients, and other key
36 stakeholders.
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45 In short, we claim that the M-CELS community must be committed to: 1) facilitating inclusive
46 deliberation about the moral considerability of M-CELS, 2) choosing and developing responsible
47 applications of M-CELS in consultation with diverse publics, and 3) developing institutional
48 mechanisms to address ethical and societal challenges. If realized, these commitments would
49 define M-CELS not only as an innovative field, but also as a model for responsible research and
50 engineering.
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55 ¹ The latter definition evokes an interesting tension within emergence-based engineering: how can we design for the
56 inherently unpredictable?
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2. Ethical and Societal Challenges

Some M-CELS researchers have already emphasized that their work raises multiple significant societal and ethical concerns (Kamm and Bashir, 2013; Kamm, et al. 2018). In discussions among workshop participants, we revisited and explored these concerns, grouping them into two categories: 1) questions of moral considerability (defined below) and 2) questions of responsible development and application. We collect them here (see Table 1) not as an exhaustive or final classification of all possible ethical concerns,² but as evidence for the need for inclusive deliberation and responsible action in M-CELS research and development (see Section 3).

Table 1. Two Groups of Societal and Ethical Questions Relevant to M-CELS

1. Questions of Moral Considerability	2. Questions of Responsible Development and Application
In which circumstances and to what degree are M-CELS creations morally considerable?	Which uses of M-CELS technology are ethical, equitable, and/or socially responsible?
How should we understand and talk about M-CELS? Are M-CELS tools or agents, objects or persons, property or nature, matter or life?	What level of control over M-CELS creations (in the lab and beyond) is necessary, and how should we prevent and/or respond to problematic loss of control?
What does the moral considerability of M-CELS require of us?	How should we deal with dual-use research of concern (DURC) or the potential for misuse of M-CELS?
What steps should be taken by regulatory bodies and by researchers when a moral boundary is crossed?	What guidelines and norms from existing research ethics are relevant for work on M-CELS?

Let's begin with Column 1. The eventual role and acceptance of M-CELS in society will depend at least partly on M-CELS' *moral considerability*, i.e. on whether or not M-CELS are or should be considered subjects of moral principles, moral attitudes, or rights (Goodpaster 1978). Intuitions about moral considerability are complex for researchers and publics alike, and are influenced by many factors. For example, the tendency to use machine-based metaphors in synthetic biology (e.g., expressions like "genetically engineered machine" and "platform organism") has been shown to decrease the likelihood that stakeholders will attribute moral considerability to complex biotechnologies (Boldt 2018). M-CELS creations are likely no

² Sorting these questions into the two groups in Table 1 is helpful for efficiently presenting a range of societal and ethical concerns, but also elides complex inter-connections. Answers to questions about moral considerability will undoubtedly impact ethical issues concerning M-CELS development and use, and judgments about desirable applications may generate new questions and concerns about moral considerability.

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3 different. If a biobot is produced from artificial mechanical components and a few non-human
4 cells, and if the language used to describe the biobot draws primarily on mechanical metaphors,
5 many in the general public might interpret it as simply an “object” or “tool,” deserving of little to
6 no moral consideration. Such biobots might be seen as analogous to nanotechnologies,
7 non-living biomedical implants or pacemakers: marvels of microscale engineering, but not
8 intrinsically deserving of respect, care, or other forms of moral consideration.
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12 Yet, M-CELS creations could also exhibit features that are culturally associated with existing
13 biological lifeforms, like mobility, autonomous behaviors, response to external stimuli, or
14 animal-like appearance (Chan et al. 2012; Webster et al. 2016). Eventually, they may even
15 display elements of intelligence and adaptability (Han et al. 2013; Nesbeth et al. 2016). It seems
16 plausible that, for some stakeholders, increasing similarity in form and function to complex
17 biological life corresponds to increasing levels of moral consideration. Our duties to these
18 creations could thus range from simple protection from harm (as with mice in the lab) to the
19 granting of positive rights like autonomy and freedom of choice (as we grant to our fellow
20 humans). Discussions in environmental ethics on the moral status of ecosystems and
21 environmental resources (Brennan 1984), and on the ethics of animal research and meat
22 consumption (Smith and Boyd 1991; Rollin 2006) provide precedents for working through such
23 questions about moral consideration. Given that these are highly contentious ethical debates --
24 think, for example, of the polarization present in debates about animal rights, factory farms, and
25 climate change -- we may not be able to directly export conclusions from these debates to the
26 M-CELS context. Nonetheless, we believe that they contain relevant and thought-provoking
27 ideas that could be mutually enriching when juxtaposed with M-CELS questions. For instance,
28 some animal and environmental ethics research on the difference between intrinsic and extrinsic
29 value suggests the possibility that the moral considerability of M-CELS should not be
30 determined solely by intrinsic features of the creations themselves (e.g. what they’re made of,
31 what they can do, how similar they are to ‘natural’ living creatures, etc.), but must be assessed in
32 light of the role that these creations play and could play in social contexts.
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42 Public concerns about moral considerability are often heightened when cells of human origin are
43 involved, as illustrated by ongoing debates about HeLa and other human cell cultures (Landecker
44 2007, Skloot 2011), tissue donation (Abouna 2003), embryo and stem cell research (Rivron et al
45 2018, Sagan and Singer 2007), and new reproductive technologies, especially gamete donation
46 and freezing (Thompson 2007). Even when cells are spatially and temporally distant from the
47 donor, their human origin and continued life outside of the body can blur the line between self
48 and other. Chimeric M-CELS, which mix animal and human-derived components, may also
49 unsettle the distinction between person and animal, or between person and thing, similarly to
50 how research on artificial intelligence and machine learning has shifted conceptions of the
51 boundary between human and machine (Garside 2014, Hyun 2018). We are thus left with the
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3 questions: When are M-CELS creations morally considerable and what language should we use
4 to describe them? Is this considerability grounded in cellular origin (human vs non-human),
5 structure (simple vs complex), or something else entirely (e.g. societal context)? These are more
6 than abstract philosophical puzzles; our collective judgments about considerability will have
7 significant implications for research ethics, regulatory practices, and technological development.
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11 Now on to the second column of Table 1. The responsible development and application of
12 M-CELS technology is a second, albeit overlapping, source of questions. Here, equity is a
13 primary concern; how do we select, pursue, and manage M-CELS applications, such that
14 potential benefits are equitably distributed, and are responsibly balanced with potential risks (e.g.
15 accidental or intentional misuse of knowledge and products)? And whose interests and values
16 will be represented in that process? As has been noted with respect to synthetic biology (van den
17 Belt 2013), we should not assume that the impacts of new technology will be fairly distributed
18 across individuals and communities. For instance, M-CELS applications that alter or enhance the
19 human body may, especially if accessible only to a select few, exacerbate existing social
20 inequalities (Savulescu and Bostrom 2009). Conversely, potential M-CELS-based dangers to the
21 environment or human health may disproportionately affect socially marginalized groups, who
22 may lack the resources to adapt or move if, for example, engineered organisms “become
23 invasive” and negatively affect existing ecosystems and related industries and economies
24 (Science for Environment Policy 2016, 14; Pollack 2004; US EPA 2014).
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32 Issues of equity also arise in the context of intellectual property (IP) (Hart 2017). Can the
33 emergent objects of biological engineering fit with traditional IP regimes, and if so, how (Calvert
34 2008; Torrance and Kahl 2014)? Is a strong patent system necessary to ensure innovation and
35 progress, or should we adopt a computer science-inspired “open-source” approach? Which
36 approach would lead to more equitable access to and distribution of benefits from M-CELS
37 research? Questions about ownership and IP thus touch not only on pragmatic concerns about
38 promoting innovation, but also on moral, ethical and political questions about moral
39 considerability (e.g. is it ethically permissible to patent a complex multi-cellular system?),
40 privatization and the commons, distributive justice, and equitable access to new and emerging
41 technologies (Parthasarathy 2017; König, Dorado-Morales, and Porcar 2015).
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47 Finally, beyond equity, it will also be necessary to consider biosecurity and the possibility of
48 malevolent applications. Regarding the former, we will have to decide: what level of control is
49 necessary for responsible development and use? Like gene drives and other “living”
50 biotechnologies, M-CELS creations relying on emergent properties -- properties that may change
51 over time and may be impossible to fully predict (see discussion of emergence in Section 1) --
52 which will only compound these concerns (Rudenko, Palmer, and Oye 2018). It is equally
53 conceivable that M-CELS research and technology could be used for violent purposes, such as
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weapons development (Regalado 2018). Additionally, because of the purposeful similarity of some embryoids, organoids and biobots to human tissues (more so than an engineered yeast cell or an animal model), M-CELS could very plausibly be categorized as dual-use research of concern (DURC).³ Even when the creations themselves do not constitute a material threat, the knowledge gained through their use may, as seen in recent controversies over gain of function experiments (e.g. the creation of new strains of transmissible H5N1 virus) (Duprex et al. 2015).

3. Commitments to Responsible M-CELS Research

Once ethical and societal questions surface (Table 1), how should we go about answering them? Broadly speaking, prominent debates in the ethics of medicine and the biological sciences have historically focused on two approaches: researchers in science and engineering should either manage ethical issues themselves (i.e. they should self-regulate), or they should submit to regulatory guidance or laws from external experts (e.g. from ethicists or policymakers). In the most famous example of the former approach, the genetic engineering research community came together in 1975 at a summit in Asilomar, California to address the ethical and societal implications of genetically engineered organisms (Berg et al. 1975). Committed to a particular vision of scientific autonomy, the summit participants did not seek out assistance or input from external groups or individuals. The Asilomar approach has become an unfortunate blueprint for many present-day responses to emerging societal and ethical challenges (Hurlbut 2015). Without involvement of diverse publics and careful consultation of stakeholders, attempts at self-governance in science and engineering may do little to foster a societal consensus on a contentious issue. For example, despite earnest ethical and societal deliberations at Asilomar, many citizens continue to express particularly vehement distrust and rejection of research on genetically modified food (Funk and Kennedy 2016), resulting in continued challenges for GMO science and technology (National Academies of Sciences 2016).

Meanwhile, in the same decade as the first Asilomar meeting, we find landmark cases of regulation imposed from outside, rather than from within, the research community. In 1979, a group of philosophers drafted the Belmont Report, a set of ethical guidelines for conducting research involving human subjects based on principles of beneficence, non-maleficence, justice, and respect, which ended up shaping federal and eventually international legislation (“The Belmont Report” 2010). In that same year, an ethics advisory board to the U.S. Department of Health, Education and Welfare proposed the “14-day rule” as a strict ethical constraint on how long research can be conducted on human embryos (Hyun et al. 2016). This too had international repercussions, and was taken up in the U.K. by the interdisciplinary Warnock Committee

³ DURC is “life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security” (NIH Office of Science Policy).

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3 (Warnock 1984). These activities set a precedent, leading to a proliferation of regulatory
4 frameworks for research, including the formation of institutional review boards (IRBs) in the
5 United States, the National Institute of Health report on embryo research (1994), and the
6 Guidelines of the International Society for Stem Cell Research (ISSCR). In contrast to Asilomar,
7 these activities and institutions delegate much of the ethical deliberation to individuals *outside* of
8 research practice. What they share with Asilomar, however, is a failure to adequately engage all
9 relevant stakeholders in deliberative processes.
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14 When questions have broad socio-ethical implications that fall outside the realms of scientific or
15 regulatory expertise, it is insufficient to consult only researchers, policy makers, or ethicists. As
16 illustrated by the cases of Asilomar and the Belmont Report, expert answers to ethical or societal
17 questions may not facilitate a wide cultural consensus on difficult topics. Because most citizens
18 will not be included in Asilomar-style deliberation or the creation and practice of IRBs, they will
19 not have any reason to adopt expert conclusions aside from deference to authority. Particularly in
20 the current moment, with increasing societal worries about an erosion of public trust in experts
21 (Czerski 2017), new ethical frameworks must be built on solid dialogical foundations. More
22 generally, justice in democratic societies is usually understood to demand robust mechanisms in
23 which citizens can shape social order and our shared future. This ideal is just as true in the
24 biotechnological realm as it is in more straightforwardly political realms. But expert scientists,
25 ethicists and policy-makers, especially if they are not holding government office, may not be
26 meaningfully accountable to citizens.
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34 A better approach is needed, one that realizes the need for robust democratic input and for
35 effective, publicly-acceptable sociotechnical systems. For this, we look to recent work in science
36 and engineering ethics. New strategies for fostering inclusive deliberation can be found in
37 frameworks for “responsible research and innovation” (RRI) (Stilgoe et al 2013), models for
38 public engagement with science (Museum of Science 2017) (Bandelli and Konijn 2013),
39 technology assessment mechanisms (Banta 2009) (Hennen 2012), public participation
40 frameworks (Gehrke 2014), citizen juries (OITA US EPA 2014; Gooberman-Hill, Horwood, and
41 Calnan 2008), the creation of global interdisciplinary “observatories” (Jasanoff and Hurlbut
42 2018), and consensus conferences like those pioneered by the Danish Board of Technology
43 (Rowe and Frewer 2005). Best practices can be drawn from each of these models to guide
44 M-CELS research. For example, a recent report within the RRI framework provides 36 concrete
45 indicators for evaluating responsible research, ranging from level of citizen interest in scientific
46 decision-making to the importance of ethics in proposal evaluation (Stilgoe 2019). Overlapping
47 in many ways, all of the above frameworks offer resources for and approaches to responsible
48 research. We propose, accordingly, that the M-CELS community orient itself around three core
49 commitments, and outline corresponding sets of strategies (drawn from the above models) for the
50 realization of each commitment (Table 2).
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Table 2. Three Commitments for Responsible M-CELS Research and Corresponding Strategies

1. Facilitate inclusive deliberation on moral considerability	2. Choose and develop responsible applications	3. Develop institutional mechanisms to address ethical and societal challenges
<p>At the laboratory level, maintain a sensitivity to questions regarding moral considerability and a focus on actual (rather than merely assumed) societal needs.</p> <p>Continuously seek to identify alternative M-CELS design choices and trade-offs, and openly discuss the values underlying these choices and trade-offs.</p>		<p>Foster ethical deliberation skills throughout the M-CELS training pipeline (i.e. high school - post-doc), with concrete learning objectives and in collaboration with humanities and social science departments.</p> <p>Allocate time and resources for faculty and students to work on societal and ethical issues by establishing norms and structures that recognize and reward such work.</p> <p>Incentivize the integration of “ethics and society” reflections in M-CELS publications and grant applications.</p>
<p>Organize events and initiatives that facilitate two-way communication between M-CELS researchers and publics about moral considerability and responsible applications.</p>		<p>Recruit partners with experience interacting with the public (e.g. at science museums, libraries, local government, places of worship, hospitals).</p> <p>Develop and share public engagement strategies and open access educational material.</p>
<p>Build on existing expertise from other disciplines (esp. social sciences and humanities), ethical review boards, and other publics.</p> <p>Comply with existing norms in research ethics, while also encouraging public and stakeholder discussion of how these norms should evolve with M-CELS research.</p>		<p>Fund research collaborations, conferences, and networks between M-CELS researchers and social scientists, ethicists and other experts and stakeholder groups.</p>
<p>Proactively seek out ethical perspectives and values that are likely to differ from those of the researchers.</p>		<p>Encourage and fund initiatives and interventions aimed at increasing diversity (in all forms) within the M-CELS research community.</p>

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4 The **first commitment** -- facilitate inclusive deliberation on moral considerability -- is a
5 collective pledge to answering pressing questions of moral considerability *in collaboration* with
6 other disciplines, institutions, and with diverse publics. While some M-CELS researchers may
7 desire precise rules or fixed procedures for how to morally assess and treat M-CELS creations,
8 such rules currently do not exist and cannot be devised without holding difficult and nuanced
9 discussions. For this reason, we believe that the research community must bring the uncertainty
10 and tough questions that arise in the lab into broader societal conversations. Involving publics in
11 this way avoids mistrust or misunderstanding and fulfills the ideals of democratic representation.
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16 This need for inclusive deliberation applies equally to the **second commitment**: choose and
17 develop responsible applications. As with moral considerability, there is no predetermined
18 formula for positive societal impact, and it is insufficient to simply assume, imagine or infer the
19 attitudes of diverse publics. Thus, the question of how M-CELS technology should be developed
20 and applied must also be answered in active consultation with publics and stakeholders.
21 However, this second commitment goes beyond dialogue. Unlike questions of moral
22 considerability, which are often highly abstract and for which researchers may not have special
23 expertise, technical and scientific questions are often delegated exclusively to researchers by
24 society. This special role requires that researchers exhibit virtues linked to it; they must exhibit
25 modesty, openness and care when envisioning the role of M-CELS in society.
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31 These two commitments can be fulfilled in a variety of ways (Left Column, Table 2). As
32 suggested above, researchers should foster a benchside sensitivity to tough ethical and societal
33 questions and proactively facilitate conversations outside of the lab. These activities should
34 begin as early as possible in a research cycle, to allow for the identification and implementation
35 of “alternative design choices” (Hyun 2017) or even alternative projects or research questions.
36 Researchers, especially those in senior positions, should thus advocate for and organize
37 opportunities for inclusive deliberation among a wide variety of publics, including engineers,
38 policymakers, patients, and others. The goal, here, is not only to represent diverse views
39 (particularly those whose values may differ from those of the researchers), but also to empower
40 those participating in the deliberations to make informed and meaningful contributions
41 (Morrison and Dearden 2013, Museum of Science 2016). Importantly, the organization of
42 inclusive deliberation processes and activities need not start from scratch but should build on
43 existing deliberative expertise and experience in non-STEM disciplines, such as philosophy,
44 anthropology and the communication fields.
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52 Finally, to support the feasibility of commitments one and two, we propose a **third**
53 **commitment**: to develop the multi-level social and institutional mechanisms and incentives that
54 make it possible, and indeed rewarding, to address ethical and societal issues (Right Column of
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3 Table 2). In terms of training, university-level M-CELS courses and pedagogical materials
4 should be developed that include modules from humanities or social sciences and that involve
5 humanities and social science researchers in the teaching process (either as guest lecturers or
6 co-instructors), and should be shared across institutions. These teaching strategies should focus
7 not just on teaching ethical content (e.g. what kinds of ethical and societal issues are triggered by
8 M-CELS research like those listed in Table 1) but on teaching skills for participating (and
9 eventually organizing and facilitating) in ethical discussions (e.g. through debates, scenario
10 exercises, role-playing, etc.). Doing so would help prepare the next generation of M-CELS
11 researchers for participation in collaborative ethical and societal deliberation. Simultaneously,
12 lab directors must allocate time and resources for their trainees to exercise these skills, in
13 research or in lab meetings, as well as processes and mechanisms for valorizing the acquisition
14 and practice of these skills.
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21 To take these discussions outside of academia, it is essential to recruit partners from other
22 disciplines (e.g., social sciences, humanities, public policy) and public-oriented institutions, such
23 as museums and funding agencies. For example, socio-ethical questions about human
24 enhancement with respect to human genome editing were adapted for public discussion through
25 an innovative Museum of Science initiative in Boston, which has since been used nationwide
26 (Sittenfeld 2018). The method and deliberative content of these public events should be recorded
27 and distributed along with other training resources (e.g., EBICS n.d.) to build a shared resource
28 for the field while simultaneously bringing socio-ethical questions from the margins into
29 mainstream discussion. Even outside the context of public engagement, such partnerships can
30 jump start ethical and societal conversations by building on existing expertise. For instance,
31 while it may seem difficult to respond to the misapplication of M-CELS by malevolent actors,
32 some researchers are already discussing the management of risk in synthetic biology and in
33 artificial intelligence (Palmer, Fukuyama, and Relman 2015). To the same effect, useful
34 questions and insights regarding personhood, rights, and the possibility of non-human minds can
35 be gained by consulting with researchers not only in bioethics but also in philosophy of mind
36 (Dennett 1988, Lavazza 2018, Nagel 1974) and many other overlapping fields.
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44 To be most effective, all of these strategies require high-level attention and dedicated resources
45 from departments, universities, and funding agencies. New university courses are not possible
46 without institutional backing for their development and ongoing support of all contributing
47 departments. Funding agencies must commit to sustained funding for independent work in
48 STEM, social sciences, and humanities, in addition to enabling ambitious collaborative projects
49 between researchers and ethicists or community groups. Grant applications should require
50 careful discussion of the ethical and social issues in and beyond research ethics as commonly
51 understood. Science and engineering journals, which also have tremendous power for
52 influencing research directions and priorities, should instruct reviewers to assess authors'
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3 discussion of ethical and social impacts -- and to pay attention to evidence of deliberative public
4 engagement -- when making publication decisions. We view these various forms of institutional
5 support as analogous in structure and complementary in spirit to STEM-wide initiatives to
6 increase diversity in all its forms (e.g. the multi-year NSF INCLUDES initiative). The need for
7 inclusion is not merely for ethical insight but for more fair and impactful scientific and
8 engineering practices.
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11 12 4. Next Steps for Responsible M-CELS Research 13

14 At our August 2018 workshop, researchers sought answers for significant ethical and societal
15 questions -- about moral considerability, about how to benefit society and avoid misuse, and
16 about potential issues of control stemming from the field's focus on emergence-based design. In
17 starting this discussion, M-CELS researchers play a crucial role in highlighting these questions,
18 but they cannot and should not answer them alone. To this end, we have suggested a set of
19 commitments and strategies that, if adopted, could facilitate collaborative and meaningful
20 deliberation, and could lead to the development of research norms and practices based on a
21 shared and robust understanding of what it means to conduct responsible and ethical M-CELS
22 research.
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28 The motivation for this work is, importantly, not grounded solely on a novel type of question or
29 on the provocative character of biological emergence. As we have noted, the ethical challenges
30 raised in this paper are not unique to M-CELS research. What is unique, in contrast to more
31 established fields, is the opportunity to engage with these issues as the field is just developing.
32 Unlike more entrenched debates, such as those on the ethics of meat consumption discussed
33 above, we have yet to form widespread social norms around and established attitudes towards
34 M-CELS creations. As such, inclusive societal debates about biobots or organoids may reveal
35 potential resolutions or compromises that are perhaps more perhaps harder to identify in
36 longstanding polarized conversations about factory farms or climate change. M-CELS
37 researchers, then, have an opportunity to proactively (rather than reactively) lead a robust ethical
38 conversation, one that goes beyond the requirements of standard ethical regulations, and beyond
39 the conventional wisdom that the public should be educated and consulted. We maintain that the
40 commitments and strategies proposed in this paper, if adopted, would help to fulfill this potential
41 and establish M-CELS as an ethically responsible community, and as a model for future
42 emerging techno-scientific fields.
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50 51 5. Bibliography

- 52 Abouna G M 2003 Ethical issues in organ and tissue transplantation. *Exp. Clin. Transplant.* **1** 125–38
53 Bandelli A and Konijn E A 2013 Science centers and public participation: Methods, strategies, and
54 barriers *Sci. Comm.* **35** 419–48
55 Banta D 2009 What is technology assessment? *Int. J. Tech. Assessm. Health Care* **25** 7–9
56
57
58
59
60

- 1
2 Basu S, Gerchman Y, Collins C H, Arnold F H, and Weiss R 2005 A synthetic multicellular system for
3 programmed pattern formation. *Nature* **434** 1130–4
4
5 van den Belt H 2013 Synthetic biology, patenting, health and global justice. *Syst. Synth. Biol.* **7** 87–98
6
7 Berg P, Baltimore D, Brenner S, Roblin R O, and Singer M F 1975 Summary statement of the Asilomar
8 conference on recombinant DNA molecules. *PNAS* **72.6** 1981–4
9
10 Boldt J 2018 Machine metaphors and ethics in synthetic biology. *Life Sci. Soc. Policy* **14** 12
11
12 Bredenoord A L, Clevers H, Knoblich J A 2017 Human tissues in a dish: The research and ethical
13 implications of organoid technology. *Science* **355** eaaf9414
14
15 Brennan A 1984 The moral standing of natural objects. *Environ. Ethics* **6** 35–56
16
17 Calvert J 2008 The commodification of emergence: Systems biology, synthetic biology and intellectual
18 property. *BioSocieties* **3** 383–98
19
20 Chan V, Park K, Collens M B, Kong H, Saif T A, Bashir R 2012 Development of miniaturized walking
21 biological machines. *Sci. Rep.* **2** 857
22
23 Csete M E and Doyle J C 2002 Reverse engineering of biological complexity. *Science* **295** 1664-1669
24
25 Cvetkovic C et al. 2014 Three-dimensionally printed biological machines powered by skeletal muscle.
26 *PNAS* **111** 10125-10130
27
28 Czernski H 2017 A crisis of trust is looming between scientists and society – It’s time to talk. *The*
29 *Guardian*, January 27. Accessed at:
30 <https://www.theguardian.com/science/blog/2017/jan/27/a-crisis-of-trust-is-looming-between-scientists-and-society-its-time-to-talk>
31
32 Dennett D 1988 Conditions of personhood. *What Is a Person?* ed. M Goodman (Clifton: Humana Press)
33 p145
34
35 Duprex W P, Fouchier R A, Imperiale M J, Lipsitch M, Relman D A 2015 Gain-of-function experiments:
36 Time for a real debate. *Nature Rev. Microbiol.* **13** 58v64
37
38 Domansky K, Inman W, Serdy J, Dash A, Lim M H, Griffith L G 2010 Perfused multiwell plate for 3D
39 liver tissue engineering. *Lab Chip* **10** 51–8
40
41 Emergent Behaviors of Integrated Cellular Systems (EBICS). Module 1 - Creating biological machines:
42 The biobot. Accessed at:
43 <https://ebics.net/knowledge-transfer/ethics/module-1-creating-biological-machines-biobot>
44
45 Endy D 2005 Foundations for engineering biology. *Nature* **438** 449–53
46
47 Funk C and Kennedy B 2016 Public opinion about genetically modified foods and trust in scientists. *Pew*
48 *Research Center: Science and Society*, December 1. Accessed at:
49 <http://www.pewinternet.org/2016/12/01/public-opinion-about-genetically-modified-foods-and-trust-in-scientists-connected-with-these-foods/>
50
51 Garside J 2014 Google, Facebook and Amazon race to blur lines between man and machine. *The*
52 *Guardian*, April 28. Accessed at:
53 <https://www.theguardian.com/technology/2014/apr/28/google-facebook-amazon-transcendence-artificial-intelligence>
54
55 Gehrke P J 2014 Ecological validity and the study of publics: The case for organic public engagement
56 methods. *Public Underst. Sci.* **23** 77–91
57
58 Girgin M, Turner D A, Baillie-Johnson P, Cossy A, Beccari L, Moris N, Lutolf M, Duboule D, Arias A M
59 2018 Generating gastruloids from mouse embryonic stem cells. *Protocol Exchange, Nature*
60 *Research*. Accessed at: <https://doi.org/10.1038/protex.2018.094>
Glen C M, McDevitt T C, Kemp M L 2018 Dynamic Intercellular Transport Modulates the Spatial
Patterning of Differentiation during Early Neural Commitment. *Nature Commun.* **9** 4111
Goberman-Hill R, Horwood J, Calnan M 2008 Citizens’ juries in planning research priorities: Process,
engagement and outcome. *Health Expect.* **11** 272–81
Goodpaster K E 1978 On being morally considerable. *J. Philos.* **75** 308-325

- 1
2
3 Hart R 2017 Should You Be Able to Patent an Organism? *Slate*, April 7. Accessed at:
4 http://www.slate.com/articles/technology/future_tense/2017/04/the_synthetic_biology_community_is_divided_on_intellectual_property.html
5
6 Hennen L 2012 Why do we still need participatory technology assessment? *Poiesis Praxis* **9** 27–41
7
8 Huch M et al. 2015 Long-term culture of genome-stable bipotent stem cells from adult human liver. *Cell*
9 **160** 299–312
10
11 Huh D, Matthews B D, Mammoto A, Montoya-Zavala M, Hsin H Y, Ingber D E 2010 Reconstituting
12 organ-level lung functions on a chip. *Science* **328** 1662–8
13
14 Hurlbut J B 2015 Remembering the future: Science, law, and the legacy of Asilomar. *Dreamscapes of
15 modernity: Sociotechnical imaginaries and the fabrication of power*. eds S Jasanoff and SH Kim
16 (Chicago: University of Chicago) p126-51
17
18 Hyun I 2017 Engineering ethics and self-organizing models of human development: Opportunities and
19 challenges. *Cell Stem Cell* **21** 718-720
20
21 Hyun I, Wilkerson A, Johnston J 2016 Embryology policy: Revisit the 14-day rule. *Nature* **533** 169-171
22
23 Hyun I 2018 The ethics of chimera creation in stem cell research. *Curr. Stem Cell Reports* **4** 235-239
24
25 Ingber D E, Mow V C, Butler D, Niklason L, Huard J, Mao J, Yannas I, Kaplan D, Vunjak-Novakovic G
26 Tissue engineering and developmental biology: Going biomimetic. *Tissue Eng.* **12** 3265-3283
27
28 Jasanoff S, Hurlbut J B 2018. A global observatory for gene editing. *Nature* **555** 435–37
29
30 Kamm R D, Bashir R 2013 Creating living machines. *Ann. Biomed. Eng.* 2013
31
32 Kamm R D et al. 2018 Perspective: The promise of multi-cellular engineered living systems. *APL Bioeng.*
33 **2** 040901
34
35 König H, Dorado-Morales P, Porcar M 2015 Responsibility and intellectual property in synthetic biology.
36 *EMBO Rep.* **16** 1055–59
37
38 Lancaster M A et al. 2013 Cerebral organoids model human brain development and microcephaly. *Nature*
39 **501** 373–379
40
41 Landecker H 2007 *Culturing Life: How Cells Became Technologies*. (Cambridge: Harvard University
42 Press)
43
44 Lavazza A, Massimini M 2018 Cerebral organoids: Ethical issues and consciousness assessment. *J. Med.
45 Ethics* **44** 606-610
46
47 Madou M J 2011 *Fundamentals of Microfabrication and Nanotechnology*. (Boca Raton: CRC Press)
48
49 Moreno E 2012 Design and construction of ‘synthetic species.’ *PLOS ONE* **7** e39054
50
51 Morris S A et al. 2014 Dissecting engineered cell types and enhancing cell fate conversion via CellNet.
52 *Cell* **158** 889–902
53
54 Morrison C and Dearden A 2013 Beyond tokenistic participation: Using representational artefacts to
55 enable meaningful public participation in health service design. *Health Policy* **112** 179-186
56
57 Museum of Science, Boston 2017 Public engagement with science. Accessed at:
58 https://www.mos.org/sites/dev-elvis.mos.org/files/docs/offers/PES_guide_10_20r_HR.pdf
59
60 Museum of Science, Boston 2016 Forums manual. Accessed at:
http://www.buildingwithbiology.org/sites/building-with-biology/themes/bwb/img/BuildingwithBiology_Forums_Manual_Final.pdf
Nagel T 1974 What is it like to be a bat? *Philos. Rev.* **83** 435-450
Narciso C and Zartman J 2018 Reverse-engineering organogenesis through feedback loops between
model systems. *Curr. Opin. Biotechnol.* **52** 1-8
National Institutes of Health 1994 Report of the human embryo research panel, volume I. Accessed at:
<https://repository.library.georgetown.edu/handle/10822/545550>
Nesbeth D N, Zaikin A, Saka Y, Romano M C, Giuraniuc C V, Kanakov O, Lapyteva T 2016 Synthetic
biology routes to bio-artificial intelligence. *Essays in Biochem.* **60** 381–91
NIH - Office of Science Policy n.d Dual use research of concern. Accessed at:

- 1
2
3 <https://osp.od.nih.gov/biotechnology/dual-use-research-of-concern/>
4 Osaki T, Sivathanu V, Kamm R D 2018 Vascularized microfluidic organ-chips for drug screening,
5 disease models and tissue engineering. *Curr. Opin. Biotechnol.* **52** 116–123
6 Pagan-Diaz G J et al. 2018 Simulation and Fabrication of Stronger, Larger, and Faster Walking Biohybrid
7 Machines. *Advanced Functional Materials*, **28** 1801145
8 Palmer M J, Fukuyama F, Relman D A 2015 A more systematic approach to biological risk. *Science* **350**
9 1471–3
10 Parthasarathy S 2017 *Patent Politics: Life Forms, Markets, and the Public Interest in the United States*
11 *and Europe*. (Chicago: University of Chicago Press.)
12 Pollack A 2004 Genes From engineered grass spread for miles, study finds. *The New York Times*,
13 September 21. Accessed at:
14 [https://www.nytimes.com/2004/09/21/business/genes-from-engineered-grass-spread-for-miles-stu](https://www.nytimes.com/2004/09/21/business/genes-from-engineered-grass-spread-for-miles-study-finds.html)
15 [dy-finds.html](https://www.nytimes.com/2004/09/21/business/genes-from-engineered-grass-spread-for-miles-study-finds.html).
16
17 Quadrato G et al. 2017 Cell diversity and network dynamics in photosensitive human brain organoids.
18 *Nature* **545** 48–53
19 Raman R, Bashir R 2017 Biomimicry, biofabrication, and biohybrid systems: The emergence and
20 evolution of biological design. *Adv. Healthc. Mat.* **6** 1700496
21 Raman R, Cvetkovic C, Uzel S G, Platt R J, Sengupta P, Kamm R D, Bashir R 2016 Optogenetic skeletal
22 muscle-powered adaptive biological machines. *PNAS*, **113** 3497–502
23 Raman R, Cvetkovic C, Bashir R 2017 A modular approach to the design, fabrication, and
24 characterization of muscle-powered biological machines. *Nature protocols*, **12** 519–33
25 Regalado A 2018 US military wants to know what synthetic-biology weapons could look like. *MIT*
26 *Technology Review*, June 19 Accessed at:
27 [https://www.technologyreview.com/s/611508/us-military-wants-to-know-what-synthetic-biology-](https://www.technologyreview.com/s/611508/us-military-wants-to-know-what-synthetic-biology-weapons-could-look-like/)
28 [weapons-could-look-like/](https://www.technologyreview.com/s/611508/us-military-wants-to-know-what-synthetic-biology-weapons-could-look-like/)
29
30 Rivron N et al. 2018 Debate ethics of embryo models from stem cells. *Nature* **564** 183–5
31 Rollin B E 2006 The regulation of animal research and the emergence of animal ethics: A conceptual
32 history. *Theoret. Med. Bioethics* **27** 285–304
33 Rowe G, Frewer L J 2005 A typology of public engagement mechanisms. *Sci. Technol. Hum. Values* **30**
34 251-290
35
36 Rudenko L, Palmer M J, Oye K 2018 Considerations for the governance of gene drive organisms. *Pathog.*
37 *Glob. Health* **112** 162–81
38 Sachs N et al. 2018 A living biobank of breast cancer organoids captures disease heterogeneity. *Cell* **172**
39 373–386.e10
40 Sagan A, Singer P 2007 The moral status of stem cells. *Metaphilos.* **38** 264–84
41 Savulescu J and Bostrom N 2009 *Human Enhancement*. (Oxford: Oxford University Press)
42 Science for Environment Policy 2016 *Synthetic Biology and Biodiversity*. (Luxembourg: Produced for the
43 European Commission by the Science Communication Unit, UWE, Bristol)
44 Skloot R 2011 *The Immortal Life of Henrietta Lacks*. (New York: Broadway Books)
45 Smith J A, Boyd K M 1991 *Lives in the Balance: The Ethics of Using Animals in Biomedical Research:*
46 *The Report of a Working Party of the Institute of Medical Ethics*. (Oxford: Oxford University
47 Press)
48
49 Spence J R et al. 2011 Directed differentiation of human pluripotent stem cells into intestinal tissue in
50 vitro. *Nature* **470** 105–9
51 Stilgoe J, Owen R, Macnaghten P 2013 Developing a framework for responsible innovation. *Res. Policy*,
52 **42** 1568-1580
53
54 Stilgoe J 2019 Monitoring the evolution and benefits of responsible research and innovation: Policy brief.
55 European Commission. Accessed at:
56
57
58
59
60

- 1
2
3 <https://publications.europa.eu/en/publication-detail/-/publication/1f32df40-4479-11e9-a8ed-01aa75ed71a1>
4
5 Tamsir A, Tabor J J, Voigt C A 2011 Robust multicellular computing using genetically encoded NOR
6 gates and chemical ‘wires’. *Nature* **469** 212–5
7 The Belmont Report. 2010 Text. HHS.Gov. January 28, 2010. Accessed at:
8 <https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html>.
9 Thompson C 2007 *Making Parents: The Ontological Choreography of Reproductive Technologies*.
10 (Cambridge: MIT Press)
11 Torrance A W and Kahl L 2014 Bringing standards to life: synthetic biology standards and intellectual
12 property. SSRN PID 2426235. *Social Science Research Network*.
13 US EPA, OA 2014 Environmental justice. Collections and Lists. US EPA, November 3. Accessed at:
14 <https://www.epa.gov/environmentaljustice>.
15 US EPA, OITA 2014 Public participation guide: citizen juries. Overviews and factsheets. US EPA, March
16 20. Accessed at:
17 <https://www.epa.gov/international-cooperation/public-participation-guide-citizen-juries>.
18 Warnock M 1984 *Report of the Committee of Inquiry Into Human Fertilisation and Embryology*.
19 (London: Her Majesty’s Stationery Office)
20 Williams B J, Anand S V, Rajagopalan J, Saif M T 2014 A self-propelled biohybrid swimmer at low
21 Reynolds number. *Nature Commun.* **5** 3081
22 Webster V A, Hawley E L, Akkus O, Chiel H J, Quinn R D 2016 Effect of actuating cell source on
23 locomotion of organic living machines with electrocompact collagen skeleton. *Bioinspir.*
24 *Biomim.* **11** 036012
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
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