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Biomanufacturing & Engineering for the Appalachian Highlands: Updates on the Development of a Scalable Bioengineering Program in Rural Settings

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Biomanufacturing & Engineering for the Appalachian Highlands - Updates on the development of a scalable bioengineering program in rural settings - Work-in-Progress

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Recently, there has been a national push to improve the competitiveness of the U.S. in the bioengineering, biomanufacturing, and biotechnology sectors, as demonstrated by the Executive Order to Advance Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe and Secure American Bioeconomy. To date, much of the country's biotech infrastructure has been concentrated near coastal areas — even though rural agricultural production could provide suitable feedstocks for bioproduction. In this work, we present updates on our current project titled "Completing the Bioindustrial Pipeline: A Multidisciplinary Workforce Development Institute for Biological and Bioprocess Engineering for the Appalachian Highlands." This work seeks to establish a regional center for innovation and education in several biotechnology sectors. We will present the current status of the project and the pitfalls that we have encountered and discuss ways in which this program can be adapted and scaled to other areas. In particular, we will highlight our organism-agnostic approach and those aspects that we consider essential to the success of the project.

Introduction

Growing and securing the national bioeconomy has recently become a federal policy priority. Instigated by supply chain shortages, industrial needs, and executive action, funding agencies as diverse as the Department of Defense to the National Science Foundation are incentivizing the development of research, industry, and training across the country [1, 2, 3]. In this work, we present an initial work-in-progress report and solicit feedback on our efforts at East Tennessee State University (ETSU) to develop a responsive program in bioengineering and biomanufacturing within the Appalachian Highlands region of south-central Appalachia. Our work so far has been motivated by a confluence of timing, opportunity, and a desire to move beyond the past socioeconomic factors that have weighed on this region. To that end, this project has elements affecting regional secondary education, workforce training, post-secondary education, and research and development. The major component of our current work involves the development of a series of industry-motivated training modules in biomanufacturing skills, which will be implemented to increase the skilled workforce in our area and serve as a launchpad for further educational modules within the nascent biological engineering degree at ETSU.

Background

Regional Characteristics

Traditionally, the central and southern Appalachian provinces of the United States are not at the forefront of thought when discussing advanced research, synthetic biology, or the bio-based future of manufacturing; other stereotypes and other realities prevail [4, 5, 6]. Instead, like many other high-tech industries, biomanufacturing and bioengineering find themselves located mostly in major metropolitan areas along the U.S. Coasts [7, 8, 9]. Some metropolitan areas centered around national universities, such as Raleigh-Durham, have managed to buck this trend, but for smaller, more rural areas, such as those served by regional universities and community colleges, penetration of the bioeconomy is a much more gradual process. One of the strategies outlined by the recent executive order and supporting documents is to broaden participation in the bioeconomy, connect manufacturing with U.S. agricultural feedstocks, and bring the bioeconomy into underserved regions and communities [2, 3, 10]. In fact, a report from the Congressional Research Service outlines the specific need for investment in smaller regional economies, noting that "the implementation of many aspects of the bioeconomy will occur on a regional scale and involve rural communities [11]." Shapira et al. suggest that a revitalized and *reimagined* bioeconomy will "empower communities to tailor new approaches to their particular situations, creating a break with industrial patterns and practices of the past [10]."

East Tennessee State University, located in Johnson City, TN, sits in the heart of South Central Appalachia in a region that is colloquially known as the *Appalachian Highlands* [12]. This area encompasses Northeast Tennessee and Southwest Virginia, with near neighbors of Eastern Kentucky and Western North Carolina. Like much of this region, its economy has consisted of small agricultural holdings, heavy industry, and manufacturing [13]. Despite national increases in the service sector, manufacturing plays an important role in the gross domestic product (GDP) in this region, and GDP shows continuous growth over the last decade [14]. Manufacturing represents more than 15% of GDP in T.N., and advanced manufacturing has seen significant investment and growth recently [15, 16]. We can use T.N.'s 1^{st} Congressional District as an example of area demographics. The area lags behind the rest of the nation with an overall poverty rate of 15.4%, while 22% of children fall below the federal poverty line [17]. Demographic data are summarized in Table 1.

In addition to traditional manufacturing industries, Tennessee as a whole has a thriving life sciences-based economy. Bioeconomic centers exist primarily around Memphis and Nashville, each home to major research medical centers and several bio-based firms operating in the pharmacological, healthcare, and non-healthcare-related segments. According to data published by industry groups in 2022, Tennessee's bioscience industry has been on an upward trajectory since 2018 [18]. Although the bioeconomy is not as well represented in the Appalachian Highlands, several medium-sized firms are located in the area. A key partner in our efforts is Crown Laboratories, a skincare-focused company, which recently launched a major product line utilizing engineered bacteria as the essential component of the product. Although not typically placed in the same category as other bioscience technologies, the fermentation, brewing, and distillation industry has recently become a major employer that is currently growing. Tennessee Hills, as one representative company, has partnered with us on this project to develop workforce

Category	Percentage	Count	% Error
Male	49.5	386,965	±0.3%
Female	50.5	394,163	±0.3%
Persons Below Federal Poverty line	15.4%	117,566	±1.2%
Children below Federal Poverty line	22.1%	32,064	±2%
Possesses a Bachelor's Degree or Higher	24%	135,078	±1.1%
Veteran Status	8.5%	53,505	±0.5%

Table 1: Demographic statistics for the First Congressional District of Tennessee. The Tennessee 1^{st} lags behind the National Average in most categories. Per capita income for the district sits at $\$32,693$, and the median household income is $\$54,716$. All data are derived from the U.S. Census Bureau American Community Survey of 2022 [17]

training in mechatronics-based automation and bioprocess skills. In informal interviews conducted with regional industry, there is consensus that there is a shortage of skilled workers at all levels, both those seeking entry-level positions and those holding baccalaureate degrees. This follows conclusions drawn at the national level that note that extensive training and education are needed at all levels to enable a robust bioeconomy [10, 19, 20]. Additionally, we have noted from our industrial partners a need to expand infrastructure for biomanufacturing at the pilot and industrial scale in line with expanding the available workforce to support bringing new products and technologies to market. Such a conclusion is in line with those across the country.

Recognizing all of the factors above, we realize that there is an opportunity for ETSU and several partner organizations to develop an innovative set of programs in engineering biology, synthetic biology, and biomanufacturing to serve the needs of extant industry while preparing our region as a hub for future innovation. Given the blend of education and training entities, existing businesses, and resources, the Appalachian Highlands is well suited to develop as a regional center of the bioeconomy given the right investments in education and infrastructure, as discussed in the following.

Report on Current Work - Overview

In 2020, The National Academies, through one of its consensus reports, adopted the following definition of the U.S. bioeconomy:

> The U.S. bioeconomy is economic activity that is driven by research and innovation in the life sciences and biotechnology, and that is enabled by technological advances in engineering and in computing and information sciences [21].

This broad definition is meant to encompass the whole of the nation's bioeconomic activities to enable policy discussions. For our program, we have tried to capture the needs of our area and align ourselves to best serve the region. To that end, work has been conducted in three major programmatic areas: the creation of a pipeline starting in secondary education to expose students to synthetic biology and biological engineering; the creation of entry-level workforce development modules in biomanufacturing and bioprocess engineering; and the creation of an

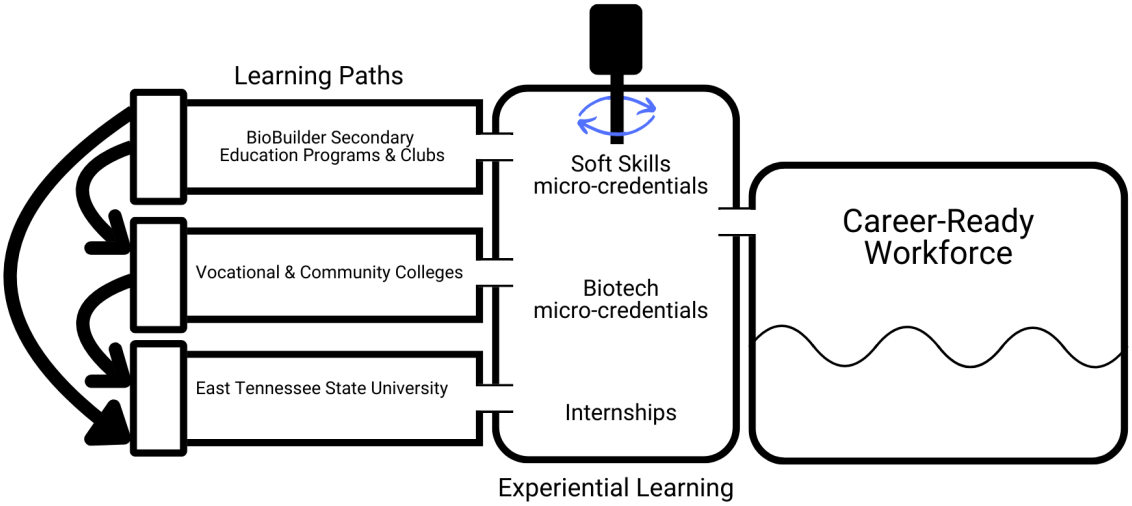

Figure 1: Infographic of the inter-relatedness of the simultaneous projects taking place in our region visualized as pipeline from first interest to careers

interdisciplinary, inter-academic unit and major in bioengineering. This major will be novel for a regional institution in that it will serve to develop students skills and domain knowledge for both the R&D industry through a synthetic biology & laboratory skills pathway and a biomanufacturing and bioprocess pathway. These interrelated projects have evolved over time and are currently progressing simultaneously; each semi-autonomous piece provides a vital feedstock to our larger vision of the regional bioeconomy. We illustrate how these pieces affect the development of the workforce in the infographic in Figure 1.

Generating Interest and Entering the Pipeline

The foundation of our efforts lies in a regional effort to develop scientific literacy around synthetic biology and interest in biotechnology careers. This effort started in 2019 when all biology teachers from the Dobbins-Bennett High School in Kingsport, Tennessee, and several faculty members from ETSU were funded by the Eastman Foundation and Carolina Biological Supply to attend a series of BioBuilder Educational Foundation designed and led workshops [22]. Teachers interviewed from the program stated that participation was from “the full spectrum of students . . . and they all enjoy it.” While this statement is intrinsically anecdotal, this general attitude from both instructors and students demonstrated a strong interest in the subject matter and style of instruction.

The BioBuilder curriculum, developed by Dr. Natalie Kuldell from experience teaching biological engineering at MIT, seeks to “provide middle school, high school, and college students with synthetic biology learning programs and hands-on experiments” to teach the foundational

skills of synthetic biology [23]. The initial interest and enthusiasm should not come as a surprise, even in a rural setting, as the literature shows that students at both the middle and high school levels are capable of forming well-developed attitudes and interest about synthetic biology when exposed to it. [24, 25]. Materials needed to participate in the program are relatively accessible to schools, and others have demonstrated the viability of translating similar labs to versions capable of being administered in the home setting [26]. Importantly, similar programs aimed at high school students have shown increased self-evaluation of an identity in STEM, particularly among underrepresented groups [27].

While introduction at a large urban school is noteworthy in itself, this region has gone to great lengths to improve STEM engagement and interest in students. The leading player in that field and one of our partners in this work is the Niswonger Foundation of Greeneville, TN [28]. In 2020, Niswonger was awarded an $8 Million USD Education Innovation and Research grant from the U.S. Department of Education (E.D.) titled *STEM.LD* to take place over five years [29]. This Learning Design project seeks to address several STEM education needs in the Appalachian Highlands. To specifically address biotechnology, BioBuilder was included as a partner on the grant. Within the structure of the grant, BioBuilder activities take the form of either experiential out-of-school time (OST) activities by way of BioBuilder Clubs or through direct integration into a school's biology and technology curriculum. To date, more than 60 area schools representing 21 regional school districts have been offered the program. It should be noted that 48% of the targeted population is considered high-risk by E.D. BioBuilder is also providing teacher professional development to support the integration of the BioSTEM curriculum in the region. Efforts are ongoing to analyze the impact of this work on the STEM trajectories of students participating in clubs, with additional analysis focused on determining whether student location (i.e., rural vs. urban) affects persistence in STEM trajectories. This project sets the stage for a pipeline of students to matriculate either into the biotechnology workforce or to post-secondary education. To quantify that impact, BioMADE, a Department of Defense-funded advanced manufacturing institute, awarded ETSU and BioBuilder a grant in 2022 to study the impact of BioBuilder clubs nationwide on students post-secondary trajectories, and the results of that analysis are expected to be published in the near future [30].

Completing the Pipeline: Education to Industry

The next step in developing the regional bioeconomy is to work towards expanding the available workforce in the region. Multiple reports and analyses have indicated that workforce preparedness is a significant bottleneck to current and future growth in the industry [31, 32]. As mentioned, members of our local bioindustry expressed the same frustrations as the national reports. At every level of industry, there is a need for trained professionals to fulfill production and R&D goals. To address this issue, ETSU is developing two pathways: a credentialing pathway for basic industry skills and a bioengineering major.

The Appalachian Highlands region currently lacks infrastructure and a pipeline for training a skilled workforce in biotechnology and biomanufacturing. In the Fall of 2023, ETSU was awarded a grant from BioMADE to develop a series of biomanufacturing microcredentials. The overarching goal of which is to make an adaptable and scalable program of education that is agnostic to a specific cell-type. In doing so, we seek to *open the valve* to support our current and

future workforce needs. As input, we will train students from diverse backgrounds, i.e., those straight from high school, community college, and those enrolled in a four-year program. In particular, this program is intended to serve non-traditional students such as veterans, those seeking retraining, and those who have attempted but never completed a post-secondary degree. Through our training, students will acquire useful, hands-on skills necessary for the biomanufacturing industry. Based on interviews with industry partners, we identified that the major area of need is in process control and engineering of downstream bioproduct separation. The principal aims of this work are summarized as:

1. Establish a biomanufacturing process teaching laboratory.
2. Create generalized lesson plans for methods in recovery, separation, and purification of bioproducts, and a certificate in industrial cleaning, sanitization, and sterilization.
3. Develop a series of soft-skills and career readiness modules in conjunction with the Niswonger Foundation and BioBuilder.
4. Implement lessons and develop modules suited to non-traditional and non-matriculating students.
5. Prototype modules suitable for integration into a four-year degree in bioengineering or biomanufacturing.
6. Implement a nexus between our educational programs, the ETSU Research Corporation, and local and prospective industry.
7. Identify the effectiveness of the proposed scope of work on student learning, industry impact, and satisfaction of industry partner hires.
8. Validate module relevance with input and assessment from BioBuilder.

This grant officially launched in October of 2023. Thus far, most of our work has focused on Aims 1 & 2 in conjunction with the ETSU Research Corporation (ETSU RC). As mentioned, there is a lack of infrastructure that could be considered a part of the biomanufacturing process. Our teaching lab is seeking to address this through the acquisition of pre-pilot scale equipment that mimics bioindustrial processes but in the range of 10L. At the same time and in the same location, the ETSU RC is seeking to develop a pilot facility up to 1000L. One need that was recently recognized was an easily assembled and controlled trainer system to demonstrate the effective and proper use of clean-in-place systems. We are currently developing a trainer based on open-source software and Ardunio-base PLCs. A working prototype of that system is expected to be operational and demonstrable by May 2025. It is our intention to make the bill of materials and design schematic for this trainer openly available to community colleges and other training programs. All parts, including actuated valves, hydraulic pump, and sensors, were chosen to minimize overall cost, and most were sourced from Amazon.com. The Python code used to control the trainer, ladder-logic PLC program, and human-machine interface (HMI) will be distributed through an open-source license. Low-cost, part availability, and readily-adapted open software should encourage adoption even at low-resource institutions

To initiate our work, we have acquired a number of bioreactors to grow organisms for use in the modules. Our downstream process starts with centrifugation, filtration, ultrafiltration and

concentration with tangential flow filtration (TFF) equipment, followed by chromatography, spray drying, and validation. As mentioned, our modules are designed to be relatively organism-agnostic. We are currently targeting the growth of *Saccharomyces cerevisiae* as the most basic organism to grow and process. Its proper handling is particularly relevant to our region and partners for its use in brewing and fermentation and for demonstrating spray drying as a processing step. As a modern workhorse fungi pertinent to industry, we will be developing a protein extraction and purification module with *Komagataella pastoris*, previously known as *Pichia pastoris*. We also plan modules on anaerobic bacterial growth using *Cultibacterium acnes* and lipid extraction as well. We anticipate that in each credential, students will become familiar with operating a specific piece of equipment, validating success with that equipment, and maintaining sterile technique. We intend to emphasize structured troubleshooting and problem-solving as a highlight of this program through the use of pedagogical approaches developed from industry to enhance problem-solving skills discussed in several ASEE conference proceedings [33, 34, 35]. One industry representative firmly insisted that students "not fall into the trap of treating equipment like a black box." They should understand it well enough to troubleshoot problems and deviate from standard operating procedures when necessary.

To design these modules, we have engaged in several planning sessions structured around an Agile-like approach to ideation [36]. We find it important for us as faculty to practice these approaches as we have recently begun implementing them as part of our pedagogy and intend to do the same when developing our bioengineering major [37]. In particular, the Agile philosophy of *fail fast, fail often* mirrors the *Design, Build, Test, Learn* cycle found in biological and metabolic engineering. We want to stress to our students the importance of trying many ideas and variations to optimize a product. For example modern biofoundries engineer and express many hundreds or thousands of slightly varied genes to select the best fit for production. Our team has tried to ideate as many industry needs as possible, and we have selected what we consider the most valuable from that pool. Feedback from industry partners will be taken between each credential cycle to modify and improve the program. Shown in Figure 2 is an example of a cluster analysis practiced with a virtual whiteboard from one of these sessions. Based on our ideation and discussion with partners, we intend to offer separate microcredentials on protein processing, lipid processing, sterilization and clean-in-place techniques, and biosafety. We intend to weave sterile practice and good manufacturing processes (GMP) into the curriculum where possible to develop the overarching certificate.

From a pedagogical perspective, we want to design this program in such a way that it allows for self-motivated and independent study. To that end, we intend to partner with students from Digital Media during the last quarter of this project to produce high-quality videos that students can watch on their own. This should keep in-person time to a minimum and optimize time spent in lab. At this stage, we are unsure of the length of any individual credential, but expect it to be a lower hour commitment than would normally be given to a three- or four-credit-hour course.

We intend for this training program to be relevant to industry. To that end, Aim 6 above will establish a nexus between our biotechnology efforts and local industry. This part of our effort is being established through the ETSU RC and is expected to be one of the priorities of a nascent center for biotechnology at ETSU. Importantly, for our training efforts, the work on the nexus will develop a program that integrates the principles of business and entrepreneurship with

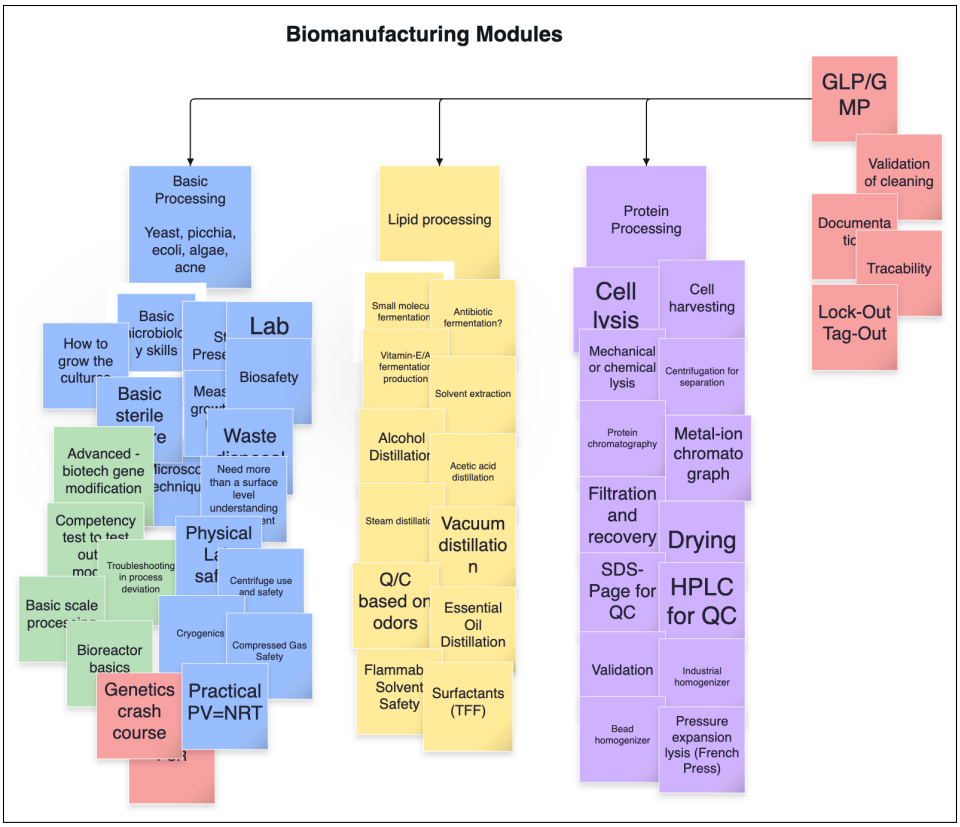

Figure 2: An example of clustering analysis performed during an ideation session to develop out topics to cover in the credential series. Colors represent topics thought to be related to one another.

bioengineering education. The program will offer training and experiential learning opportunities that bridge the gap between scientific knowledge and the commercialization of biotechnology products. It will include industry collaborations, mentorship, and exposure to business strategies and regulatory frameworks. To prepare students for industry placement, we will offer a version of the Niswonger Foundation's CareerConnect and Work Ethics Distinction programs, which seek to equip students with the soft skills needed to function effectively in a work environment such as time management, personal reliability, teamwork, and leadership (Aim 3).

Conversely, our industry partners have identified that there will be employees from the business and non-technical divisions of our industry partners who desire and would benefit from training in the biology and engineering aspects related to their company. We intend to offer credentials in bio-business for this group of participants so they are more intimately familiar with biological and industrial processes. We anticipate that many of the students participating in the skills training above will participate in culminating experiences with our industry partners. We see this as a method of validating the training we provide to students, as students will directly work with industry practitioners who will provide us with feedback for iterative changes in our modules.

Particularly important for this current report is that we are in the initial planning stages for Aims 7 & 8. This project aims to disseminate our training modules to other nascent biomanufacturing

education programs, but only if it is shown to be an effective approach. Current plans for assessment are based on the approaches in [25] and [30]. Surveys will assess learners' preknowledge, interests, and career plans. We will survey again after the completion of credentials, and as we plan for our program to feed into internships with our industry partners, we will survey preceptors about the ability of students at the industry site. Surveys will be conducted prior to the start of a credential, after completion of a credential, after completion of an internship and one year following program completion. We anticipate using post-survey interviews to extract insights into the motivations of students and their identities as practitioners after completion of our program. Additionally, content validation will be performed against existing biomanufacturing credentialing programs such as Biotility's *Biotechnician Assistant Credentialing Exam (BACE)* and the programs offered by Worcester Polytechnic Institute's *Biomanufacturing Education & Training Center*. Though, it should be noted that both of the previous have a stronger focus on pharmaceutical biomanufacturing, while our program focuses more on commodities production.

Next Steps & New Programs

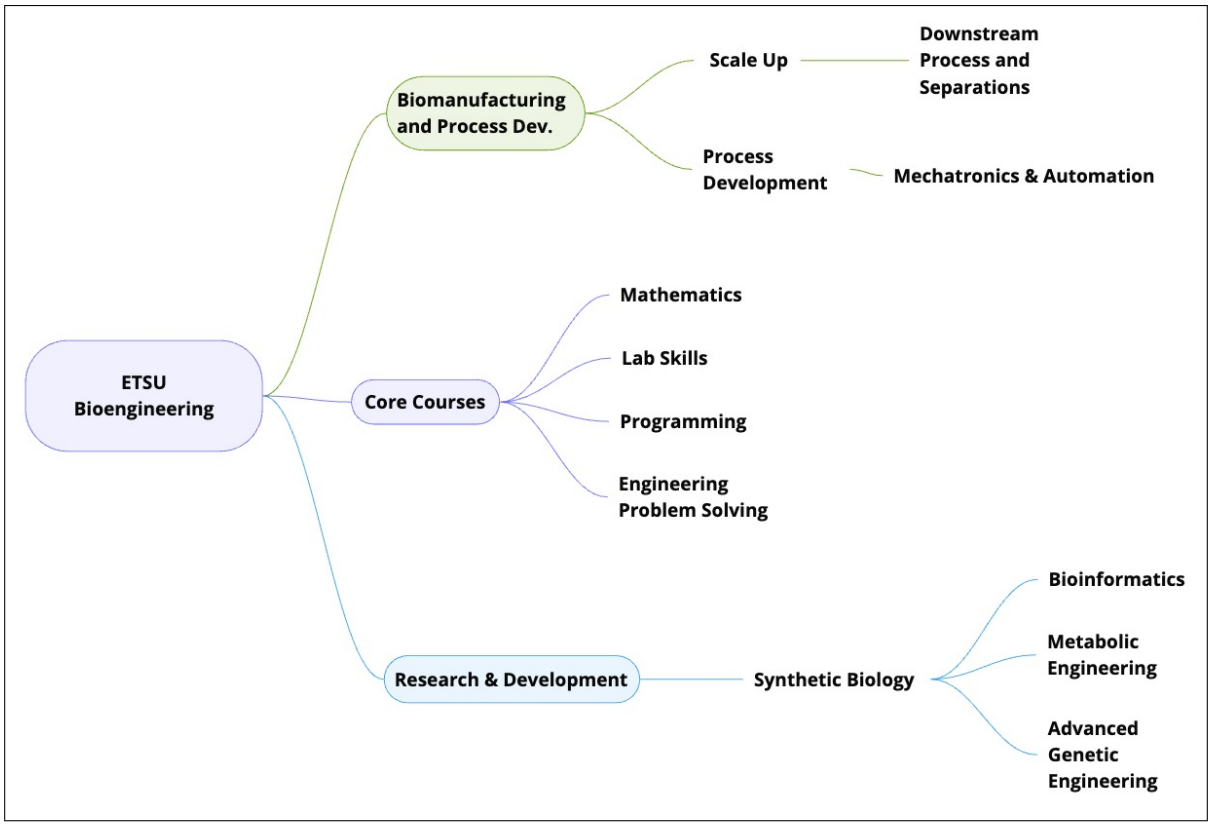

Figure 3: A graphical representation of the core curriculum and two concentration pathways for a bioengineering degree at ETSU. Students will be able to choose between a synthetic biology-focused track and a biomanufacturing track

While still nascent, our program has the potential and the intention to be translated into a four-year bioengineering degree. Particularly, we see the rapid nature of the training program as

an advantage for prototyping labs to be implemented in portions of a degree program. This degree is still in the early planning stages, but we are able to share some specifics about the intended structure. Firstly, the degree will be implemented with a common bioengineering core for all students involved. Given the demographics of our region, the accessibility of the degree to students from underserved backgrounds is of utmost importance. To that end, we are implementing the engineering mathematics model developed at Wright State University by Klingbeil and colleagues [38]. The course teaches mathematics from an engineering perspective as a tool to understand nature. This program has been shown to increase retention of students within the major, increase scores in Calculus 1 and Calculus 2 courses, and develop students' self-identity as engineers [38, 39]. This course will be piloted for the first time at ETSU in Fall 2024. Additionally, students will take courses in practical electronics design, molecular biology, genetics, organic chemistry, physics, and laboratory techniques to establish a shared language and cohort before choosing a concentration.

Given the particular needs of local and national industry, we are designing the degree such that students will choose between two specializations. This is shown graphically in Figure 3. The first specialization will focus on the theory and techniques of synthetic biology, bench-scale laboratory techniques, and genetic engineering. Emphasis will be placed on the Design-Build-Test-Learn paradigm originally developed in metabolic engineering [40]. Courses for this pathway are expected to prepare students for a career in R&D. Our second concentration will focus on aspects of biomanufacturing with emphasis on translating bench scale work to small bioreactor scale, process development and control, automation, and downstream product development. Students will develop the skills needed to work and lead in bioindustrial settings [41]. Design and management of industrial projects will be incorporated with industry case studies and practices such as the recently developed Bio Manufacturing Readiness Levels (BioMRLs) [42]. This later concentration meshes well with ETSU's mechatronics engineering degree program. Students from both concentrations will be expected to complete an interdisciplinary capstone design project. We intend for students to be able to compete in the International Genetically Engineered Machine (iGEM) competition as a part of their capstone, a model developed with the advice of faculty at U.C. Santa Cruz, where it has been implemented for over a decade.

Conclusion

The national bioeconomy is projected to see record growth and a potential renaissance over the coming decade. While previously, the economic benefits of such growth have been limited to metropolitan areas, we are poised to translate these advances from the ground up into thriving regional centers advancing local economies. To manifest this goal, we must be proactive in developing talent pipelines. At ETSU, we have embarked on a multi-project journey to establish the Appalachian Highlands as a center for biotechnological excellence. While still in the early stage and seeking input and feedback, the program described above develops a response plan to grow and sustain a bioeconomy in our area.

Acknowledgments

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References

[1] Office of the Undersecretary of Defense for Research and Engineering, "DOD approves $87 million for newest bioindustrial manufacturing innovation institute," October 2020. [Online]. Available: https://www.defense.gov/News/Releases/Release/Article/2388087/dod-approves-87-million-for-newest-bioindustrial-manufacturing-innovation-insti/

[2] Executive Office of the President, "Executive order 14081: Advancing biotechnology and biomanufacturing innovation for a sustainable, safe, and secure american bioeconomy-request for information; national biotechnology and biomanufacturing initiative-measuring the bioeconomy," *Federal Register*, vol. 88 FR 25711, no. 2023-08841, pp. 25 711–25 715, 2023.

[3] White House Office of Science and Technology Policy, "Bold goals for U.S. biotechnology and biomanufacturing," March 2023.

[4] "Industrial make-up of the appalachian region," Appalachian Regional Commission, Tech. Rep., 2019.

[5] K. T. Cummings-Lilly and S. S. Forrest-Bank, "Understanding appalachian microaggression from the perspective of community college students in southern West Virginia," *The Journal of Sociology & Social Welfare*, vol. 46, no. 2, 2019.

[6] C. E. Rittenour, J. P. Baker, K. B. Burgess, K. E. Shields, and L. B. Okai, "Communicated stereotypes, attitudes, and intended accommodations of appalachians," *Journal of Intercultural Communications Research*, vol. 49, no. 4, 2020.

[7] "Top 10 U.S. biopharma clusters 2023," GEN: Genetic Engineering & Biotechnology News, Tech. Rep., 2023.

[8] K. Steele, "Medtech and biomanufacturing fuel life sciences growth," JLL, Tech. Rep., 2023.

[9] I. Cameron, "Life sciences: which US regions are on the rise?" Tech. Rep., 2023.

[10] P. Shapira, N. E. Matthews, C. A. Cizauskas, E. R. Aurand, D. C. Friedman, D. S. Layton, M. E. . Maxon, M. J. Palmer, and L. Stamford, "Building a bottom-up bioeconomy," *Issues in Science and Technology*, vol. 38, no. 3, 2022. [Online]. Available: https://issues.org/building-bioeconomy-engineering-biology-shapira/

[11] M. E. Gallo, "The bioeconomy: A primer," *Congressional Research Service*, vol. R46881, September 2022. [Online]. Available: https://crsreports.congress.gov/product/pdf/R/R46881/3

[12] ARC, "Subregions of appalachia," Appalachian Regional Commission, Map and Data, 2021. [Online]. Available: https://www.arc.gov/map/subregions-in-appalachia/

[13] T. Lee, *The Tennessee-Virginia Tri-Cities: Urbanization in Appalachia, 1900-1950*. University of Tennessee Press, 2010.

[14] B. D. Tables', "CAGDP1 county and MSA gross domestic product (GDP) summary," U.S Bureau of Economic Analysis, Tech. Rep., December 2022. [Online]. Available: https://apps.bea.gov/

[15] L. M. Kessler, "An economic report ot the governor of the state of Tennessee," University of Tennessee Boyd Center, Tech. Rep., January 2023.

[16] S. Udavant, "How Tennessee became a draw for manufacturers," Manufacturing Dive, Tech. Rep., 2023. [Online]. Available: https://www.manufacturingdive.com/news/tennessees-strategy-to-become-a-major-manufacturing-hub/644163/

[17] U.S. Census Bureau, "American community survey 5-year estimates," Tech. Rep., 2022.

[18] T. Partners, "Tennessee: U.S. bioscience industry: Fostering innovation and driving America's economy forward," Life Science Tennesse, Tech. Rep., 2022. [Online]. Available: https://www.lifesciencetn.org/reports-data/#:~:text=Tennessee's%20bioscience%20industry%20has%20grown,to%20the%20overall%20job%20gains%E2%80%A6

[19] A. W. Hinman and D. C. Friedman, "Actions to enable and equitable and innovative u.s. bioeconomy," EBRC: Engineering Biology Research Consortium, Tech. Rep., May 2022. [Online]. Available: https://ebrc.org/actions-to-enable-an-equitable-and-innovative-us-bioeconomy/

[20] OSTP, "Building the bioworkforce of the future," Office of Science and Technology Policy, Tech. Rep., 2023. [Online]. Available: https://www.whitehouse.gov/wp-content/uploads/2023/06/Building-the-Bioworkforce-of-the-Future.pdf

[21] National Academies of Sciences, Engineering, and Medicine, Ed., *Safeguarding the Bioeconomy*. National Academies Press, 2020, ch. 2 Defining the U.S. Bioeconomy. [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK556424/

[22] Biobuilder Educational Foundation, "Synthetic biology for tennessee schools: Biobuilder partners with Niswonger Foundation on $8.8 million federal grant for STEM education," Press Release, December 2020. [Online]. Available: https://www.send2press.com/wire/synthetic-biology-for-tennessee-schools-biobuilder-partners-with-niswonger-foundation-on-8-8m-federal-grant-for-stem-education/

[23] N. Kuldell, R. Bernstein, K. Ingram, and K. M. Hart, *BioBuilder: Synthetic Biology in the Lab*, 1st ed. O'Reilly, 2015.

[24] Y. Kafai, O. Telhan, K. Hogan, D. Lui, E. Anderson, J. T. Walker, and S. Hanna, "Growing designs with biomakerlab in high school classrooms," *IDC '17: Proceedings of the 2017 Conference on Interaction Design and Children*, pp. 503–508, June 2017.

[25] J. T. Walker, "Middle school student knowledge of and attitudes toward synthetic biology," *Journal of Science Education and Technology*, 2021.

[26] J. K. Jung, B. J. Rasor, G. A. Rybnicky, A. D. Silverman, J. Standeven, R. Kuhn, T. Granito, H. M. Ekas, B. M. Wang, A. S. Karim, J. B. Lucks, and M. C. Jewett, "At-home cell-free synthetic biology education modules for transcriptional regulation and environmental water quality monitoring," *ACS Synth. Biol.*, vol. 12, no. 10, pp. 2909–2921, September 2023.

[27] K. Watts and W. Richardson, "Inclusive pedagogy strategies to introduce high schoolers to systems biology," *Biomedical Engineering Education*, October 2023.

[28] L. Johnson, "Niswonger foundation improving education in the area," Online, November 2023. [Online]. Available: https://www.wjhl.com/news/local/niswonger-foundation-improving-education-in-the-area/

[29] S. Robertson, "The niswonger foundation's $8 million plan to revolutionize stem education," online, January 2021. [Online]. Available: https://bjournal.com/game-changer/

[30] P. J. Mims, "Investigating high school students' participation in biobuilder clubs on their bioindustry pathway interest and knowledge change over time," *in progress*, 2025.

[31] J. L. Pandey, "Building the bioeconomy workforce of the future," *BioScience*, vol. 71, no. 1, pp. 9–10, January 2021.

[32] A. Hodgson, M. E. Maxon, and J. Alper, "The U.S. bioeconomy: charting a course for a resilient and competitive future," *Industrial Biotechnology*, vol. 18, no. 3, 2022.

[33] A. M. Abu-Khalaf, "Developing troubleshooting skills in the unit operations laboratory," *Chemical Engineering Education*, vol. 36, no. 2, 2002.

[34] P. Rivera-Reyes and R. E. Boyles, "Training in troubleshooting problem-solving: Preparing undergraduate engineering students for industry," in *120th ASEE Annual Conference & Exposition*. American Society for Engineering Education, 2013.

[35] B. M. Diong, C. A. Chin, S. Das, A. Tekes, and W. Thain, "Enhancing engineering students' troubleshooting skills," in *2021 ASEE Annual Conference*. American Society for Engineering Education, 2021.

[36] V. Kumar, *101 Design Methods: A structured Approach for Driving Innovation in your organization*. Wiley, 2012.

[37] R. M. Felder and R. Brent, *Teaching and Learning STEM: A Practical Guide*, 1st ed. Jossey-Bass, 2016.

[38] N. Klingbeil, "A national model for engineering mathematics education: Uncorking the bottleneck to URM student success," *Research and Policy Journal: 2013 NACME National Symposium*, 2013.

[39] N. Klingbeil and T. Bourne, "The Wright State model for engineering education: Longitudinal impact on initially underprepared students," in *Proceedings 2015 ASEE Annual Conference and Exposition*. American Society for Engineering Education, 2015.

[40] S. Kitano, C. Lin, J. L. Foo, and M. W. Chang, "Synthetic biology: Learning the way toward high-precision biological design," *PLoS Biology*, vol. 21, no. 4, 2023.

[41] Y.-H. P. Zhang, J. Sun, and Y. Ma, "Biomanufacturing: history and perspective," *Journal of Industrial Microbiology & Biotechnology*, vol. 44, no. 4-5, pp. 773–784, 2017.

[42] M. J. Smanski, A. Aristidou, R. Carrutth, J. Erickson, and M. Gordon, "Bioindustrial manufacturing readiness levels (biomrls) as a shared framework for measuring and communicating the maturity of bioproduct manufacturing processes," *Journal of Industrial Microbiology and biotechnology*, vol. 49, no. 5, 2022.