**Background: Biotechnology** is the manipulation (as through genetic engineering) of living organisms or their components to produce useful products (as pest resistant crops, new bacterial strains, or novel pharmaceuticals); *also*: any of various applications of biological science used in such manipulation (Merriam-Webster Dictionary). Here we will also include technologies based on DNA sequencing, use of biological molecules, and biomaterials and includes biochemistry, biosynthesis, cellular biology, physiology, biochemical engineering, and understanding the interface between biological and engineered systems. There is great promise to solve big medical, environment, energy, agricultural, and military problems based on current and future applications of biotechnology. This promise is from direct application of biotechnology and from the growing area of multidisciplinary research that combines biotechnology with other sciences like materials science, physics, chemistry, and engineering just to name a few. However, there is also growing concern over possible dangers from this area of science based on the potential for mishaps from honest scientists and applications purposefully developed to cause harmful or even devastating effects. As freely accessible knowledge, materials, and ease of development grows, the potential groups that can develop these applications has also grown from governments and large corporations to ever smaller groups including non-nation state actors such as criminal and terrorist organizations and even individuals.

**A rapid evolution of technologies.** Rapid technological advancement over the last three decades has resulted in extraordinary discoveries and advancements in the biotechnology field. For example, the Human Genome Project created a detailed map of human DNA. The hereditary instructions inscribed in DNA guide the development of the human being from fertilized egg cell to death. Therefore, decoding the DNA sequence of the human genome has great power. DNA sequencing technology has rapidly evolved so that an individual human genome which cost $100 million to sequence in 2001, only cost $5,000 in 2014.[1] In parallel, technology for synthesizing and assembling artificial DNA has increased in efficiency so that entire genes and whole genomes of viruses and bacteria genomes can be recreated.[2-5] Recent breakthroughs in technologies for genome engineering have made the genetic manipulation of microbes, insects, plants and animals, including gene therapy in humans, more feasible.[6,7] For example the development of herbicide resistant corn, soybeans, and cotton has increased national yield, decreased cost, decreased the amount of pesticides applied, and increased personal safety.[8]

**Advancing areas of biotechnology.** As a result of these technological advances, both old and new areas of biotechnology will have significant impacts on soldier performance, the way the Army operates, and society in general. Specific areas of biotechnology show promise for likely application in 2025 such as personalized medicine, genome engineering, human gene therapy, biomanufacturing, biofuels, environmental remediation, genetic engineering of disease and drought resistant plants, synthetic biology, and technologies at the intersection of nanotechnology, biotechnology and engineering.

**What existing biotechnologies will be used in new ways in 2025?**

**Personalized medicine** is the customization of healthcare that is tailored to the individual patient where a patient's genetic content, or other molecular analysis such as genetic polymorphisms for drug metabolism, is used to select medical treatments. Biotechnology products will enable personalized medicine. Soldiers can be prescreened for potential vulnerabilities and diseases so that accurate treatments can be available. **Personalized medicine is likely to be used in new ways in 2025** Screening for susceptibility or tolerance to post traumatic stress may enable minimization of soldier injuries through monitoring. Advanced integration of personalized medicine with soldier training will permit more intensive and demanding training scenarios. Understanding potential health and physical vulnerabilities of soldiers based on their genome will enable identification of soldiers susceptible to certain stressors or diseases to facilitate mission assignments. For example, genetic polymorphisms for the enzyme butyrylcholinesterase (BChE) affect an individual's differential capacity to metabolize and eliminate acetylcholinesterase inhibiting chemicals such as nerve agents.[9] Individuals that have this polymorphism, and are therefore more tolerant to nerve agents, can be identified and strategically selected for high risk operations where nerve agents may be used or for decontamination missions.

**Microbiome manipulation.** A microbiome is the collection of different microbial populations that live in a specific niche, such as the gut, skin surface, mouth, soil, or water. The bacteria that live in our guts have been found to directly influence many facets of our physiology. Probiotics containing the bacteria Lactobacillus or Bifidobacterium are currently used to improve digestion and gastrointestinal problems. Direct, or indirect, manipulation of the microbiome of Soldiers' stomach using tailored probiotics, genome engineering, synthetic biology or other approaches will result in improved tolerance of food and improved resistance to disease. Additional research has implicated the gut microbiome control of a person's mood, metabolism, and physical performance. For example, the gut microbiome has been demonstrated to have a connection to neurodevelopmental disorders such as autism; suggesting a potential probiotic therapy.[10] **Microbiome manipulation is likely to be used in new ways in 2025** to yield probiotics to improve soldier performance so that training could be shorter and more intensive. This technology may extend or increase learning capacity, alertness, ability to perform in a stressful environment, enable integration of sensing in novel ways. More unpredictable but game changing uses include probiotics that will establish microbes in the gastrointestine (GI) capable of responding to stressors, events, threats, needs through initiation of a cascade of responses in the presence of a stimulus such as a chemical. These probiotics could produce a unique flavor such as mint or a sour flavor that could be detected upon exposure to toxic chemicals or chemical and biological warfare agents. Similar effects could be produced by changing the mouth microbiome using gum with a probiotic or an inducer of a genetically modified microbiome. Other game changing applications may include the ability to digest grasses or other plants as food sources.

**Biomanufacturing** uses biotechnology approaches to produce commodity products, biologically based molecules, or molecules that can be used in construction of materials. Currently, most efforts are focused on pharmaceutical production or bulk chemical production. New biomanufacturing approaches utilizing bacteria where synthetic biology has been used to create artificial pathways for synthesis of chemicals that are useful in energy (biofuels), in product synthesis (chemical precursors) or production of complex biochemicals for antibiotics.

**This area is likely to be used in new ways in 2025** for production of energy and controlled synthesis of pharmaceuticals and biochemicals. New biomanufacturing approaches using bacterial virus proteins are poised to deliver conformable, lightweight batteries that could greatly lighten the soldiers load. Bioassays integrated into Band-Aids like platforms have already been developed to monitor different proteins or chemicals in sweat. In the future these platforms are likely to result in novel, on-demand, multiplexed delivery systems for stimulants, medicines, or other functional molecules. On demand biomanufacturing integrated into temporary tattoos or band-aids will provide unique capabilities to augment soldier sensing, medication, and identification. Sensing threats might include chemicals (TICS/TIMS), CBRN, temperature and humidity. Sensors will be wearable, integrated into clothing or even temporary tattoos using nanosilver ink (Figure 1). These tattoos will be imprinted on soldiers prior to deployment

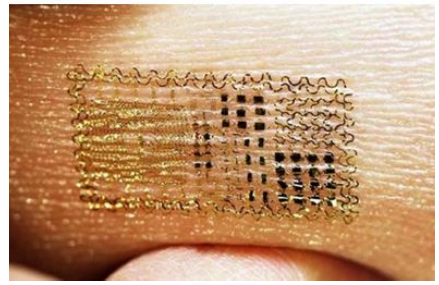

Figure 1. Printed electronic tattoo. John A. Rogers, U of Illinois (https://www.youtube.com/watch?v=fl1VS_kONlQ for video)

that include physiological sensors that do not require blood to monitor metabolic products (to determine energy levels), hydration level, cortisol level to determine stress and fatigue, and use as feedback to determine emergency medical states. For example a soldier might be experiencing a high level of stress or exhaustion. Sensors will detect and process the event, then synthetic biology created microbes will respond with the correct treatment by produce and release biomolecules such as endorphins to alleviate the stress. If a soldier is exhausted, the sensors detect a metabolic signal and initiate, through a synthetic protein (to avoid false initiation events), a genetically modified microbe in the Soldier's gastrointestinal system to release a biomolecule such as a steroid or other stimulating agent. If a soldier is exposed to a chemical agent, the same cascade could release a pharmaceutical agent directly to the blood stream or produce it through genetically modified microbes.

**Synthetic biology**, a discipline that focuses on making synthetic organic, living organisms or devices with properties that do not occur in nature, offers great promise in controlled design of new technologies using biological engineering. Although Synthetic Biology has great potential for useful applications, there is also a risk of a synthetic organisms escaping and potentially damaging the environment or the intentional creation of harmful organisms. As the technologies needed to create these organisms continue to become less expensive and pervasive, this risk will increase. Several agencies are promoting development of practical synthetic biology products. For example, DARPA has started a program called Biological Robustness in Complex Settings that supports developing synthetic biology approaches that are more stable and safe to use in complex biological environments. One of the stated goals of the DARPA program is safety, defined as the development of methods to control the growth and proliferation of engineered organisms in complex settings. **This area is likely to be used in new ways in 2025**. Development of synthetic pathways and organisms to synthesize biofuels and medicines will continue. Technologies based on synthetic biology emerge in 2025 that provide new mechanisms for sensing and responding to different signals (chemical, biological, magnetic, electric). Primitive ultralow power, or energy generating, synthetic organisms will be used to control simple devices, calculate events, and for general monitoring of the environment. This will enable unprecedented situational awareness. Synthetic biology will also likely provide new approaches for modulating soldiers physical responses to the environment where through manipulation of microbiomes or direct interference with biological pathways for medical treatments or performance enhancement.

**Gene therapy** or the use of gene replacement to cure disease has had recent successes in treating previously uncurable diseases such as the metabolic disease metachromatic leukodystrophy.[11] Recent advances indicate that humans could be engineered using these technologies leading some to call for a moratorium on germ line cell (embryo) editing.[12] **This area is likely to be used in new ways in 2025.** More common diseases such as diabetes I could be preventable. People with sensitivity to certain chemicals may be made insensitive. This could reduce risk to soldiers when operating in urban theaters where high concentrations of industrial chemicals are likely to be found. **This technology could be a game changer in 2025** if state actors with access to the technology are able to enhance soldier performance. The ethics and communication to the public regarding use of this technology will affect the Army’s use of technologies for Soldiers.

Diagnostics use biological markers, such as DNA, RNA, or proteins, to identify disease and pathogens in a manner similar to using fingerprints to identify criminals. Diagnostics systems are becoming faster and cheaper enable rapid or near real time monitoring of diseases or pathogens. For example, Nanobiosym's Gene-Radar diagnoses diseases in a matter of a few hours. This area is likely to be used in new ways in 2025. **Development of faster, more ubiquitous monitoring of pathogens and diseases will occur.** Applications include faster and more efficient diagnosis and treatment of diseases, emanation of genetic diseases, human gene therapy, biomanufacturing, biofuels, personalized medicine, environmental remediation, and disease resistant crops. However, other more controversial or even nefarious applications of this freely available information could include bioengineering of diseases targeting select groups of people, plants, or animals or even the creation of genetically enhanced humans that are stronger, faster and more deadly than normal. Imagine a disease targeted at a regional staple crop, such as rice or wheat, and the ensuing regional destabilization and the world-stress on economic and agricultural markets that a disaster such as this would create.

**End Notes**

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