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Synthetic biology in Indonesia: Potential and projection in a country with mega biodiversity

Immanuel Sanka [a,b,*], Ali Budhi Kusuma [a,c], Faustina Martha [a,d], Andre Hendrawan [a], Ihsan Tria Pramanda [a,e], Adhityo Wicaksono [a,f], Afif Pranaya Jati [a,g], Maulida Mazaya [h], Ari Dwijayanti [a], Nurul Izzati [a,c], Muhammad Farhan Maulana [a], Aulia Reski Widyaningrum [a]

[a] *Synthetic Biology Indonesia (Synbio.id), Jl. Raya Lintas Sumbawa-Bima, Block AA No. 1, Boak Village, Subdistrict Unter Iwes, 84316, Sumbawa, Indonesia*
[b] *Department of Chemistry and Biotechnology, Tallinn University of Technology, Akadeemia tee 15, 12618, Tallinn, Estonia*
[c] *Indonesian Centre for Extremophile Bioresources and Biotechnology (ICEBB), Faculty of Life Sciences and Technology, Sumbawa University of Technology, Jl. Raya Olat Maras Sumbawa, 84371, Indonesia*
[d] *Science Communication Steering Committee, iGEM Foundation, 45 Prospect St, Cambridge, MA, 02139, United States*
[e] *Department of Bio Technology, Indonesia International Institute for Life Sciences (i3L), Jl. Pulomas Barat Kav. 88, Pulomas, Jakarta, 13210, Indonesia*
[f] *Division of Biotechnology, Genbinesia Foundation, Jalan Swadaya Barat no. 4, Gresik, 61171, Indonesia*
[g] *Infection Program, Monash Biomedicine Discovery Institute and Department of Microbiology, Monash University, Melbourne, Victoria, Australia*
[h] *Research Center for Computing, Research Organization for Electronics and Informatics, National Research and Innovation Agency (BRIN), Cibinong Science Center, Jl. Raya Jakarta-Bogor KM 46, Cibinong, 16911, West Java, Indonesia*

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ABSTRACT

Synthetic biology has gained many interest around the globe in the last two decades, not only due to its rapid development but also the potential to provide addressable solutions using standardized design of biological systems. Considering its huge population, biodiversity, and natural resources, Indonesia could play an important role in shaping the future of synthetic biology towards a sustainable bio-circular economy. Here, we provide an overview of synthetic biology development in Indonesia, especially on exploring the potential of our biodiversity. We also discuss some potentials of synthetic biology in solving national issues. Furthermore, we also provide the projection and future landscape of synthetic biology development in Indonesia. In addition, we briefly explain the potential challenges that may arise during the development.

1. Introduction

Synthetic biology is an emerging field of biotechnology that allows biologists and engineers to create de novo designs or modifications to biological systems to perform novel tasks and provide applicable solutions.[1,2] The motivation of this growing field is to provide standardized DNA assembly techniques and allow researchers to focus on the research topic or its development.[3] The current applications of synthetic biology encompass cellular products (e.g., soy leghemoglobin, Januvia diabetic drug, etc.) and the cell itself as a product (e.g., PROVEN biological nitrogen fertilizer for corn from Pivot Bio, high-oleic oil from Calyxt, etc.).[4] Moreover, synthetic biology has been used to provide solutions in biomedical research, pathogen modification, bioproduct optimization, environmental monitoring, and bioremediation.[5] However, the information related to synthetic biology in developing countries such as Indonesia is still limited.

Indonesia is known for its mega biodiversity,[6] which includes plant, animal, and microorganism. For instances, there are 96 species of plants in West Timor that are used to treat malaria, including *Acorus calamus* L, *Drynaria quercifolia* (L.) J. Smith., *Alstonia scholaris* (L.) R.Br.a, *Cleome rutidosperma* DC., and etc.[7] There are 283 plant species that have been officially regulated and can be used as herbal medicine in Indonesia.[8] Not only from the plants, there are some fermented foods that are processed using local bacteria as well, such as mustard cabbage, soybeans, cassava, and the flesh of durian.[9] In a recent genome mining study, 422 actinomycetes strains were isolated from three different regions in Indonesia, and nine of them indicated potential for producing bioactive compounds.[10] A study of 205 bacterial isolates from sponges and corals

* Corresponding author. Synthetic Biology Indonesia (Synbio.id), Jl. Raya Lintas Sumbawa-Bima, Block AA No. 1, Boak Village, Subdistrict Unter Iwes, 84316, Sumbawa, Indonesia.
E-mail address: immanuel.sanka@taltech.ee (I. Sanka).

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in Indonesia also found 12 isolates that showed the ability to produce antibacterial compounds.[11] Despite these opportunities, the exploration and application of novel DNA sequences or proteins to advance synthetic biology in Indonesia has yet to be thoroughly discussed.

On the other hand, synthetic biology has made remarkable advancements,[12] from utilizing DNA for data storage up to completing a full synthesis of *E.coli* genome.[13,14] There are some reports regarding synthetic biology development in different countries and regions, including in Europe,[15] United Kingdom,[16] Netherlands,[17] Germany,[18] Slovakia,[19] and Czech Republic.[20] Although there are some articles regarding synthetic biology development in developing countries, e.g., Argentina,[21] Africa,[22] and Asia,[23] the discussion of exploring national potential such as Indonesia's mega biodiversity has not been reported.

In this article, we discuss i) the development of synthetic biology in Indonesia, ii) the potential of synthetic biology research on biodiversity, iii) the projection and potential roles of Indonesian stakeholders for synthetic biology advancement in Indonesia, and iv) the challenges of using synthetic biology to maximize the biodiversity in a country with mega biodiversity like Indonesia.

2. From research and competition to community

Synthetic biology was first introduced in an international forum as a competition in 2004 in the United States of America, known as the International Genetically Engineered Machine (iGEM) competition.[24] There were only 5 teams when the first iGEM was held and as of 2022, the competition has grown immensely and 356 teams joined from over 70 countries.[25] Along with the competition, synthetic biology enthusiasts in the region also organized the first international meeting (SB1.0) at Massachusetts Institute of Technology (MIT).[26] The following years, in the private sector, some companies were founded, such as Ginkgo Bioworks which was originated from a research group in MIT which also involved in iGEM team, and Synbiobeta which constantly provide a space for synthetic biology enthusiasts to meet and connect.[27,28]

In Indonesia, synthetic biology research was primarily initiated by academic research groups which work closely with genetic engineering and biotechnology (Fig. 1). Students from these groups formed teams and participated in iGEM. The first Indonesian team which participated in iGEM was BAU-Indonesia from the Bogor Agricultural University (IPB). The team participated in 2012 with the focus on finding solutions for effective plastic degradation.[29] The team used cutinase genes (parts BBa_K923001 and BBa_K923002) isolated from *Thermobifida fusca* and delivered the degradation module in pSB1C3. In the following years, more iGEM teams are coming from Indonesia, e.g., from Bandung Institute of Technology (ITB_Indonesia),[30–34]Technology University of Sumbawa (Sumbawagen),[35,36] University of Indonesia,[37–43] Brawijaya University (UB_Indonesia),[44–46] Sriwijaya University (Sriwijaya),[47] and Gadjah Mada University (UGM_Indonesia).[48] The projects were ranging from designing enzymes (e.g., polyethylene-degrading enzyme, esterase enzyme, etc.), detecting compounds (e.g., diphteria toxin, glucose concentration in honey, etc.), and diagnostic tools (e.g., tumor seromarker, Tuberculosis, Human Papillomavirus – HPV, dengue, etc.). Recently, one Indonesian university (Universitas Sanata Dharma) also teamed up with iGEM team Sogang_Korea 2022 to participate in the competition.[49] Each team brought different topics where it relies on the iGEM tracks, but not limited to solving the local or/and national problems, including to preserve biodiversity (Supp. Table 1). In addition, a number of Indonesian students who have finished their study abroad also came back and built national communities to promote synthetic biology, e.g., Synbio.id, and initiated various activities that involves journal clubs, seminars, and competitions.[50] In some other cases, synthetic biology enthusiasts initiated independent community and participated in different events, such as the Synbiobeta Activate in Singapore (2014) and Synbio for Indonesia gathering which was held in 2014 in Malang, West Java - Indonesia.[51] Over the years, conference forums such as Synbio.id Initiative events (e.g., Bioinformatics and Synthetic Biology Competition - BIOS, SynbioTalks, SynbioVirtualSummit, Synbiotechfest, etc.) and Synthetic Biology and Biotechnology Conference have supported the growth of synthetic biology in Indonesia.[50,52] Recently, there are some organizations which also start providing courses for synthetic biology enthusiasts, e.g., Bioinformatics Institute of Indonesia (INBIO-Indonesia)[53] and Generasi Biologi Indonesia (Genbinesia).[54] Moreover, there are some governments and higher education institution initiatives which could accommodate synthetic biology enthusiasts to perform research, such as Indonesian Culture Collection (inaCC), Indonesian Natural Product Library (INPL) and Biomedical and Genome Science Initiative (BGSi) in 2014, 2021 and 2022, respectively.[55–57] There are newly introduced facilities called techno parks (named STPs) which will be discussed on later section.

Synthetic biology implements the principle of design, build, test, and

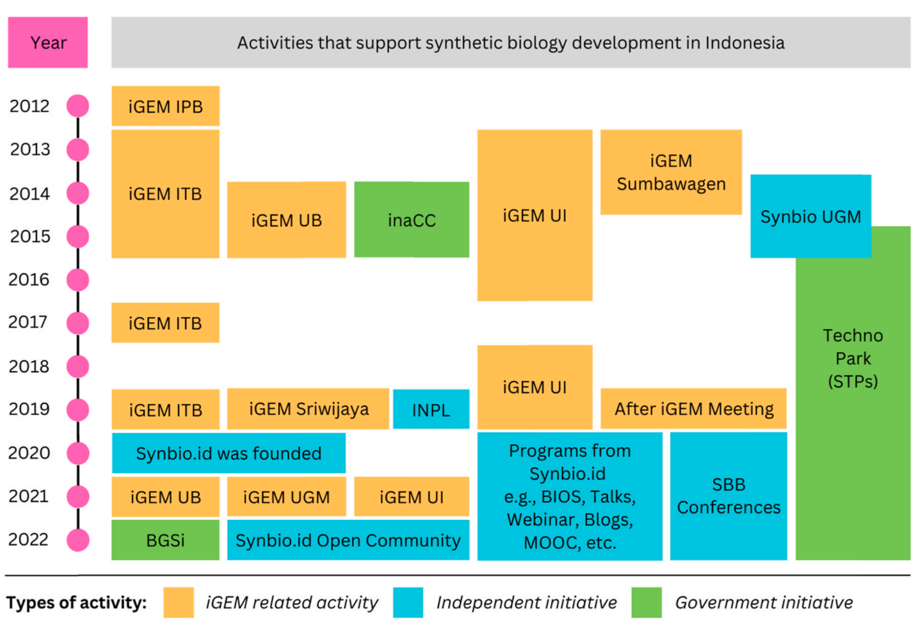

Fig. 1. Initiatives from synthetic biology enthusiasts in Indonesia over the years. In brief, there are three initiatives which came from research groups (iGEM teams), student/open community (independent initiative) and government institutions/ministries (government initiative).

learn (DBTL) to re-engineer or produce desired genetic circuits or pathways.[58,59] These four pillars guide the researchers and practitioners to tweak biological systems and turn them into beneficial products. Apart from the projects that have been mentioned in the previous section, competitions which are held by Synbio.id have empowered Indonesian students to adopt the same principle through bioinformatics and synthetic biology competition (BIOS) (Fig. 2A). In this competition, teams of students were required to develop ideas by using bioinformatics and/or synthetic biology approaches to address local issues in Indonesia. The results of the most recent competition held in 2022 are available on jogl.io – an open platform for community science and innovation.[60] Using these results, the word analysis and counts are visualized to show the participants' interests (Fig. 2B and 2C). The topics which were discussed in the competition ranged from energy to health. Both groups discussed Indonesia since the theme of the competition was "bringing collaborative action using local wisdom in Indonesia''. Even though the participants mainly performed in silico research, the initiative was meant to push more synthetic biology educative space for students in Indonesian universities.

3. Research between synthetic biology and biodiversity are growing in Indonesia

Synthetic biology has shown various applications in different subjects, including in preserving biodiversity.[61] In Indonesia, research in biodiversity is closely related to bioprospecting. For instance, in microbial resources, the bioprospecting campaign in Indonesia has now been determined to explore pristine extreme habitats, notably in the search of novel extremophilic microbes for industrial biotechnology purposes. Some novel extremophilic actinomycetota species were discovered from Indonesian extremobiosphere, for example *Streptomyces harenosi*,[62] *Streptomyces sabulosicollis*,[63] and *Actinospica acidithermotolerans*.[64] These species possess a large genome size (>8 Mb) which contain various biosynthetic gene clusters known to be associated with its capacity to produce various antibiotics and some other valuable secondary metabolites. While many of these gene clusters are silent or cryptic under laboratory conditions, they can potentially be isolated and expressed under specific promoters in other organisms to produce enzymes involved in the biosynthesis of desired metabolites. This would allow for the production of valuable chemicals that would be beneficial for society.

Indonesian researchers also attempted to use synthetic biology to address waste issues in the palm oil industry. In 2015, a research team at Surya University received foreign funding to investigate the use of waste materials from palm oil production to produce valuable chemicals using *Pseudomonas putida*.[65] Initially, the team focused on inserting additional genes into *P. putida* to transform γ-valerolactone, a chemical compound derived from lignocellulose waste found in empty fruit bunches, into pentanol. However, the gene expression tools they had, which were developed for *E. coli*, did not work as intended with *P. putida*. As a result, the focus of the research shifted to developing a set of genetic tools that would allow better genetic manipulation and gene expression in *P. putida*. This included by replacing the promoter driving lacI expression on the vector with weaker promoters, creating a BBR1-B5 origin of replication, and developing a λ Red/Cas9 recombineering method for genome editing in *P. putida*.[66] This case illustrates that real-world problems can serve as a starting point for the development of synthetic biology tools.

Although the use of synthetic biology in Indonesia is still limited, there are some examples where synthetic biology can be used to preserve Indonesian biodiversity. For instance, the production of synthetic peptide DRGN-1 originated from Komodo Dragon (*Varanus komodoensis*) which was predicted to have potent antimicrobial and anti-biofilm activity. This discovery would help to prevent the exploitation of Komodo dragons, which could otherwise contribute to their extinction.[67] Another example is from Rafflesia, there is one species *Rhizanthes lowii* (local name: *ulur-ulur*; Rafflesiaceae) which has been actively sold as a local medicine, and this has happened in Malaysia as well.[68] There are at least 21 metabolites that have been identified across Rafflesiaceae family and some of them are predictably potent as medicines under both in vitro and in silico studies.[69–72] Even though the plants have such secondary metabolites which could be used for potential medicine, uncontrolled harvest with no possibility of cultivating the plant may also lead to the extinction. This also happens to marine invertebrates, including corals and sponges. Izzati et al.[73] reported that 105 novel compounds have been found in marine invertebrates from Indonesia since 2017. These compounds have been used in medical research (e.g., antimicrobial, antiviral, anti-inflammatory, etc.). Though the organisms hold such potential, sponge and corals can only grow 0–2.2 cm annually.[74] Notwithstanding, producing those kinds of compounds through a synthetic biology approach would eliminate the actual sample retrieval from nature and support biodiversity preservation. In addition, Indonesia is also known for its unique coffee beans that are derived from feces of civet cat (*Paradoxurus hermaphroditus*), known as one of the most expensive coffees in the world, named as *kopi luwak*.[75] The production of *kopi luwak* requires wild civet cats to eat the beans and the process will

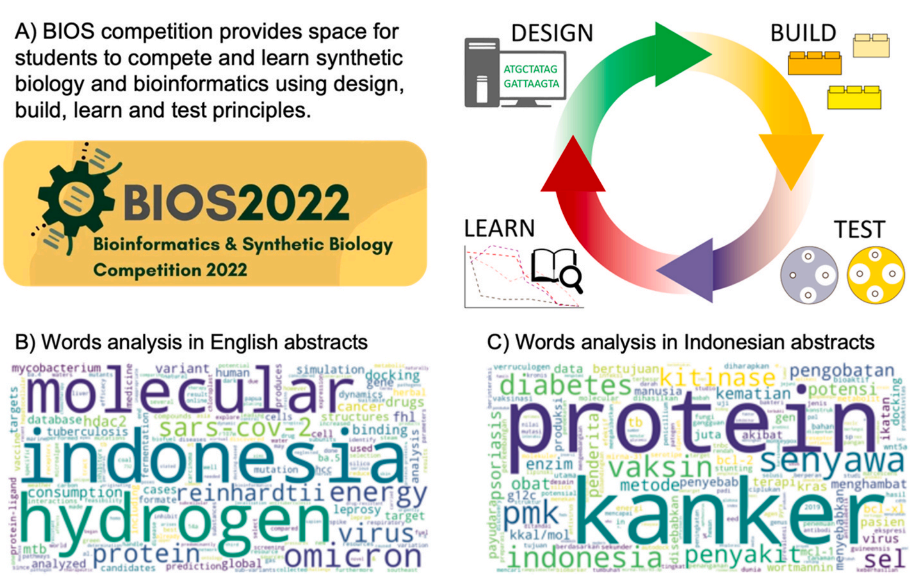

Fig. 2. Synthetic biology enables more opportunities to explore Indonesia and solve local problems in different angles. A) Activity such as BIOS competition can accommodate synthetic biology enthusiasts to design, build, learn and test their research. B) Using the abstract written in English, there are some topics related to COVID (omicron, sars-cov-2, etc.), energy (hydrogen), etc. C) In Bahasa Indonesia, the topics "kanker" (cancer), "penyakit" (disease), "vaksin" (vaccine), "senyawa" (compound), protein, diabetes are discussed more in the projects.

follow through naturally until the collection of feces. The beans will be collected as partially digested beans which are then cleaned, dried and roasted to be commercialized worldwide.[76] Some researchers have identified the microbiome which contribute to the civet cat's gastrointestinal digestions.[77,78] With synthetic biology, there is an opportunity to construct a microbiome which could digest coffee beans without exploiting the wild civet cats. Even though the mentioned examples are only the study case, these may help to provide prospectus examples in conserving and preserving biodiversity in Indonesia.

From some Indonesian iGEM teams, there are some examples where the teams tried to protect the local environment which may affect the biodiversity. A case from iGEM UGM, they had concern regarding toxic residues of cyanide from artisanal and small-scale gold mining (ASGM) which would present during the gold extraction process. By utilizing *Chromobacterium violaceum*, they were able to design prospectus model for both producing and degrading cyanide in gold extraction process.[48] They implemented the design, build, test and learn (DBTL) cycle to maintain the regulation of HCN synthase (cyanide degradation enzyme)[79] through activation process which can be triggered by the presence of glucose and arabinose. From different university, iGEM team ITB in 2014 and 2017 tried to design *E. coli* which were able to degrade Polyethylene terephthalate (PET) plastic.[31,33] The idea came from the concern of long degradation time of plastic which have already polluted the environment, including in Indonesia. Both teams created modules to optimize plastic degradation by constructing modular systems of PET degradation enzymes and speeding up the bacteria-plastic interaction through biofilm production. Even though these examples did not intersect to the biodiversity directly, the mentioned teams were able to deliver prospectus solutions which have disrupted the environment and potentially harm the biodiversity.

4. Projection and outlook of Indonesian synthetic biology landscape

Synthetic biology is still considered a relatively new field compared to well-established concepts such as biotechnology, molecular biology, bioinformatics, etc. Combining engineering principles into biology demands more stakeholders to get onboard, not only from the research institution but also from various available stakeholders. In Fig. 3, each stakeholder that potentially suits the role in promoting synthetic biology in Indonesia is discussed. Using the activity system proposed by Engerström (1987)[80] which was discussed in Alexander and Hjortsø (2019),[81] the potential stakeholders can be organized and connected to make a rigid system for synthetic biology development. Adding start-up as a new variable to support the subjects could bring a robust environment in Indonesia. From Fig. 3, tools (conferences, lecturers, etc.) could be used to mediate the subjects (students, lecturers, etc.) to produce objects (publications, thesis, etc.). In brief, the communities (Synbio.id, MABBI, etc.) can act as catalysts to support the rules (research agency, related ministries, etc.) and each division of labor (between stakeholder) to strengthen the synthetic biology development in Indonesia. For instance, MABBI[82] (biodiversity and bioinformatics organization) and Genbinesia[54] (a foundation focused on education and empowerment in biology) have expanded their base community to discuss synthetic biology. Moreover, having short term and long-term goals using this abstraction enables synthetic biology enthusiasts in Indonesia to map the gap and potential which need to be fulfilled and explored, respectively. For example, having more platforms in local language as a short goal will eliminate the language barrier and ease the dissemination of synthetic biology principle and concept. Since Bahasa/Indonesian language is used nationwide, the use of local language will not only help education practitioners (e.g., lecturers, docent, etc.) to share the knowledge easier but also to provide inspiration to other synthetic biology initiatives globally for using their languages in introducing synthetic biology in their region.

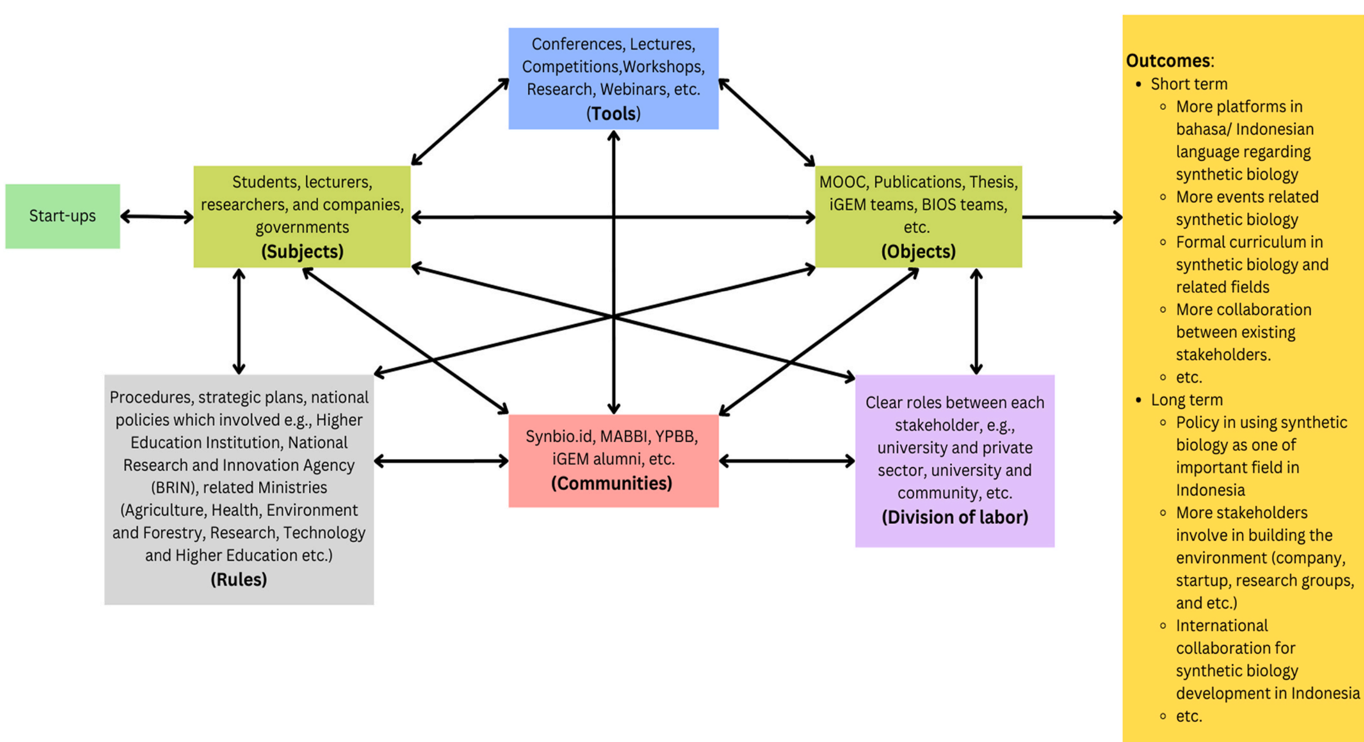

Fig. 3. Indonesia has potential stakeholders to boost synthetic biology and enhance its potential to explore biodiversity and provide solutions for local problems. This scheme requires different subjects, tools, community, rules, roles, and newly introduced industries like start-ups to work together. Using this scheme, the short term and long-term goals/outcomes could be determined.

In the light of accelerating the national capacity in translating STEM's research and increasing the number of technological-based-start up in Indonesia, the Indonesian government has launched a program to build 100 science and techno parks (called STP) that are located in several provinces around the country since 2015. Each STP develops and incubates a specific research focus that aligns with the development strategic plan of the assigned province. Some of the STP were designed to support the development of life sciences-based business in sustainable utilization of natural resources, as exemplified by Sumbawa Technopark and Diponegoro University Technopark that are flagging biotechnology and marine sciences as their core themes, respectively. The STP is later known as the Science and Technology Area (to be called Kawasan Sains dan Teknologi) which is declared in presidential regulation no. 106 in 2017 (Perpres No. 106, 2017).[83]

As a cutting-edge research tool, synthetic biology plays a vital role in supporting at least 6 out of 9 research fields as mapped out in National Research Plan 2017–2045 (named as Rencana Induk Riset Nasional 2017–2045) (Perpres No. 38, 2018)[84] and its subsequent derivate, National Research Priority 2020–2024 (named as Prioritas Riset Nasional 2020–2024,[85] which covers the field of food, energy, health, engineering, maritime and multidisciplinary (Permenristekdikti No.38, 2019). In the recent agenda, the National Research and Innovation Agency (BRIN) of Republic of Indonesia just launched four new STPs (Keputusan Kepala BRIN No. 313/I/HK/2022) that are focusing on integrated research center for biology, food, health, and the environment, center for radiopharmaceutical products and irradiation-based medical therapy, center for rocket and satellite, center for communication and information technology, especially for Big data and Artificial Intelligence.[86] Additionally, Indonesia is preparing a national repository for genome (RNA/DNA) sequencing database and discovery analysis.

Thus, the Pentahelix collaboration of government institutions, universities, industries, social entrepreneurs, and civil society is important to spread the spirit of research in this field as synthetic biology is not well recognized in Indonesia. The Ministry of Health of Indonesia took a significant step forward in 2022 by launching the Biomedical and Genome Science Initiative (BGSi) in collaboration with BRIN. This initiative has opened up new possibilities for synthetic biology enthusiasts in the country by offering a range of services such as sequencing facilities and repositories like biobanks and registries.[57] Although the focus of BGSi is on the health sector, these resources can be utilized by researchers and students, providing a strong foundation for the advancement of synthetic biology in Indonesia.

5. Challenges on biodiversity applications

The gap between high potential biodiversity[87,88] and its utilization[6,89] in Indonesia has widened due to a number of variables. This includes the high cost of conservation[90] and the access of genetic information of the biodiversity, especially in terms of nucleotide sequences.[91,92] Indeed, nucleotide sequences are the fundamental components to understand genetic function and evolution which can be used to explore the untapped potential of biodiversity.[93,94] To briefly explain the gap, there are several points which can be described here. First, there is neither public nor private database storage available locally. This makes some researchers can only publish their results in well-established repositories, such as .[111–113] Since the submission processes do not provide local language (or in Bahasa), not all researchers from Indonesia are able to put their work in the repositories. Second, most of the research regarding nucleotides and biodiversity tend to be sporadic, where each institution has its own data standard. Therefore, standardization in a national level is required to support the data sharing system. Third, the government supports the research and development in Indonesia by providing different facilities, including Sanger Sequencing, Illumina, ONT-Nanopore, CryoEM, etc. Yet, the promotion to Indonesian researchers, academicians, and other users are still limited. As a result, some researchers prefer to use commercial services which have already known in the market compared to those offered by the government. Thus, more promotion and user-friendly access to the facilities could improve their visibility and use, respectively. In addition, the knowledge gap regarding bioinformatics analysis, synthetic biology, DBTL principles and related fields need more supports from different stakeholders in Indonesia. These all challenges would be important to advance synthetic biology in Indonesia. Moreover, DNA sequencing is essential to the development of synthetic biology in many ways.[95] For example, to understand the diseases mechanism and treatment,[96] drug discovery and production,[97,98] vaccine development,[99,100] and medical diagnosis[101] towards personalized and precision medicine.[102,103] In order to bridge the gap, research collaboration and thorough studies are essential to prevent identical results that overlap each other.[104] Thus, the government through BRIN is taking consideration in developing national nucleotide repository database and employing the National Scientific Repository (RIN - https://rin.brin.go.id/). This will provide a strong and tidy database that can be shared for joint and ongoing research, including for synthetic biology development in Indonesia. In the private sector, unfortunately, there is still no startup which focuses on synthetic biology in Indonesia. However, there are biotechnology companies which may support synthetic biology enthusiasts to perform their research, e.g., Formulatrix Indonesia,[105] Nusantics (Nusantara Genetics),[106] and PT GeneCraft Labs.[107] These companies/ startups provide the automation of lab equipment, microbiome analysis, and distribute reagents and consumables in Indonesia, respectively. In addition to these, there are also some state-owned enterprises such as Biopharma which now is the main vaccine producer from Indonesia.[108]

Furthermore, partnerships between public and private sectors are critical to the field's long-term development. Long-term government funding is critical in supporting early-stage research on "grand challenges" where the risk is too high for industry to accept. However, in addition to long-term investments in basic science, an effective mechanism to catalyze technology translation and commercialization is required, which is often best accomplished through private-public partnerships. Gauvreau et al. discussed a "Key Innovation Technologies and Systems (KITS)" model as an ecosystem to propel research and technology deployment, in which an integrated operation of research, industry, entrepreneurship, and investment works to ensure the ecosystem's sustainability.[23] Additionally, national decision-makers may be required to consider a variety of factors when assessing risk, including socioeconomic concerns as well as impacts on indigenous and local communities. Informed consent or approval, as well as the participation of potentially affected indigenous peoples and local communities, should be required before releasing engineered gene or synthetic organism(s) into the environment. Legislation may include provisions for monitoring regulated activities, with regulations being revised on a regular basis to keep up with technological advances.[109] However, a public institute's research projects will be guided by key industry and societal needs in a close working relationship, and an effective two-way consultation ensures that the products and processes being developed can be turned into viable business models.[23]

6. Conclusion

Synthetic biology provides potential benefits to conserve biodiversity, especially in Indonesia. By identifying local problems, some researchers and students have delivered examples and applicable solutions using synthetic biology approaches. Moreover, the local problems could eventually lead us to unprecedented ideas of basic research related to synthetic biology. In order to boost the enthusiasm, Indonesian students, researchers, and some organizations have conducted and initiated various events, including workshops, webinars, conferences, and competitions. Moreover, a considerable number of communities, universities, and other stakeholders including the government have started to support the environment of synthetic biology in Indonesia. Providing a clear role and collaboration between stakeholders could pave a clear direction for synthetic biology development in the near future.

Credit author statement

IS led the project, conceived the research, conducted article review, and data analysis. ABK and MM were responsible to provide government's regulation, notably those related to the life sciences and synthetic biology research. AH provided the case of metabolic engineering research in Indonesia and proofread the article. APJ contributed in adding information related to natural products in Indonesia. FPA conceived the study of latest synthetic biology initiatives both within iGEM community and in Indonesia. AW conceived the review idea and supervised on the initial outline. NI was responsible in enriching the manuscript with iGEM competition and community initiatives in Indonesia. ITP provided critical review on manuscript, prepared iGEM teams information table and discussions. MFM and ARW also contributed in proof-reading and discussions of the article. All author were involved in the writing process and project.

Declaration of competing interest

All authors declare that they have no conflicting interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.biotno.2023.02.002.

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