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Confronting risks of mirror life

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Broad discussion is needed to chart a path forward.

All known life is homochiral. DNA and RNA are made from "right-handed" nucleotides, and proteins are made from "left-handed" amino acids. Driven by curiosity and plausible applications, some researchers had begun work toward creating lifeforms composed entirely of mirror-image biological molecules. Such mirror organisms would constitute a radical departure from known life, and their creation warrants careful consideration. The capability to create mirror life is likely at least a decade away and would require large investments and major technical advances; we thus have an opportunity to consider and preempt risks before they are realized. Here, we draw on an in-depth analysis of current technical barriers, how they might be eroded by technological progress, and what we deem to be unprecedented and largely overlooked risks (*1*). We call for broader discussion among the global research community, policy-makers, research funders, industry, civil society, and the public to chart an appropriate path forward.

Others have noted some dangers from mirror life (*2*, *3*), but a thorough analysis of risks has not previously been completed. The need for such an analysis has grown with advances in key enabling technologies. To address this gap, a group with diverse expertise qualitatively assessed the feasibility and risks of creating mirror bacteria, considering factors including the nature, magnitude, and likelihood of potential harms; the ease of accidental or deliberate misuse; and the effectiveness of potential countermeasures. Our group includes expertise in synthetic biology; human, animal, and plant physiology and immunology; microbial ecology; evolutionary biology; planetary life detection; biosecurity; global health; and policy-making and includes researchers who have held the creation of mirror life as a long-term aspirational goal. The findings are summarized below and detailed in a separately released, in-depth technical report (a cross-referenced version of this article is provided in the supplementary materials) (*1*). We focus on mirror bacteria, but many of the considerations might also apply to other forms of mirror life.

Our analysis suggests that mirror bacteria would likely evade many immune mechanisms mediated by chiral molecules, potentially causing lethal infection in humans, animals, and plants. They are likely to evade predation from natural-chirality phage and many other predators, facilitating spread in the environment. We cannot rule out a scenario in which a mirror bacterium acts as an invasive species across many ecosystems, causing pervasive lethal infections in a substantial fraction of plant and animal species, including humans. Even a mirror bacterium with a narrower host range and the ability to invade only a limited set of ecosystems could still cause unprecedented and irreversible harm.

Although we were initially skeptical that mirror bacteria could pose major risks, we have become deeply concerned. We were uncertain about the feasibility of synthesizing mirror bacteria but have concluded that technological progress will likely make this possible. We were uncertain about the consequences of mirror bacterial infection in humans and animals, but a close examination of existing studies led us to conclude that infections could be severe. Unlike previous discussions of mirror life, we also realized that generalist heterotroph mirror bacteria might find a range of nutrients in animal hosts and the environment and thus would not be intrinsically biocontained.

We call for additional scrutiny of our findings and further research to improve understanding of these risks. However, in the absence of compelling evidence for reassurance, our view is that mirror bacteria and other mirror organisms should not be created. We believe that this can be ensured with minimal impact on beneficial research and call for broad engagement to determine a path forward.

Toward mirror life

Our analysis suggests that mirror bacteria could survive and spread in nature, yet we do not observe them today. Although mirror life could be just as functional as natural-chirality life, it cannot arise from existing life: Evolution proceeds in incremental steps and would be unable to invert

the chirality of complex biomolecules such as DNA or proteins, let alone all biomolecules simultaneously. It is also exceedingly unlikely that we will encounter mirror life that has arisen independently. However, with scientific advances, a mirror organism might be created in a laboratory.

Creating a mirror organism, even as simple as a bacterium, would be a far more complex feat of biological engineering than has ever been accomplished. Yet progress on key enabling technologies is underway. Scientists are increasingly able to synthesize complex mirror-image biomolecules (*4*, *5*); recent advances have enabled chemical synthesis of mirror-image kilobase-length nucleic acids and large functional proteins (*6*). Their reversed chirality makes these biomolecules resistant to normal forms of biological degradation, leading to emerging applications such as long-lasting and nonimmunogenic therapies (*1*, *4*, *5*).

In parallel, researchers are making rapid progress toward constructing synthetic cells (of natural chirality) from nonliving parts (*7*, *8*). Once a method is developed that enables construction of a natural-chirality bacterium entirely from synthetic DNA, synthetic proteins, and synthetic lipids, and once mirror versions of these components can also be synthesized, a living mirror bacterium could be constructed in the same way (*1*, *9*). Other pathways to constructing a mirror bacterium are also plausible; for example, with further advances in synthetic biology, a natural-chirality bacterium might be engineered to produce mirror proteins and nucleic acids in vivo, which could provide a starting point for stepwise conversion into a mirror bacterium (*1*).

Although plausible paths to the creation of mirror bacteria exist, numerous technical barriers remain to be overcome. The synthesis of mirror biomolecules is highly expensive, and complex structures such as ribosomes would be challenging to construct in their entirety. The development of a protocol for constructing a mirror bacterium from mirror components would require substantial breakthroughs in synthetic cell research. However, although timelines are necessarily uncertain, it is likely that barriers will be eroded as research progresses on related technologies, many of which are pursued for applications unrelated to mirror life (*1*).

In isolation, mirror bacteria would function identically to their natural-chirality counterparts if provided with achiral or mirror-image nutrients—and be as feeble or robust as the strain that served as their template. Genetic engineering could transform a slow-growing, specialized mirror bacterium into a mirror version of a fast-growing, generalist bacterial strain (*1*). Many bacteria, including *Escherichia coli*, can grow robustly in growth media without chiral nutrients (*10*); hence, mirror versions of those bacteria would do the same. Achiral nutrients are available in quantities sufficient for growth of common bacteria in a wide range of natural environments, including within potential hosts (*1*). Further genetic engineering could provide mirror bacteria with pathways needed to consume abundant chiral nutrients such as D-glucose.

Growth of mirror bacteria outside of the laboratory is therefore plausible. However, their interactions with other lifeforms would differ profoundly because of their reversed chirality.

Immune evasion, ecosystem invasion

Our analysis suggests that mirror bacteria could broadly evade many immune defenses of humans, animals, and plants. Chiral interactions, which are central to immune recognition and activation in multicellular organisms, would be impaired with mirror bacteria. This could result in weakened immune recognition, a weakened response by innate immune systems, and (in vertebrates) limited downstream activation of adaptive immune functions (*1*). For example, experiments show that mirror proteins resist cleavage into peptides for antigen presentation and do not reliably trigger important adaptive immune responses such as the production of antibodies (*11*, *12*). We are thus concerned that the function of many vertebrate immune systems against mirror bacteria would be severely impaired. Invertebrate and plant immune systems are less well studied but appear to suffer analogous limitations (*1*).

Given the potential for severe immune evasion, mirror bacteria might not require host-specific factors to invade hosts and cause infection. In animals (including humans), bacteria regularly cross barriers in the skin, mouth, gut, lungs, and other mucosal surfaces because of routine damage and intrinsic leakiness (*13*, *14*); mirror bacteria would be expected to do the same. In healthy animals, translocated natural-chirality bacteria are typically cleared by immune defenses. However, if the immune response against mirror bacteria is sufficiently impaired, translocated mirror bacteria might replicate within the host and establish an infection. Unchecked replication of mirror bacteria within internal tissues is likely to be deleterious to the host organism and may be lethal (*1*).

The precise extent of immunological dysfunction is necessarily uncertain. Several immunological defenses, such as the alternative complement pathway and some antimicrobial peptides, are less sensitive to chirality (*1*). Although it is hard to be confident about the implications, allelic disorders, such as myeloid differentiation primary response protein 88 (MyD88) or major histocompatibility complex (MHC) class II deficiencies, show that even partial impairment of either innate or adaptive immunity can leave patients vulnerable to bacterial infection. Similar evidence is seen in a wide variety of animal and plant immune systems (*1*). Overall, we are concerned that mirror bacteria might act as serious pathogens with an unusually broad host range.

Mirror bacteria could also pose ecological risks more broadly. By virtue of their reversed chirality, mirror bacteria may evade many forms of predation and microbial interference. They would be intrinsically resistant to infection by natural-chirality bacteriophages, may be resistant to consumption by many predators, and may be resistant to most antibiotics produced by microbial competitors. This resistance could allow mirror bacteria to be unusually persistent outside of multicellular hosts, facilitating transmission. Reduced mortality from predation could provide a fitness advantage that might allow colonization of some external environments, despite potential disadvantages such as reduced ability to acquire chiral nutrients (*1*). Transport by multicellular hosts could disperse mirror bacteria across many environments. Much like an invasive species with few natural predators, we are concerned that mirror bacteria could rapidly proliferate, evolving and diversifying as they spread. Persistent and potentially global presence of mirror bacteria in the environment could repeatedly expose human, animal, and plant populations to the risk of lethal infection.

Biosafety and biosecurity

Biocontainment and biosafety approaches might be proposed to reduce these risks. Scientists could intentionally hobble mirror bacteria by engineering dependence on molecules not present in nature (synthetic auxotrophy), safeguards intended to prevent growth outside controlled laboratory environments. However, escape from these safeguards through evolution or human error could occur. Multiple auxotrophies would reduce but not eliminate the chance of escape. Physical containment approaches could be used, but laboratory accidents happen with some regularity, even in high-containment laboratories, because of human error and equipment failure (*15*).

Even if a mirror bacterium unable to grow outside controlled laboratory environments could be created, it would not be secure—that is, permanently controlled in a way that would prevent large-scale harm through negligence or intentional misuse. Once a biocontained mirror bacterium has been created, it would be comparatively straightforward to engineer it to be free of safeguards (*1*). Methods for construction of mirror bacteria could also be replicated by others in pursuit of various (perhaps safeguard-free) mirror bacteria.

Countermeasures such as mirror antibiotics, crops engineered to be resistant to mirror bacteria, and mirror phages appear very unlikely to be sufficient to stop or reverse the spread of mirror bacteria throughout global ecosystems or to prevent unacceptable loss of life and irreversible ecological changes that could result. The primary challenge with these countermeasures is our inability to deploy them throughout the ecosphere at sufficient scale to prevent or counter dissemination and evolutionary diversification of mirror bacteria in the wild. They could therefore only protect against a fraction of the potentially immense harm.

Foreseeable benefits of the creation of mirror bacteria are limited. Mirror biomolecules have scientific and potential therapeutic applications that are worth pursuing; however, although mirror bacteria could plausibly help to manufacture them, such molecules can be made through other means. More speculatively, mirror bacteria might be pursued as a chassis for live cell therapeutics, but again, alternative pathways are available. The potential risks of creating mirror bacteria cannot be justified by the relatively limited potential benefits.

A path forward

We encourage relevant expert communities to critically engage with the analysis summarized here and detailed in the accompanying technical report (*1*), and we welcome arguments and evidence about mirror life that we have not yet considered. In light of our initial findings, we believe that it is important to begin a conversation on how the risks can be mitigated, and we call for collaboration among scientists, governments, funders, and other stakeholders to consider an appropriate path forward. Below, we offer recommendations as a starting point for further discussion.

Unless compelling evidence emerges that mirror life would not pose extraordinary dangers, we believe that mirror bacteria and other mirror organisms, even those with engineered biocontainment measures, should not be created. We therefore recommend that research with the goal of creating mirror bacteria not be permitted, and that funders make clear that they will not support such work. Governance of a subset of enabling technologies should also be considered to ensure that anyone attempting to create mirror bacteria will continue to be hindered by multiple scientifically challenging, expensive, and time-consuming steps.

We recommend that initially, steps be taken to prevent the production of mirror genomes and proteomes, or functional equivalents sufficient to enable the construction of a mirror cell. We recommend research to determine which, if any, other enabling technologies warrant oversight. Systems for monitoring the purchase of mirror oligonucleotides and precursors, and regulations and laws to prevent the creation of mirror life, should also be considered. As science progresses and opens additional pathways to the creation of mirror life, measures should be regularly reviewed. Further discussion and analysis should carefully consider the institutions and mechanisms that would be best suited to determine the form and implementation of such measures. The unprecedented scope and scale of the risk from mirror bacteria may challenge the applicability of existing national and international systems.

Many related technologies, such as the chemical synthesis of mirror-image nucleic acids and proteins—not aimed at the creation of a mirror bacterium—have scientific and potential therapeutic applications. Diverse mirror proteins and RNAs could be made for research applications such as aptamers, biocatalysis, and phage display, and D-amino acids could be incorporated into synthetic peptide or protein drugs. We do not recommend any new restrictions on such research. Similarly, much synthetic cell research does not directly enable the creation of a mirror bacterium, is of great value to basic science, and should continue.

We also recommend research to better understand and prepare for risks from mirror bacteria, as long as neither mirror bacteria nor any key enabling precursors are produced. Such research might include studying the interaction of mirror biomolecules with the immune system as well as developing detection methods and biosurveillance systems. Although countermeasures could not prevent widespread harm, they might offer some limited or localized protection. It is essential that any research on countermeasures takes place in an open, international setting to engender trust. None of these research directions would require mirror bacteria to be built.

We believe that there is a productive path ahead in which a range of stakeholders collaboratively consider the risks from mirror life and develop appropriate governance without unnecessarily impeding scientific research. Drawing inspiration from the Tianjin Biosecurity Guidelines and other relevant frameworks, we invite the global research community, policy-makers, research funders, industry, civil society, and the public to join this discussion. To facilitate greater understanding of the risks associated with mirror life and further progress on governance, we plan to convene discussions on these topics in 2025. We are hopeful that scientists and society at large will take a responsible approach to managing a technology that might pose unprecedented risks.

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SUPPLEMENTARY MATERIALS

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