

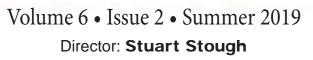
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TRANSFORMING MILITARY MEDICINE WITH 3D-PRINTED BIOELECTRONICS



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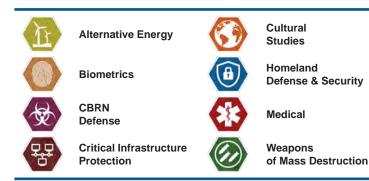
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ON THE COVER

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HDIAC



Stuart Stough HDIAC Director

The Homeland Defense & Security Information Analysis Center (HDIAC) works to support Department of Defense (DoD) research and development (R&D), science and technology (S&T), and scientific and technical information requirements. In support of this mission, HDIAC continuously looks for ways to enhance networking efforts within the DoD community and engage with communities of interest (COIs) and communities of practice (COPs).

In recent months, HDIAC staff and Subject Matter Experts (SMEs) exhibited/presented at several conferences, providing opportunities to engage and develop relationships with COIs and COPs. At the 2019 Operational Medicine Symposium, HDIAC interacted with members of the Biomedcal COI and SME Randy Alley delivered a presentation on innovative attachment systems for improved performance of prosthetics and exoskeletons. And while attending the Border Security Expo, the AFCEA Homeland Security Conference, and the NCT USA 2019 CBRNe Conference, HDIAC engaged in technical discussions with members of the CBRN COI and the Homeland Defense & Security and Weapons of Mass Destruction COPs.

As a result of discussions held at the Border Security Expo in San Antonio, Texas, HDIAC conducted a Technical Inquiry (TI) to support of a member of U.S. Border Patrol (DHS-CBP) in the Biometrics COP. In response to a DHS-CBP technical requirement, HDIAC analyzed emerging methodologies for heterogeneous data fusion across various border security sensors. HDIAC later conducted additional TIs for DHS-CBP on the topics of alternative energy solutions for field cameras and machine learning algorithms for data fusion.

In order to leverage the most relevant information and guidance when performing TIs and other projects, HDIAC invites individuals from relevant COIs/COPs to join our SME Network. Recently, HDIAC reached out to a valuable SME from the CBRN COI in order to gather information for a TI we completed for the U.S. Navy on end-user requirements for alarms respective to the different threat types (i.e., chemical versus biological). Additionally, Medical/CBRN SMEs Kyle Giesler and John Saindon have contributed to several Spotlight articles on microbiological weapons, countering antimicrobial resistance, and esketamine for the treatment of depression.

HDIAC also works to contribute to COIs/COPs through trainings on new and novel S&T and R&D. HDIAC invites members of COIs/COPs to attend monthly webinars where our SMEs present on topics across all of our eight focus areas. These webinars discuss new and developing technologies applicable to several COIs and COPs. For example, the HDIAC Webinar "Digital Twins for Defense Applications" discussed the ways in which the concept of the Digital Twin can be used to modernize and protect DoD's critical infrastructure. This webinar was of particular interest to the Critical Infrastructure Protection and HDS COPs. Notably, attendees of these webinars represent such organizations as NRL, AFOSR, USAMMDA, and DTRA. These webinars lead to valuable technical discussions and the initiation of TIs.

Message from the Director

HDIAC staff virtually attends webinars and trainings held by other agencies in order to stay abreast of emerging technologies and concerns among the COIs/COPs. In April, HDIAC staff watched the day-long Biodefense Summit held by the Assistant Secretary for Preparedness and Response. Featuring speakers from DHS, DHHS, DTRA, and NSC, this webinar provided HDIAC with valuable information on how the biodefense community informs national enterprise efforts to counter biological threats and prevent, prepare for, respond to, and recover from biological incidents. Additionally, HDIAC staff joined the livestream of the U.S. Army Training and Doctrine Command's Mad Scientist Conference, hosted by the University of Texas at Austin. Speakers discussed the potential impact of AI on future warfare, the use of robots in disaster response/recovery, developing human-robot trust, and space traffic management and situational awareness. The information leveraged from this conference will be useful in further engagements with the Space COI and the HDS and Cultural Studies COPs.

Finally, in order to maintain constant contact and engage with leading organizations and members of COIs/COPs, HDIAC has built a sizable social media presence. Through daily posts of original content, news items, and announcements, HDIAC provides COI/COP followers a resourceful social feed applicable to numerous interests.

HDIAC will continue to engage and leverage expertise from our SME Network and external members of COIs and COPs. These valuable relationships allow HDIAC to deliver highquality support to the DoD and the warfighter.

If you have expertise in one of our focus areas and would like to help HDIAC support the DoD, please apply to join our SME Network at: www.hdiac.org/sme_network/

FOR LIGHTWEIGHT VEHICLES AND POWERED BODY ARMOR

RUCEUCE:

Anish Patel & Jodie Lutkenhaus

Modern aircraft and ground vehicles rely on traditional power and energy storage devices. Due to their high mass and volume requirements, these systems can limit the effectiveness and range of Department of Defense (DoD) vehicles and other assets. Structural energy and power systems-those that act as both the structural support and the energy storage device through the use of multifunctional materials-offer a unique strategy for reducing the mass or volume of traditional systems by simultaneously managing energy storage and mechanical stress. The concept centers on combining the performance of structural composites with batteries and supercapacitors [1-3]. This bears

specific relevance to DoD in that structural energy storage could reduce mass in cube satellites and aircraft, for example, allowing for the maximization of propulsion resources (see Figure 1a).

Additionally, mechanically robust supercapacitors and batteries may be able to resist damage from micrometeoroids and orbital debris, high-velocity ballistic impacts, unexpected collisions, and explosions—providing enhanced safety for vehicles and their occupants. The U.S. Army Research Laboratory has long been interested in developing structural composites with battery functionality to improve battery efficiency while reducing weight and volume [4]. Furthermore, when fabricated to the form factor of body armor, structural energy and power systems may provide the warfighter with ballistic protection and electrical power simultaneously. Such a technology would be integral in aiding the development of the future Special Forces hyper-enabled operator [5].

However, the major challenge to developing structural energy materials is that an inherent trade-off exists between mechanical and electrochemical performance [1]. For example, improvements in mechanical properties come at the cost of losses in electrochemical performance, and vice versa. This article first provides a brief overview of materials for structural energy and power, as well as a discussion of the metrics used to describe this multifunctional concept. Then, we will focus specifically on the use of reduced graphene oxide nanosheets and Kevlar nanofibers as key enablers of novel structural energy and power systems.

Background

Batteries and supercapacitors, two common devices used to provide energy and power, are comprised of two electrodes, an electrolyte, and a separator (see Figures 1b-c). The electrodes allow redox reactions to occur in batteries or to create electrostatic charge separation in supercapacitors. The electrolyte facilitates ion transport between the electrodes, and the separator prevents direct electrical contact between the two electrodes—an important component of battery safety. Typical battery electrode materials, such as lithium cobalt oxide (LiCoO₂), lithium manganese oxide (LiMn₂O₄), and lithium iron phosphate (LiFePO₄), are poor candidates for structural electrodes due to their brittle nature. Carbon aerogel, a common supercapacitor electrode material, also pos-

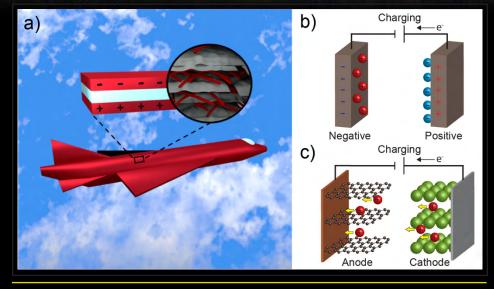


Figure 1. a) Conceptual design for structural energy and power systems as outer paneling of a plane [6] and schematic representations of a b) battery and c) supercapacitor

sesses poor mechanical properties, having a strength of 0.15 MPa and a Young's modulus of 2.8 MPa [7]. Poly(ethylene oxide)-based solid electrolytes have low mechanical properties (Young's modulus of 0.36 GPa) [8]. Common separators also have low moduli; for example, poly(propylene) separators have a Young's modulus of only 430 MPa and a strength of 14.2 MPa [9]. Clearly, typical energy storage materials do not possess the sufficient mechanical properties required for structural energy and power.

Previous work on structural energy storage by the Wetzel [1, 2], Greenhalgh [3], Pint [10], and Asp [11] groups has focused on using carbon fibers as a multifunctional electrode material. These electrodes typically possess good mechanical properties (Young's modulus of 41 GPa), but have exhibited a low capacitance of 93 mF g⁻¹ [2]. Carbon nanotube-based structural electrodes produced by the Pint group faced a similar trend, as the Young's modulus was 6.2 GPa but the capacitance was 16 mF g⁻¹ [10]. These previous studies prioritized mechanical performance over energy storage. The aforementioned carbon-based materials have exhibited good mechanical properties thus far, but improvements in energy storage performance are still needed.

While much attention has been placed on structural electrodes, structural electrolyte/ separator reports by the Lutkenhaus [12], Veith [13], Yang [14], and Shaffer [15] groups have described promising materials that conduct ions and withstand mechanical forces or impact. For example, the Lutkenhaus group developed a shear-thickening electrolyte consisting of anisotropic silica nanorods [12], and the Veith group used nonfumed, monodisperse silica [13]. Yang demonstrated poly(vinylidene fluoride) and palygorskite ((Mg,Al)₂Si₄O₁₀(OH)) nanowire composites that showed a Young's modulus of 96 MPa and strength of 1.5 MPa [14]. Finally, Shaffer used glass fiber fabric in ionic liquid-based epoxy matrices as structural separators in structural supercapacitors that exhibited a shear modulus of 895 MPa and a shear strength of 8.71 MPa [15].

Multifunctional Efficiency

A notable result from prior work was the emergence of a multifunctional efficiency metric (equations 1–3) for assessing the structural energy materials' ability to reduce mass without sacrificing energy storage ca-

pabilities [1]. This is described by the multifunctional efficiency, η_{mf} , which is the sum of the energy and structural contributions, η_e and η_e respectively:

$$\eta_{mf} \equiv \eta_e + \eta_s > 1 \qquad (1)$$
$$\eta_e = \frac{\overline{\Gamma}_{mf}}{\overline{\Gamma}} \qquad (2)$$

$$\eta_s = \frac{\overline{E}_{mf}}{\overline{E}} \text{ or } \eta_s = \frac{\overline{UTS}_{mf}}{\overline{UTS}}$$
 (3)

where $\overline{\Gamma}_{mf}$, \overline{E}_{mf} , and \overline{UTS}_{mf} are the specific energy, specific Young's modulus, and specific ultimate tensile strength, respectively, of the multifunctional material. Similarly, $\overline{\Gamma}$, \overline{E} , and \overline{UTS} are the specific energy, specific Young's modulus, and specific ultimate tensile strength, respectively, of a traditional energy or structural material. When η_{mf} is greater than unity, the system is considered to deliver energy at a mass savings [1].

The Lutkenhaus group proposed an alternative selection criterion that allows the user to weight the structural energy and power material according to a specific project's need. This is described as the utility (U), equations 4–6 [16]:

$$U = (1 - a)ECU + (a)MU$$
(4)

$$ECU = \frac{1}{n} \sum_{i=1}^{n} \frac{C_{mf}(v_i)}{C(v_i)}$$
(5)

$$MU = \frac{1}{4} \left(\frac{\sigma_{mf}}{\sigma} + \frac{E_{mf}}{E} + \frac{\varepsilon_{mf}}{\varepsilon} + \frac{T_{mf}}{T} \right)$$
(6)

where *ECU* is electrochemical utility, *MU* is mechanical utility, and *a* is a weighting coefficient that varies from 0 to 1 (0 prioritizes electrochemical performance and 1 prioritizes mechanical properties). C_{mf} is specific capacitance or capacity at different scan rates or current densities v, σ_{mf} is the ultimate tensile strength, E_{mf} is the Young's modulus, ε_{mf} is the ultimate strain, and T_{mf} is the toughness of the multifunctional material. *C*, σ , *E*, ε , and *T* are the capacitance or capacity, strength, Young's modulus, ultimate strain, and toughness, respectively, of a traditional energy or structural materials.

The benefit of this approach is that it can be tailored to specific applications using the weighting coefficient *a*. For example, a multifunctional material can be designed to withstand significant mechanical stresses while providing a small amount of energy storage for replacing vehicle paneling or support by biasing *a* toward 1. This metric also accounts for rate capability and several other mechanical properties simultaneously. The utility equation can be easily modified to add or remove terms to suit the user's needs. However, while utility can compare the ability of materials to effectively deliver energy and act as a structural support, it cannot supply a condition that would indicate mass-savings as with η_{mf} [1]. Another option is to use a multifunctional metric that is multiplicative rather than summative [17].

Composite Systems

One potential method to fabricate structural electrodes with greater energy storage capabilities is to use composite systems. Aramid nanofibers (ANFs), a recently discovered nanoscale building block derived from Kevlar fibers, are an ideal filler candidate for mechanical reinforcement [18]. Kevlar fibers are popular for their use in bulletproof vests because of Kevlar's high Young's modulus and tensile strength of 129 GPa and 4.1 GPa, respectively [19].

In addition, ANFs are easily fabricated through the dissolution of Kevlar in dimethyl sulfoxide and potassium hydroxide via deprotonation of the amide groups. These desirable properties have led to a surge in the production of mechanically robust composite materials using ANFs, making them a natural choice for structural energy materials.

Our team has focused on developing structural supercapacitors electrodes based on reduced graphene oxide (rGO) and ANF composites using experiments [6, 20, 21] and computation [16, 22]. rGO nanosheets are related to graphene, a single-layered sheet of sp²-hybridized carbon. Oxidizing the parent material, graphite, into graphene oxide with various oxygen-containing functional groups (epoxy, hydroxyl, and carboxyl groups) disrupts the sp²-hybridization and allows for easier processing of the sheets which are otherwise prone to agglomeration.

Graphene oxide nanosheets may be reduced using chemical, thermal, or electrochemical means to partially restore the sp²-hybridization and yield rGO nanosheets [23]. rGO was chosen due to its excellent electrical properties, promising mechanical properties, and ease of processing [24, 25]. Also, rGO nanosheets are capable of noncovalent interactions, such as hydrogen bonding and π - π stacking, which lead to enhanced mechanical properties for the rGO/ ANF composite electrode.

RGO/ANF Structural Electrodes

Vacuum-assisted self-assembly of rGO and ANF dispersions was used to fabricate the composite, free-standing electrodes with a brick-and-mortar morphology (see Figure 2a) [20]. The incorporation of ANFs led to a dramatic increase in the mechanical properties. Tensile stress-strain curves in Figure 2b show that Young's modulus increased by ~350% (from 3.7 GPa to 13.0 GPa) and tensile strength increased by ~290% (from 34.4 MPa to 100.6 MPa) when 25 wt% ANF was added to rGO. This massive increase was attributed to the noncovalent interactions between the rGO sheets and the ANFs. As for the supercapacitor performance, small amounts of ANFs slightly improved the rate capability of the electrodes due to promoting rGO sheet separation, leading to more facile ion diffusion. However, the specific capacitance of the electrode decreased with the introduction of ANF, which is electrochemically inactive. Cyclic voltammetry curves are displayed in Figure 2c. Despite this decrease in capacitance, the rGO/ANF electrodes possessed an excellent η_{mf} of 3.2 (modulus-based) and 1.5 (strength-based) for 25 wt% ANF electrodes when compared against carbon aerogels and epoxy.

Micromechanics Modelling

Along with experimental investigations, computational methods were also used to study rGO/ANF electrodes. Using the Mori-Tanaka method, Boyd and Lagoudas developed a model to capture the effects of rGO nanosheet and ANF waviness on the mechanical properties of the overall composite [22]. Waviness describes the conformation of the nanomaterials, as it is known that they are not perfectly flat or straight. The flowchart for the modelling depicted in Figure 3 shows how the nanomaterials were modelled individually and then combined into a real volume element that described the composite. This model identified the significant influence of rGO and ANF waviness on the elastic modulus of the composite electrode, with increased waviness resulting in lower modulus. Accordingly, the rGO nanosheets and ANFs should be as flat or straight as possible to maximize the mechanical properties.

Interfacial Engineering

Recognizing that interfacial interactions between the rGO nanosheets and ANFs play a major role in the success of previously

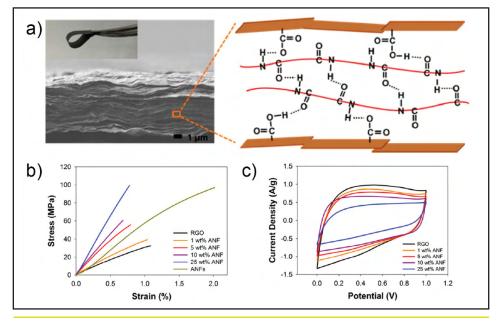


Figure 2. a) Cross-sectional SEM image of rGO/ANF electrode with inset image shows electrode under bending and schematic of brick-and-mortar morphology and interaction of rGO sheets and ANFs through hydrogen bonding. b) Stress-strain curves and c) cyclic voltammetry curves for rGO/ANF composites [20]. Reproduced with permission. Copyright 2017 American Chemical Society.

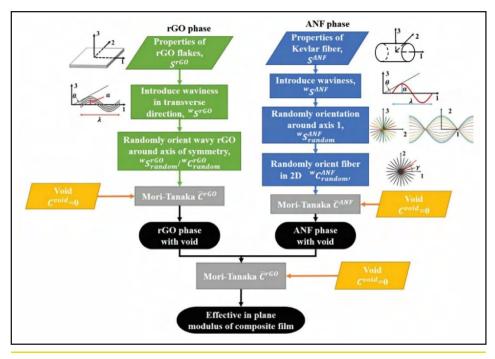


Figure 3. Flowchart for micro-mechanical modeling of rGO/ANF electrodes [22]

developed structural electrodes, the Lutkenhaus group explored enhancing these interactions through functionalization of the rGO nanosheets with carboxylic acid (-COOH) or amine (-NH₂) groups [6]. The functionalized rGO nanosheets were then combined with ANFs using vacuum-assisted self-assembly to obtain electrodes. The Young's modulus and strength increased because of the additional hydrogen bonding provided by the -COOH and -NH₂ groups, with the -NH₂ functionalization showing the greatest enhancement. Specifically, the Young's modulus increased by 18% (from 9.9 GPa to 12.2 GPa), and the strength increased by 24% (from 79 MPa to 98 MPa) for 25 wt% ANF electrodes containing $-NH_2$ functionalized rGO nanosheets. However, the electrochemical performance decreased with functionalization due to the introduction of defects in the sp² carbon network. Fortunately, the functionalized rGO/ANF electrodes showed



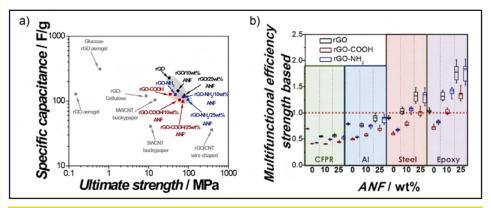


Figure 4. a) Ashby plot comparing specific capacitance versus ultimate strength for various electrodes and rGO/ANF composites. b) η_{mf} (strength-based) based on carbon aerogels and either carbon fiber reinforced epoxy (green), aluminum (blue), steel (red), and epoxy (purple) [6]

an excellent combination of mechanical and electrochemical properties as compared to similar materials (see Figure 4a). The electrodes exhibited a high η_{mf} , indicating potential mass-savings for replacing steel and epoxy (see Figure 4b).

Materials Informatics Analysis

Data science was also applied to this work using materials informatics analysis [16]. As opposed to traditional computational modelling, materials informatics does not use physics-based modelling, but instead uses previous data to predict properties and performance. The benefit of materials informatics is that it reduces the number of experiments and cost required to identify a global optimum in structural energy and power materials performance.

Lutkenhaus and Arróyave specifically examined rGO, ANF, and carbon nanotube (CNT) composite electrodes. CNTs were added to improve electronic conductivity between rGO nanosheets [26]. Materials informatics was used to guide experimental design toward an optimal combination of the three components by suggesting the next experiment to execute. After performing the suggested experiment, the new data were added to the model to obtain a new suggested experimental condition. Using this data science approach, an optimal composition (with a 78.8% increase to Young's modulus and a 34.0% increase to strength relative to the initial data set) was identified in only six iterations.

Research Summary

Summarizing the work on rGO/ANF structural energy and power electrodes for supercapacitors, it is generally shown that these electrodes exhibited excellent η_{mf} . The rGO/ ANF composite electrodes exhibited a higher capacitance but lower modulus as compared to carbon fibers. Chemical functionalization of the rGO nanosheets improved the mechanical properties by providing non-covalent interactions with the ANFs. However. functionalization yielded drops in electrochemical performance due to defects in the graphene's sp² carbon network. Further, addition of ANFs might enhance mechanical properties, but ANFs ultimately dilute the electrochemically active components. Accordingly, computational modeling was applied to understand further routes to improve the performance by physics-based modeling of the waviness of the nanomaterials or by data science to determine an optimal electrode composition.

Future Research and Potential DoD Applications

Despite significant strides toward viable structural energy and power materials, the ultimate challenge still remains: finding the right balance amid the trade-off between mechanical and electrochemical performance. To meet this challenge, comprehensive physics-based models that holistically capture mechanoelectrochemical response are needed. Also, the complex interactions between energy storage and mechanical stress must be deduced using in situ mechanoelectrochemical testing. Finally, the role of the interphase and the interactions between rGO nanosheets and ANFs should be elucidated so that interphase might be engineered without reduction in electrochemical performance.

Components that act as both batteries and structural panels hold great promise for high-value DoD applications. For example, DoD could incorporate this technology into ground and aerial vehicles to increase power storage without increasing mass or volume of the vehicle, or to increase operational range. This would allow additional energy for onboard devices or for propulsion in electric vehicles. The technology could also be used to reduce the mass and volume of the vehicle while maintaining energy storage, resulting in higher fuel efficiency and smaller footprints. This is particularly pertinent in applications where mass or volume are highly valued, such as satellites, unmanned aerial vehicles, and powered protective vests for the warfighter [27].

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ANALYTICAL

OF STRESS ODORS FROM HUMAN BREATH

George Preti, Pamela Dalton, & Christopher Maute

Chemical analysis of human breath, bodily secretions, and odor signatures is an emerging focus of the biometrics and human systems research communities. As the Air Force Office of Scientific Research has noted, sweat and breath in particular are leading candidates for the development of novel biomarkers useful in multiple mission sets, in both cooperative and non-cooperative settings [1].

Our laboratories are currently investigating the change in volatile organic compounds (VOCs) from the oral cavity when participants are in different states of psychological arousal and emotional states, with the goal of identifying a set of VOCs as a biometric reliably associated with stress in individuals. To date, our findings demonstrate that states of psychological arousal reliably change the volatile organic compound (VOC) or biometric chemical signatures that are produced in both breath and bodily secretions. The ability to rapidly and non-invasively detect whether an individual is psychologically stressed could provide numerous analytical and operational benefits to the Department of Defense (DoD) and federal agencies charged with homeland defense missions.

Sensor-driven instrumentation for the detection and identification of stressed individuals from VOC signatures could advance DoD capabilities in several areas. One, VOC sensors calibrated to detect stress compounds could facilitate the detection and identification of stressed (and potentially dangerous) individuals at entry points to critical facilities, complementing or improving current methods of (a) flagging potential false

utterances via thermal infrared imaging [2, 3] or (b) observing and interpreting behavioral indicators of stress and duplicity. Two, odors from human breath could be used to complement other biometric characteristics in continuous identity authentication systems [4]. Three, physiological measures of psychological stress levels could advance the medical monitoring of warfighters. Current means rely on self-reporting of stress severity, which can vary across contexts and time (and can return undependable data in a culture where individuals are trained to compete for optimal performance) [5, 6], and semi-invasive physiological testing methods [7].

Background

The Stress Response and Stress Odors

Animal models have demonstrated that a state of stress produces a distinctive odor [8, 9] that can be detected by conspecifics and affect the behavior and physiology of recipients [10–14]. Research conducted by our laboratories and others has demonstrated that this is also true for humans, with evidence for the ability to discriminate stress from non-stress body odor and for



stress sweat to have an effect on task performance and brain activity.

Stress-related odors are thought to arise from an increased production of body odorants mediated by increases in stress-related hormones. However, the chemical identity of these odorants has not been determined. In humans, the autonomic nervous system (ANS) is responsible for producing a stress response triggered by the hypothalamus, sending hormonal signals to the pituitary and adrenal glands. Characteristic physiological changes that ensue include:

- increased heart rate
- increased blood supply
- decreased salivary flow
- increased secretions from eccrine and apocrine sweat glands

These changes are thought to occur as a result of the increased production of stress-related hormones, such as epinephrine (adrenaline) and cortisol, and their effect on odor-producing body structures, such as eccrine and apocrine glands found in the underarm [15] and salivary glands in the mouth.

To experimentally induce psychological

stress, we employed a standard laboratory stress task, known as the Trier Social Stress Test (TSST) [16, 17]. In this test, subjects are required to engage in a public speaking task and a mental subtraction task while being observed and evaluated. The test has been widely validated and shown to produce reliable increases in heart rate, skin conductance response, and stress hormones—allowing us to collect samples that can be reliably paired with physiological indices of stress.

Underarm Odor

Studies focusing on human underarm sweat have shown that sweat sampled from a cohort of donors while experiencing a form of psychological stress can change the task performance [18–25] and brain activity [26–29] of a separate set of participants who are exposed to this "stress sweat" as an odor stimulus, as compared against a control stimulus (neutral, baseline, or mechanical, exercise-induced sweat). Exposure to stress sweat has been demonstrated to affect a wide range of behaviors, including:

 changing perceived competence, confidence, and trustworthiness of women [18]

- potentiating the startle reflex [19, 23]
- modulating fear recognition in faces
 [20]
- inducing empathy [21] and anxiety
 [24] in the participants who are exposed to the sweat

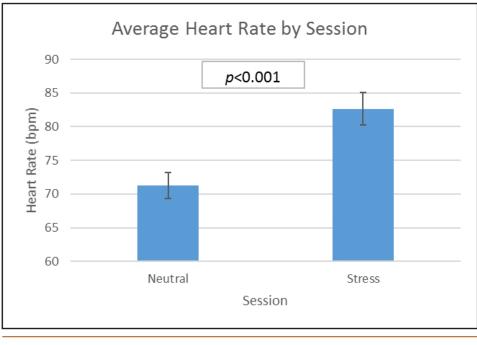
The neurological underpinnings of the effect of smelling stress sweat have also been explored in depth [27], with studies showing its effect on the neural processing of neutral faces [29] as well as activation of the amygdala [26].

Most of these studies align with research, extending from the animal models mentioned above, that is focused on chemical communication between conspecifics of emotional states via "chemosignals" embedded in the VOCs which constitute our body odor [25, 30–32]. Taken together, these studies demonstrate that there are compositional differences between stress sweat samples and control samples collected under non-stressed/normal conditions.

Our own laboratories have demonstrated that human evaluators can reliably discriminate stress sweat from non-stress sweat [33]. Eighteen donor participants (13 male and five female) engaged in a washout

| Compound | Proposed Origin | | |
|---------------------------|---|--|--|
| Acetone: | carbohydrate metabolism and lipid oxidation | | |
| Isoprene: | suggested link to cholesterol biosynthesis (also from plants) | | |
| Dimethylsulfide: | microbiome and human metabolism-related,* sulfur-containing amino acid derived (e.g. methionine | | |
| Dimethyldisulfide: | microbiome-related*, sulfur-containing amino acids | | |
| Acetoin: | carbohydrate metabolism | | |
| Dimethyltrisulfide: | microbiome-related,* derived from sulfur-containing amino acids | | |
| 1-Octen-3-ol: | microbiome-related and lipid oxidation | | |
| 6-Methyl-5-hepten-2-one: | lipid oxidation from ROS | | |
| Furfural: | found in a variety of human body fluids but origin most likely from foods | | |
| Acetic Acid: | microbiome-related, amino acid/albumin metabolism | | |
| Butyric Acid: | microbiome-related, amino acid/albumin metabolism | | |
| Isovaleric Acid: | microbiome-related, leucine metabolism | | |
| 3-Methylbutyric Acid: | microbiome-related, isoleucine metabolism | | |
| Hexanoic Acid: | human and microbial metabolism of unsaturated lipids | | |
| Diacetylglycerol: | carbohydrate metabolism | | |
| Cresol: | human and microbial metabolism of the aromatic amino acid tyrosine | | |
| Benzoic acid: | human metabolism of phenylalanine; also food derived | | |
| Indole: | human and microbial metabolism of the amino acid tryptophan (microbiome-related*) | | |
| Skatole (3-methylindole): | human and microbial metabolism of tryptophan (microbiome-related*) | | |

Table 1. Compounds analyzed in breath and their proposed origins.* Indicates microbiome-related odors removed from analysis





week—using only unfragranced soaps and prohibiting colognes or fragranced products. This continued during the collection of underarm samples before and after both a neutral and stress manipulation task.

These samples were pooled together and presented in a counterbalanced manner to a separate cohort of evaluator participants, screened for olfactory sensitivity, in a three-alternative forced-choice (i.e., triangle test) method in which two samples were the same and one was different.

We evaluated participants' ability to detect the "different" sample when comparing various combinations of the following sweat samples:

- pre-neutral
- post-neutral
- pre-stress
- post-stress

A Chi-Square analysis revealed that although no differences were seen when comparing the pre- and post-neutral session samples, χ^2 (2, *N*=18) = 2.03, p=0.36, statistically significant differences were seen both when looking at post-neutral and post-stress samples, χ^2 (2, *N*=18) = 52.08, p<0.001, and pre- and post-stress samples, χ^2 (2, *N*=18) = 15.44, p<0.001. This is compelling evidence that humans can detect a difference when comparing stress-sweat samples with samples collected under non-stressed conditions. Unfortunately, few of these studies include a chemical analysis of the sweat samples, leaving open the question of which VOCs are changing in the sweat from one state of arousal to another. The unique combination of expertise in our studies allows us to investigate both the psychological and physiological markers of stress and the analytical evidence of changes in the VOCs emitted.

Breath and Saliva

With support from the Air Force Office of Scientific Research, our laboratories have worked towards finding biomarkers for psychological stress that are reliable and more accessible than underarm sweat samples. We focused on the oral cavity, which provides two abundant and easy-to-collect samples to be used for chemical analysis: breath and saliva.

Previous research using human subjects has demonstrated that stress-related hormonal changes from either physiological [34] or psychological stress [35] create alterations in the oral cavity—perhaps tied to alterations in salivary flow and composition—which consequently upregulate production of specific VOCs, such as volatile sulfur compounds, and possibly oxygenated compounds related to oxidative stress. Based on these previous results, we hypothesized that analysis of expired breath and saliva would yield VOCs characteristic of stress states.

To test our hypothesis, we collected breath and saliva samples from human subjects before and after inducing psychological stress with the TSST.

Method

Participants began the study by taking part in three to five days of an oral "washout" period during which they used a laboratory-provided, non-flavored toothpaste; refrained from using mouthwash; and maintained a bland diet devoid of foods that contribute to oral odors (e.g., garlic, onions, curries). Participants then came in for two sessions of testing, on separate days, while maintaining their oral washout regimen.

The sessions started with a collection of saliva and breath samples before the recording of baseline physiological measures (e.g., heart rate). Participants were then either presented with a 15-minute DVD of cinematic landscape videos (neutral session), or the TSST (stress session). Physiological measures were collected throughout the manipulations (both neutral and stress sessions) with breath and saliva samples collected after each manipulation.

From this dataset, we did a manipulation check with an analysis on heart rate change from baseline—a solid indicator of stress as a byproduct of adrenaline release—and excluded any participant whose heart rate did not increase from baseline during the stress session. This ensured that samples collected from these individuals were not included in the chemical analysis, thereby guaranteeing that all samples used for analysis were from quantifiably stressed individuals. This left us with a pool of 46 participants (27 female and 19 male), with an average age of 26.9 years.

Participants provided breath samples by blowing into a 1L ALTEF polypropylene bag (Restek, Bellefonte, PA) until filled, and saliva samples by chewing unflavored gum base (Wrigley Company, Chicago, IL) and expectorating saliva into a 20 ml tube at one-minute intervals for three minutes. VOCs for each breath sample were collected using solid-phase micro-extraction (SPME), then separated and analyzed by gas chromatography–mass spectrometry (GC/MS).

VOCs from each saliva sample were collected after incubating a 1 ml aliquot of each sample for 30 minutes, via magnetic stirring, at 37 degrees Celsius in a 4 ml glass vial fitted with a silicone/tetrafluoroethylene septum-containing screw cap to enhance the headspace VOC content. A SPME fiber was then inserted into the vial and VOCs collected for 30 minutes, followed by injection into the GC/MS for separation and identification. A variety of compounds were identified (see Table 1) and their relative amounts were manually calculated prior to statistical analyses.

Results

Stress Manipulation

As a check for the stress manipulation, we looked at heart rate as an indication of stress during both the neutral and stress manipulations. As Figure 1 indicates, participants experienced a significantly higher heart rate during the stress session than during the neutral session.

VOC Analysis

Several of the compounds listed in Table 1 were clearly seen in selected individuals but not in others (e.g., skatole, dimethyl di-, and dimethy trisulfide), and were not included in our analyses; we made the assumption that these compounds were derived from the tongue microbiome and associated with putative breath odor problems.

For the remaining compounds, a repeated-analysis of variance (ANOVA) of the breath samples demonstrated that the concentration of these compounds in poststress samples was significantly greater than pre-neutral samples (p < 0.05). Post-hoc analysis (Bonferroni corrected) showed that this difference is mainly driven by acetone (p < 0.001) and isoprene (p < 0.05).

When we further examined each of the individual VOCs using ANOVA, three of the volatiles showed a statistically significant difference from pre-neutral to post-stress at the 0.05 alpha level: acetone and isoprene (as predicted and demonstrated by the above post-hoc analysis), as well as dimethyl sulfide (see Table 2). While this suggests dimethyl sulfide as a putative stress biomarker, more testing is required for a definitive confirmation. In contrast, salivary levels of these compounds were not significantly altered, suggesting a nonsalivary origin.

VOCs and Physiological Measures

We next examined the relationships between the VOCs that were significantly altered by stress and subjects' physiological stress measures. As shown in Figure 2, acetone was positively correlated with heart rate, p < 0.05, but not with post-stress cortisol measures, whereas both isoprene (p < 0.05) and diemthylsulfide (p < 0.05) showed significant positive correlations with post-stress cortisol measures as seen in Figures 3 and 4 (respectively), but not with heart rate.

Conclusions

Physiological changes documented in our subjects demonstrated that the stress in-

| | Pre-Neutral | Post Stress | p |
|------------------|-------------|-------------|-------|
| Acetone | 0.698 | 1.035 | <0.01 |
| Isoprene | 0.644 | 0.789 | <0.05 |
| Dimethyl sulfide | 0.038 | 0.047 | <0.01 |

Table 2. Results of ANOVA for three breath VOCs

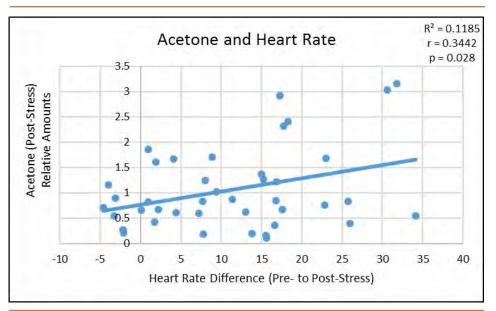


Figure 2. Significant positive correlation between relative amounts of Acetone in breath, poststress, and heart rate difference from baseline to post-stress duction was effective. Analytically, three volatile organic compounds found in breath were found to be significantly elevated by stress: acetone, isoprene, and dimethylsulfide. In contrast, the concentration of these compounds was not significantly elevated in saliva. This suggests that these compounds are not formed in saliva, but are produced by changes in metabolic processes in either the kidneys or liver. Dimethylsulfide may also originate from the oral microbiome, but it is unlikely that a single episode of psychological stress would affect this.

The data show that the breath-borne biomarkers which increase significantly with stress may not all be dependent on the same aspects of the stress response. Increased heart rate was correlated with acetone and is part of the "fast, short term stress response" (also known as the fight-or-flight response) associated with a release of adrenalin/epinephrine. Release of epinephrine also causes the liver to release glucose, which in turn may account for the significant increase in breath acetone. Longer-term stress response is associated with cortisol release, which our data show are correlated with dimethylsulfide and isoprene.

Although our preliminary data show promise, further research on the reliability of these compounds to predict and indicate individual states of psychological stress are needed to realize the ability to identify a psychologically stressed and potentially dangerous suspect or target or to monitor warfighters' stress levels. Once a set of compounds are established as reliable indicators of stress, they may be transitioned into nano-enabled sensor systems fitted to the face masks of pilots or headset-microphones of deployed ground personnel [36-37]. These sensor systems, calibrated to detect the presence and concentration of stress-related VOCs in exhaled breath, could provide real-time, non-invasive individual monitoring of physiological status

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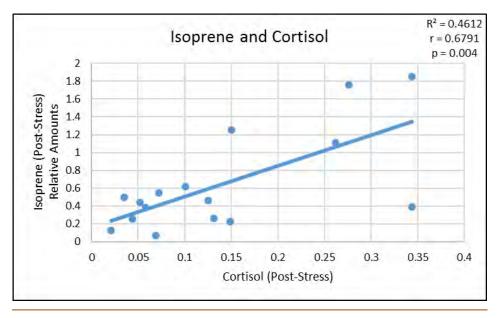


Figure 3. Significant positive correlation between relative amounts of Isoprene in breath, poststress, and post-stress cortisol levels

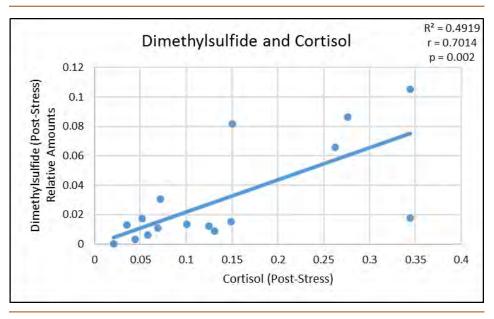


Figure 4. Significant positive correlation between relative amounts of Dimethylsulfide in breath, post-stress, and post-stress cortisol levels

to allow for continuous evaluation of warfighter stress. In addition, sensors systems calibrated to detect stress may be fitted to hand-held devices that could be employed by personnel at critical points of entry or secured buildings to detect stressed or deceptive individuals. This technology could deliver a significant improvement to the "suspicious individual" detection methods currently used that rely primarily on a set of behavioral indicators to identify persons who may pose a security risk.

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Preservation of Health Care Assets During a Biological Incident

John M. Saindon, Trenton C. Elliott, & Kyle E. Giesler

The preparedness and adaptability of our public health infrastructure is critical in the event of a biological incident (i.e., bioterrorism) [1, 2]. Unfortunately, many health care facilities and administrators have acquired a sense of complacency and are inadequately prepared to deal with the reality of bioterrorism [3, 4].

To address these concerns, this article covers important considerations for hospitals and health care workers in the wake of a biological incident. These considerations are divided into three distinct phases: pre-incident preparedness, preservation of life and resources during an incident, and post-incident response.

Phase 1: Pre-Incident Preparedness

There is a possibility that the U.S. may encounter a threat pathogen (either nat-

ural or intentional) in the near future [5]. The number of fatalities during a biological incident depends not only on the nature and location of the threat, but also the ability to react and effectively treat the wounded [5].

Health care systems across the U.S. and all levels of government continuously engage in preparedness-based activities to minimize potential threats, safely treat victims, and minimize loss of life [6].

Infrastructure Preparedness: Hospital Accreditation

For health care facilities, preparedness against threats like bioterrorism begins with hospital accreditation. The largest independent non-profit health care accreditation organization in the U.S. is The Joint Commission (TJC), which accredits over 75% of hospitals and most Department of Defense health facilities [7, 8]. In order to receive federal funding, the Centers for Medicare and Medicaid require TJC accreditation. The accreditation program requires the successful implementation of more than 50 key points to ensure compliance, some of which are pertinent to bioterrorism, including:

1) Agreement with an Outside Blood Supplier

• An outside blood supplier ensures that hospitals can sustain life among multiple casualties during both normal operations and a potential crisis.

2) Infection Control Plan

• An infection control plan is essential for the day-to-day operation of any health care facility and is of critical importance during a communicable disease outbreak. Staff should be trained and adequately protected from an array of different pathogens. Patients should be properly isolated, and non-suspected patients should be protected from cross contamination.



3) Patient Flow Documentation

• This can include triage and isolation of suspected infected patients and separation from the general hospital (non-infected population).

4) Emergency Operations Plan (EOP) and Annual Evaluation

- Conduct a Hazard Vulnerability Analysis, as per standard EM.01.01.01, EM.03.01.01, to inform development of an EOP [7].
- EOP also includes proper staffing, logistics, triage, and the full spectrum of activities during emergency operations.

5) Emergency Management Drill Records and After-Action Reports

• These drills can be "all hazard" type of incidence and are good practice to test the hospital's incident management system in order to effectively identify recommendations for afteraction reports.

• Hospitals generally don't conduct emergency management drills on their own, but since it is a requirement for accreditation, hospitals are better positioned to conduct emergency readiness activities [5].

Federal Preparedness

Several laws grant the U.S. Health and Human Services (HHS) secretary national authorities in response to a potential biological threat. These laws include, but are not limited to, the Pandemic and All-Hazards Preparedness Act, the Public Readiness and Emergency Preparedness Act, and the Public Health Service Act [9].

If any of these emergency powers is invoked, the HHS secretary may enforce broad legal authorities to support federal, state, and local entities for declared or undeclared public health emergencies. Such actions include: 1) Implementing procedures to assist state and local governments to control epidemics and mitigate other medical emergency situations.

2) Allocating resources for research studies to better understand the etiology and medical counter measures (MCM) to treat or mitigate the spread of threat pathogens.

3) Establishing isolation and quarantine centers.

4) Authorizing the Food and Drug Administration (FDA) to temporarily allow usage of a medical device or treatment if the product can further prevent loss of life and alleviate suffering (Emergency Use Authorization).

Phase 2: During a Biological Incident

Indications of a Biological Incident

The national surveillance of infectious dis-

eases is paramount in controlling potential epidemics. Syndromic surveillance, or the collection of symptom and health-related data, aids in the early detection of patterns signaling a possible bioterrorism attack.

While this approach forms the backbone of the National Electronic Disease Surveillance System and the World Health Organization's Global Outbreak Alert and Response Network, reports of non-specific illnesses weaken the specificity of such systems [10].

It is often frontline health care professionals in clinics, emergency departments, and pharmacies that first encounter potential biological threats as an increased number of patients seek medical care. Therefore, it is critical that health care professionals recognize the various symptomatology of viral and bacterial infections-especially since non-specific symptoms (such as fever and malaise) are typically the initial presentation. Other clinical indications of a biological incident may include a rise in unexplained illnesses, a single incident of a rare pathogen (e.g., anthrax), and atypical routes of exposure. Several potential biological threats are listed in Table 1.

Once a potential threat has been identified, confirmatory testing is the next step to initiate the appropriate cascade of medical countermeasures. In the last decade, there have been tremendous advancements in sequencing technologies to permit rapid and accurate pathogen detection. Portable systems allow health care workers to diagnose and communicate results in a matter of hours. For example, a cartridge-based assay has been developed for tularemia and anthrax, while rapid antibody assays can now diagnosis Ebola and Lassa virus [11, 12]. At the initial point of care, blood, sputum, and nasal cultures should be sent for evaluation along with a complete panel of blood work.

Protection of Health Care Personnel

The protection of health care workers is of critical importance during a biological incident. Doctors, nurses, and other medical personnel are at serious risk of exposure and may unknowingly propagate the spread of infectious agents after contact with patients. Personal protective equipment (PPE) provides a reliable and immediate first line of defense to reduce the risk of exposure. PPE refers to clothing and respiratory devices that shield individuals from chemical, physical, or biological hazards. There are four tiers of PPE protection (A–D), with A conferring maximum protection, and D the least protection.

Most health care workers are familiar with Level D PPE (hospital gown, goggles, surgical mask, and latex gloves). Person-to-person transmission is exceedingly rare when Level D PPE guidelines are appropriately followed, and patients can be cared for without isolation units or specialized respiratory devices. However, Level D PPE is inappropriate for hemorrhagic viruses (Ebola, Marburg, Lassa, and Muchupo), smallpox virus, aerosolized pathogens, and, to a lesser extent, Y. pestis. Unless the agent can be unambiguously identified as non-life-threatening, Occupational Safety and Health Administration regulations call for Level B protection [13].

Level A protection is necessary for Ebola and requires fluid-resistant body suits, cover aprons, double gloves, shoe covers, and an air-purifying respirator [14]. These stringent guidelines were difficult to realize in Africa and led to the death of more than 300 health care workers during the Ebola outbreak of 2014 [15]. This example highlights how proper access to the appropriate level of PPE is essential to mitigate cross-contamination and preserve the lives of health care workers.

Vaccines are venerable MCMs that arguably confer the best protection against infectious diseases. Commercial vaccines are available for a wide array of viral and bacterial diseases including anthrax, smallpox, botulinum toxin, ricin, *Y. pestis, tularemia*, and Junin virus. No vaccines for hemorrhagic fevers have been licensed apart from yellow fever and Junin virus. However, a new vaccine for Ebola is under development that proved successful in the 2018 epidemic in the Democratic Republic of the Congo [16].

In contrast to PPE, vaccines have many pragmatic limitations that hinder their application during a biological incident. First, it is not standard practice to preemptively vaccinate health care workers or the general public against common biological agents used in warfare. According to the Centers for Disease Control and Prevention, routine smallpox vaccination stopped in 1972 after the disease was eradicated in the U.S. [17]. Second, vaccination demands knowledge of the pathogen prior to inoculation and an induction time is necessary to generate a robust antibody response. Third, some vaccines, such as the anthrax vaccine, require multiple shots and boosters on different days to confer protection.

U.S. Centers for Disease Control and Prevention Bioterrorist Agents and Associated Conditions

Bacteria

- Bacillus anthracis [anthrax]
- Clostridium botulinum (botulism)
- Brucella species (brucellosis)
- Burkholderia mallei (glanders)
- Burkholderia pseudomallei (melioidosis)
- Coxiella burnetii (Q fever)
- Escherichia coli 0157:H7 [haemolytic uramic syndrome]
- Francisella tularensis (tularemia)
- Salmonella species (salmonellosis)
- Shigella species (shigellosis)
- Vibro cholera [cholera]
- Yersing pestis (plague)

Viruses

- Arenavirus [Junin and Lassa Fever]
- Ebola virus
- [Ebola virus hemorrhagic fever]
- Lassa virus [Lassa fever]
- Marburg virus
- [Marburg virus hemorrhagic fever]
- Variola major (Smallpox)

Toxins

- Botulium toxin
- Ricin toxin

 Table 1. U.S. Centers for Disease Control and Prevention Bioterrorist Agents and Associated

 Conditions

When taken together, the urgency and uncertainty that surrounds a biological incident restricts the power of many vaccines to pre-exposure prophylaxis. These limitations are minimalized when vaccines are administered to health care workers and first responders before potential threats unfold. Of note, an effective post-exposure prophylaxis vaccine is available for smallpox when administered three or four days following exposure [18].

Vulnerable Populations

In the context of a public health emergency, children and the elderly constitute the largest vulnerable populations. Children have specific physiologic vulnerabilities, such as increased skin surface area and faster respiratory rate, metabolism, and cell division portending greater susceptibility to biological agents [19]. Various stages of behavioral development increases their risk for post-traumatic stress disorder (PTSD) and other acute stress disorders, while physical limitations can lead to various levels of dependency on adult care.

Both doxycycline and ciprofloxacin are relatively contraindicated in pregnant women and children under the age of twelve, and should only be administered if no other alternatives exist. With respect to the elderly, the disruption of key resources or services during an incident may have detrimental consequences to their overall health and impact their ability to respond to threats.

Phase 3: Post-Incident Response

Decontamination

Decontamination is of paramount importance in the wake of a biological incident. Most viruses and non-spore forming bacteria are sensitive to alcohols, bleach, ultraviolet light, and commercial disinfectants containing tetraalkylammonium salts. The versatility of alcohols has been somewhat compromised by their pervasive use, leading to a notable increase in resistance to ethanol and isopropanol in hospitals around the world [20].

In general, decontamination should occur as soon as possible to reduce potential exposure. Soapy water is advised for mass decontamination due to its abundant onsite availability and low potential for adverse reactions. Although diluted solutions of commercial bleach are also highly effective, bleach irritates mucous membranes and should not be used on open wounds. PPE can be sufficiently decontaminated with bleach without issues. Note that children and the elderly are more susceptible to hypothermia during decontamination and should be thermally insulated after exposure to cold water [21].

Critical Infrastructure Vulnerability Assessment

It is imperative that hospitals conduct frequent infrastructure vulnerability assessments to identify and address potential weaknesses, mitigate unnecessary human suffering, and execute proper management of limited supplies [22]. Examples of potential infrastructure vulnerabilities include:

1) Facility contamination

- 2) Limited communication capabilities
- 3) Security concerns (lack of perimeter protection, riots, etc.)
- 4) Lack of utilities such as clean water, electricity, and waste management
- 5) Lack of minimal staffing and logistics to sustain operations

Sustainment of Care and Continued Use of MCMs

Supportive treatment and assessment of airway, breathing, and circulatory systems remains the cornerstone for any biological incident given that many clinical presentations are non-specific. Rapid diagnosis of anthrax, botulism, and plague are paramount, as mortality can be prevented with timely administration of antibiotics, antisera, and/or vaccines. Working off a presumptive diagnosis and initiating prompt treatment is crucial as the prodrome phase of many biological agents is when treatment is most effective (Y. pestis is universally fatal if treatment is delayed by more than a day). At the time of this writing, doxycycline is generally effective against B. anthraces, Y. pestis, Brucella, Coxiella, and F. tularensis.

For certain viral infections, nucleoside analogues are highly effective MCMs that should be generously distributed post incident. Cidofovir was found to be more effective at preventing mortality in non-human primates infected with monkeypox virus than post-exposure vaccines—suggesting that antivirals may play an important role in mitigating a potential smallpox outbreak [23]. Although the FDA has yet to approve any antiviral agents for hemorrhagic viruses, GS-5734 is currently in clinical trials for the treatment of persistent Ebola virus [24].

The continued use of appropriate MCMs, such as vaccines, antivirals, and antibacterial agents, should be widely implemented for several days after an incident to prevent future manifestations of disease. Note that quarantine can be problematic for those with a suspected exposure, since the population would consist of both exposed and unexposed, thus potentially driving transmission [25].

Individuals that remain unexposed still have the potential to suffer from unrelated physical and behavioral ailments and health care providers must be prepared to address their psychological needs. A robust and proactive line of communication from public health and other government authorities is crucial to allay concerns and help mitigate mass panic. Such a traumatic event has the potential to trigger PTSD in survivors and unexposed alike, and access to behavioral health experts in the aftermath is important to debrief and process the event.

Conclusion

Hospitals and healthcare workers play a pivotal role in ensuring that preparedness protocols are properly followed and executed during a biological incident to reduce suffering, mitigate exposure, and preserve human life.

While the incidence rate of bioterrorism on U.S. soil is relatively low, preparedness exercises should be practiced regularly to swiftly counter a potential threat. Recent trends toward highly coordinated terrorist tactics significantly increase health care vulnerability to covert attacks and bolsters the need to ensure a top-notch preparedness program. This is a shared responsibility among healthcare administrators, communities, and all levels of government to promote homeland defense and preservation across the healthcare spectrum.

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Solar-Enabled Water Treatment in Resource Limited Settings

Young-Shin Jun, Deoukchen Ghim, Xuanhao Wu, Sisi Cao, & Srikanth Singamaneni

Assured access to clean and potable water remains a challenge across the globe. In 2018, the United Nations estimated that 1.8 billion people live in regions affected by water scarcity due to land degradation and drought, and more than 4 billion people lack access to safe sanitation [1]. This need is expected to become even more urgent, given current trends in population growth and the consequent need for increased food production [2].

The Department of Defense (DoD) is a major producer and consumer of clean water, both at home and abroad. In fiscal year 2017, DoD facilities and bases worldwide consumed a total of 82.5 billion gallons of potable water (i.e., water purchased from utilities and treated freshwater sources) [3]. However, domestic installations face increasing vulnerability to water scarcity. In July 2018, DoD reported that 21 homeland military installations are located in areas

under "severe" or "extreme" drought, as identified by the U.S. Drought Monitor of the National Drought Mitigation Center [3].

As the United Nations' global drought statistics indicate [1], providing clean and potable water to DoD forces abroad can be a challenge. A major study published in 2010 surveyed water provision to forward operating bases (FOBs) in Iraq and Afghanistan and found that a base camp size of 1,500 warfighters requires at least 13.6 million gallons of water annually—and potentially twice as much [4]. Many FOBs must be

Image Credit Photo illustration created by HDIAC and adapted from author photo and Adobe Stock.

supplied with potable water by transportation, which is costly and inefficient [4, 5]. Additionally, the many FOBs that lack wastewater treatment facilities must truck out their wastewater, and FOBs that have treatment facilities often rely on activated sludge processing—which is energy intensive [6].

In order to realize sustainable and effective FOBs, water supply and wastewater treatment methods should be dramatically improved. For these reasons, DoD has sought sustainable and energy-efficient wastewater treatment processes that require less frequent maintenance [7].

Photothermal Water Treatment

Photothermal water treatment has emerged as a promising technique to provide drinking water and increase the working life of pressure-driven membrane filtration. Photothermal materials in a membrane convert incident light, most typically sunlight, into heat by the photothermal effect. Incident photons excite electrons in the photothermal material, which then release their absorbed energy as heat and regain initial state. The locally high temperature produced can inhibit membrane biofouling-a main concern for pressure-driven membrane processes [8, 9]-and it can also promote effective evaporation for clean water generation.

Desirable photothermal membranes exhibit broad-band light absorption across the solar spectrum; have high photothermal conversion rates; and are readily scalable, cost effective, and low in environmental toxicity [10].

This article introduces three of our research group's recent developments in photothermal water treatment:

- fouling-resistant photothermal membranes in pressure-driven reverse osmosis (RO) and ultrafiltration (UF) systems
- photothermal solar steam generation (SSG) by interfacial evaporators
- photothermal membrane distillation (PMD)

In the anti-fouling membrane, the light-induced high temperature at the membrane surface damaged the cell walls of micro-

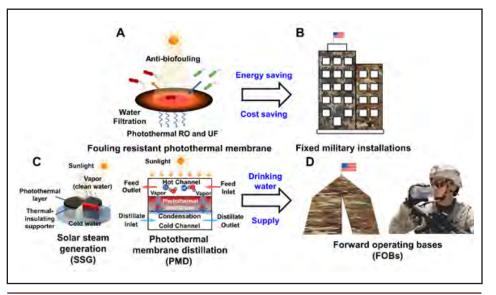


Figure 1. Possible photothermal membrane utilization in various DoD installations: (A) Fouling resistant photothermal reverse osmosis and ultrafiltration membrane. Reproduced with permission [16]. Copyright 2019 American Chemical Society. (B) Fixed military installation. (C) Photothermal solar steam generation and photothermal membrane distillation. Reproduced with permission [36]. Copyright 2017 Elsevier. (D) Forward operating bases.

organisms and subsequently inhibited the biofilm growth, which improved the membrane's durability and performance. In SSG, interfacial solar evaporators achieved high evaporation rates by using engineered nanostructures that are scalable and non-toxic. In PMD, simple and scalable polymeric photothermal materials have been optimized to treat even highly saline water.

Photothermally-enabled Biofouling Resistance in Membranes for Pressure-driven Filtration

Pressure-driven membrane filtration processes, such as RO and UF, are widely used in DoD installations, owing to their fast water production and large treatment capacities [4, 11]. However, membrane fouling is a persistent challenge in these processes, decreasing the energy efficiency and life span of the membrane, and increasing the cost of water treatment [12]. Among the various types of fouling, biofouling-microorganism sticking to membrane surfaces and forming biofilms-accounts for more than 45% of all membrane fouling and reduces the membrane performance significantly [13]. In the worst case, biofouling contributed to approximately 70% of transmembrane pressure increase in RO [14].

To combat biofouling, we first coupled the photothermal effect with pressure-driven

membrane filtration. A commercial polyamide (PA) membrane for RO was surface-modified with gold nanostars (AuNS), graphene oxide (GO), and hydrophilic polyethylene glycol (PEG) (see Figure 2B) [9].

GO nanosheets were employed as templates to grow AuNS in situ, and the AuNS was used to photothermally heat up the membrane surface, as their branched shape can be easily tuned to achieve maximum light absorption in solar spectrum. The localized surface plasmon resonance (LSPR) of AuNS, which involves the collective oscillation of dielectrically confined conduction electrons, can be tuned over the visible to near-infrared (NIR) wavelengths by optimizing the size and aspect ratio of the AuNS branches [15]. The excited electrons relax to ground state, releasing thermal energy (heat). Through photothermal conversion, the PA-GO-AuNS-PEG membrane achieved a locally high surface temperature (T= ~70°C) within one minute under 808 nm laser irradiation (see Figure 2C).

This localized heating effectively killed bacteria (e.g., *E. coli*) on membrane surfaces. In addition to its bactericidal property, the hydrophilic PEG coating on the PA membrane further reduced mineral scaling (CaSO₄ and CaCO₃) and organic fouling (humic acid), owing to the circumneutral charge and hydrophilic nature of PEG. The newly developed AuNS-GO-PEG-PA membrane reduced organic-, inorganic-, and

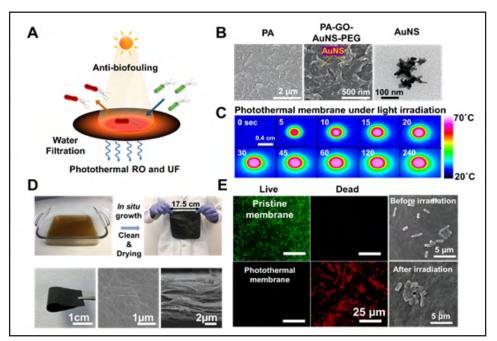


Figure 2. (A) Working principle of photothermal membrane with bio-fouling resistance. Reproduced with permission [16]. Copyright 2019 American Chemical Society. (B) SEM images of PA and PA-GO-AuNS-PEG membranes and TEM image of AuNS. (C) NIR camera images of photothermal membrane under 808 nm laser irradiation (4 kW/m²), showing locally high surface temperature. (B) and (C) are reproduced with permission [9]. Copyright 2015 American Chemical Society. (D) Fabrication of RGO/BNC membrane and its SEM images and photographs. (E) Bactericidal activity against E.coli bacteria on photothermal membrane observed in fluorescence (left) and SEM images (right). (D) and (E) are reproduced with permission [16]. Copyright 2019 American Chemical Society.

bio-fouling without any drop in membrane flux or ion rejection efficiency—showing its great promise for adoption in pre-existing pressure-driven membrane filtration processes.

However, AuNS are expensive, and deposited AuNS can be detached from the membrane under high pressure. To overcome this problem, we employed abundant and scalably produced reduced GO (RGO) as a photothermal material and incorporated it into bacterial nanocellulose (BNC), a scalably produced and environmental benign matrix (see Figure 2D) [16]. RGO exhibits broad-band light absorption in the solar spectrum and has high photothermal conversion efficiency due to the facile π - π^* transition of loosely held electrons [17]. Thus, the RGO/BNC membrane reached a high surface temperature under simulated sunlight with the same spectrum as sunlight, but three times higher intensity-2.9 kW/m². Its high temperature inactivated E.coli within three minutes by deteriorating the bacterial cell wall (see Figure 2E).

Moreover, the incorporation of RGO into BNC during bacteria growth results in good mechanical strength without any discernable damage under high pressure (10 bar). Our findings clearly demonstrate that the photothermal membrane under abundant sunlight strongly resisted biofouling, so high membrane performance can be maintained longer, reducing the frequency of membrane replacement. As the DoD possesses numerous membrane filtration units that provide water to warfighters and civilian communities, adapting photothermal membranes in these applications could save energy and reduce the cost of water production.

Non-pressure-driven Drinking Water Production Using Photothermal Membranes

Although pressure-driven membrane filtration can treat massive volumes of water with high efficiency, it requires large plants to be efficient and it consumes considerable electricity, which may not be available in small FOBs. Most potable water is transported to FOBs at costs ranging from \$4.78 to \$50.00 per gallon [4]. In this case, SSG and PMD are promising alternatives for supplying clean drinking water because they utilize abundant sunlight as a primary energy source, are efficient even in small scale setups, and have low installation costs [18].

Solar Steam Generation

SSG is direct vaporization of wastewater or saline water by thermal energy from sunlight. The solar evaporator for SSG is composed of a photothermal material with broad-band light absorption as a top surface and a heat insulating supporter as a base [19, 20]. Unlike traditional solar-driven water treatment units, an interfacial solar evaporator with a porous support floatsthus, the heat generated by photothermal effect is confined to the evaporative surface (see Figure 3A) [20]. This locoregional high temperature, together with the controlled amount of water transported by capillary action, promotes evaporation as the evaporation rate is proportional to the temperature at the interface. Considering that SSG requires only sunlight to produce drinkable water and has a low installation cost, it is a promising solution for small FOBs where centralized water treatment is not available. To create cost-effective and efficient solar evaporators, we incorporated well-controlled and functionalized photothermal materials into membranes, making scalable, chemically and mechanically stable, and environmentally-benign photothermal membranes.

First, we developed a RGO/BNC bilayer aerogel as a solar evaporator, composed of a porous BNC supporter and a RGO/ BNC layer on top as the solar absorber (see Figure 3B). Owing to broad-band light absorption of RGO and the heat localization by the thermally insulating BNC layer, the RGO/BNC aerogel achieved high solar evaporation efficiency (~83%) under 10 kW/m² [20]. Furthermore, the mechanically-interlocked RGO with BNC showed good chemical and mechanical stability. The easy fabrication of these robust RGO/BNC interfacial evaporators makes SSG attractive for real-world applications.

For cost effectiveness and scalability, we introduced two different approaches, using either inexpensive and abundant support (wood) or environmentally-benign photo-thermal materials (polymerized dopamine [PDA]) [21, 22]. GO was deposited on natural wood by drop casting (see Figure 3C). The hydrophilic vessels in wood transported water from the bottom to the top surface, where the water was effective-ly vaporized by the photothermal effects of GO under simulated sunlight [21]. These

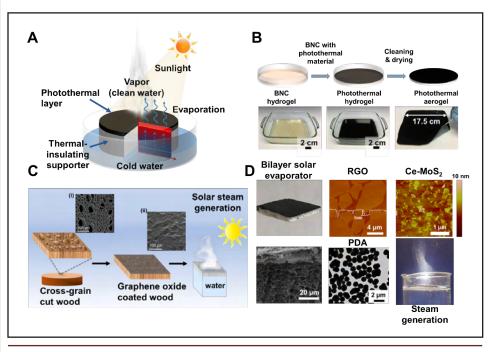


Figure 3. (A) Working principle of SSG. Reproduced with permission [36]. Copyright 2017 Elsevier. (B) Fabrication of bilayer solar evaporator using BNC as supporting layer. Reproduced with permission [22]. Copyright 2017 Royal Society of Chemistry. (C) Fabrication of bilayer solar evaporator based on wood. Reproduced with permission [21]. Copyright 2017 American Chemical Society. (D) (Left) Photograph and SEM image of BNC based solar evaporator, AFM and TEM images of photothermal materials (RGO, ce-MoS₂, and PDA), and (Right Bottom) photograph of steam generation. Reproduced with permission [19, 20, 22]. Copyright 2017 Royal Society of Chemistry.

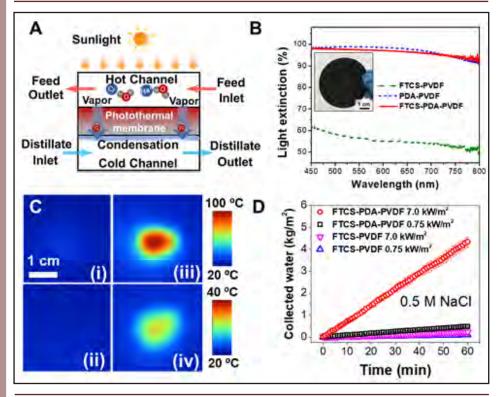


Figure 4. (A) Working principle of photothermal membrane distillation (PMD) process. (B) Light extinction of FTCS–PVDF, PDA–PVDF, and FTCS–PDA–PVDF membranes. Inset: optical image of FTCS–PDA–PVDF membrane. (C) IR camera images of the FTCS–PVDF membrane under irradiations of 7.0 kW m² (i) and 0.75 kW m² (ii), and the FTCS–PDA–PVDF membrane under 7.0 kW m² (iii), and 0.75 kW m² (iv), all after 600 seconds illumination. (D) Collected clean water flux of FTCS–PVDF and FTCS–PDA–PVDF membranes when treating 0.5 M NaCI solution at 0.75 kW m² and 7.0 kW m² using a PMD system. Reproduced with permission [32]. Copyright 2018 Royal Society of Chemistry.

results clearly demonstrated that abundant and inexpensive wood can be used as a supporting layer for solar evaporators.

PDA is a mussel-inspired polymeric material that exhibits strong light absorption and high photothermal conversion efficiency. In PDA synthesis, the monomer, dopamine, can be self-polymerized under alkaline conditions (pH > 7.5) at room temperature without any complicated instruments making its synthesis scalable and cost effective [23]. Synthesized PDA particles have been incorporated into BNC, similar to RGO/BNC aerogel, and served as a solar evaporator. The fabrication of PDA/BNC aerogel is highly scalable, and the materials are completely biodegradable at the end of its functional life [22].

Molybdenum disulfide (MoS₂) has emerged as an attractive 2D photothermal material owing to its high light absorptivity in the solar spectrum and its low toxicity [24]. For the first time, we examined the effects of MoS₂ phases on light absorption and solar evaporation efficiency [19]. During Li intercalation of the synthesis process, the naturally existing trigonal prismatic crystal phase of MoS₂ is transformed to the octahedral phase of MoS_2 —called chemically exfoliated (ce-) MoS_2 . The crystal phase change by Li intercalation narrowed the bandgap of MoS₂, increasing its solar evaporation efficiency. In addition, the cell toxicity of 2D MoS, was found to be lower than that of GO with a similar size. Low toxicity and good photothermal conversion efficiency make the ce-MoS₂ a promising photothermal material for solar-enabled water treatment and biomedical applications.

Photothermal Membrane Distillation

Membrane distillation (MD) is a thermally-driven membrane separation process [18]. Unlike pressure-driven membrane filtration, MD can purify water containing high total dissolved solids by using low-grade heat at low pressures, making it less energy intensive [25]. In MD, the temperature difference (Δ T) between two sides of a hydrophobic membrane drives vapor-phase water to transport across the membrane [26]. Recently, to utilize solar energy as the main energy source for desalination, MD has been implemented with the aid of photothermal membranes, called PMD [27-29]. In PMD, photothermal materials are coated on the membrane surface (see Figure 4B). The generated heat is localized on the membrane's top surface, resulting in a higher temperature gradient across the membrane. Furthermore, localized heating by photothermal materials alleviates the temperature polarization that decreases the system efficiency in conventional MD systems [30-32].

To develop an efficient PMD membrane, we synthesized a PDA-coated polyvinylidene fluoride (PVDF) membrane [32]. Facilitated by the outstanding light absorption (Figure 4B) and photothermal conversion properties of PDA (Figure 4C), the membrane achieved high solar conversion efficiency (45%) and a clean water generation flux of 0.49 kg/m²•h when treating highly saline water (0.5 M NaCl) in a solar-driven direct contact membrane distillation system (Figure 4D) [32]. A simple and easy synthesis method, in situ oxidative polymerization of dopamine on PVDF, makes the membrane highly suitable for potable water generation. Meanwhile, the high salt rejection (> 99.9%) and long-term stability of the membrane make it promising for real-world applications.

Compared to conventional thermal water

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treatment, our SSG and PMD systems can obtain thermal energy from abundant sunlight to treat wastewater or saline water, making them attractive in FOBs where electricity and potable water are limited. Furthermore, the simple, low-cost setups for SSG and PMD are desirable for small FOBs where drinking water is currently supplied by costly transportation. Thus, these techniques benefit supplying potable water to FOBs by treating gray water produced on site, reducing the amounts of wastewater.

Conclusion

The newly-developed photothermal membranes are an appealing way to provide safe, clean drinking water. They can be used in both large-scale water treatment plants for fixed military installations and small-scale water treatment facilities at FOBs. However, translating these laboratory scale studies into portable devices and utility-scale plants without compromising efficiency remains a challenge.

To exploit the anti-biofouling property of photothermal membranes, the conventional spiral-wound shape modules in closed RO/UF systems will need to be redesigned for sunlight accessibility [16]. In SSG, wa-

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ter droplets formed on the condensation surface can reflect and scatter light, reducing the light absorption by the evaporator [33]. In the future, improved steam condensation and collection systems should be developed to maximize the clean water generation rate. Future PMD systems should achieve improved water generation rates and solar conversion efficiencies. New modules with multilayer heat recovery setups can improve the overall energy efficiency of PMD [34, 35]. Combining PMD with low grade heat energy sources, (e.g., engine cooling waters and waste incineration), can further increase its water production rate. For both SSG and PMD, portable and modular devices need to be developed to generate potable water for FOBs.

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COMPUTATIONAL ANALYSIS OF INTERNATIONAL POLITICAL DISCOURSE FOR GLOBAL THREAT MONITORING

Leah C. Windsor

The language people use can reveal a tremendous amount of insight into their preferences, beliefs, and attitudes. When we examine language use through quantitative or computational analysis, we can uncover patterns of behavior that are not discernable through evaluation of their content alone.

This article explores ways in which computational discourse analysis can help the U.S. Department of Defense (DoD) and the Intelligence Community (IC) better understand and monitor international political developments, crises, and threats, especially in nation-states or places where true preferences and strategies are difficult to observe. These include authoritarian regimes, violent extremist organizations, and other insular groups who display seemingly unpredictable behavior.

Specifically, quantitative analysis of syntax—the arrangement of words and phrases in speech or text—can provide information about group membership and perception of status in the international system [1], reveal how leaders and the political systems they represent conceptualize problems [2, 3], and indicate audience design, or how leaders may emulate or mirror the language of others [4]. Linguistic style matching is a phenomenon whereby speakers adopt—either consciously or unconsciously—the speaking styles of others in a shared space, such as the United Nations General Assembly (UNGA) general debate [5].

Whereas to date the study of states and language in international relations has tended to focus on specific leaders and conditions [6–11], some research has taken a cross-national time series approach to understanding how language helps estimate policy positions in the world [12].

Studying syntactic and semantic patterns of language in the world can help national security and defense intelligence analysts understand and predict problems related to international events and crises, such as democratization and democratic backsliding [13], coalition formation and dissolution [14], and longevity of foreign leaders in political office [15].

Quantitative analysis of syntax can aid entities like the Defense Intelligence Agency in its annual worldwide threat assessment, which evaluates the military capabilities and political intents of nation-states and regional actors [16]. The discourse analysis techniques demonstrated below can help DoD and IC intelligence analysts foresee or anticipate political instability, explain changes in state governance or military capacity, and decode intentions behind bellicose rhetoric.

Language in the International System

Scholars of international relations already use annual, aggregate observational data to analyze and make predictions about global political dynamics—including gross domestic product per capita, governance, annual military expenditures, conflict involvement, trade volume, and population demographics. To this discussion, I add robust language data using text data from UNGA general debate sessions from 2004 to 2018 as a sample dataset (the techniques presented below are applicable to other datasets and corpora).

Some of the standard covariate indicators are dynamic and responsive to exogenous shocks, such as civil wars or interstate conflicts. Others, however, are slower moving and exhibit little variation over time—such as indicators of governance. For example, while some countries experience many internal changes in leadership and coalition dynamics, the level of governance may not change much, if at all, except in the cases of coup d'états [17].

Figure 1 illustrates this point: the blue horizontal line shows that the United States has remained consistently classified as "free", while the language used in the UNGA general debate has fluctuated over time, as shown by the red line on the second y-axis, which I will discuss in the next section.

Syntactic and Semantic Elements of Language

I examine five elements of language to demonstrate how they convey information about politics in the international system: syntactic simplicity, word concreteness, narrativity, deep cohesion, and referential cohesion [18]. Syntax simplicity describes how syntactically simple or complex a sentence, paragraph, document, or corpus is. This refers to the grammatical structure of the textbase, where more simple syntax is more easily understood and less cognitively demanding on the audience. On the other hand, complex grammar requires more cognitive effort to parse. Syntactic simplicity can indicate the relative status of a member of an organization, as complex syntax can mark hierarchy. For example, a junior member may use more complex language deferentially toward senior members as a sign of respect. Complex syntax can also identify in-group and out-group status.

Word concreteness measures tangibility and intangibility. Concrete words correspond to real-life referents (i.e., concrete nouns such as people, places, and things). Abstract words can be emotionally evocative, such as hope, fear, community, terrorism, support, or peace. Using abstract words can help an audience connect to broader themes, frame complex issues, and potentially build consensus without necessarily identifying specific details.

A narrative text tends to follow the traditional narrative, storytelling arc: introduction, rising action, climax, denouement, and resolution. Information presented in this format is easier to remember than expository (list-like) presentation as it helps the audience to contextualize the information within familiar heuristics. Expository language may instead present as a list or set of related concepts, relying on the audience's working memory to sort the information.

Deep cohesion can be understood as global cohesion; in other words, the extent to which the entire body of information is broadly thematically related. Semantically and conceptually related ideas may thread throughout the textbase, but are presented in a more nuanced and complex format. Referential cohesion, on the other hand, is more locally cohesive. Particular words, phrases, or ideas may be repeated in proximate sentences, or subsequent pronouns may refer back to antecedent concrete terms. Texts with high referential cohesion tend to be more quotable, memorable, or useful as soundbytes, whereas texts with deep cohesion often need to be summarized in order to be communicated succinctly.

These five syntactic and semantic aspects of language combine to form a composite feature called *formality*. Low levels of formality indicate familiarity, shared experiences and lexicon, and status parity. In short, people who use less formal language may view themselves as a part of a social system or community. High levels of formality may indicate that the speaker perceives himself or herself as an out-group member—showing deference to an in-group with higher status or hierarchy in the system.

How Democracies Speak

Regime type influences leaders' use of formal language in three ways: through institutional constraints from the domestic bureaucracy and legislative branch, advisory oversight from the leader's trusted inner circle, and accountability to both domestic and international audiences. Democratic regimes are defined by several political features, including meaningful competition for publicly held offices, an independent judiciary, and regular and fair elections [19–21]. These features serve to constrain democratic leaders in their daily activities, as well as in the international commitments they make, and the rules of

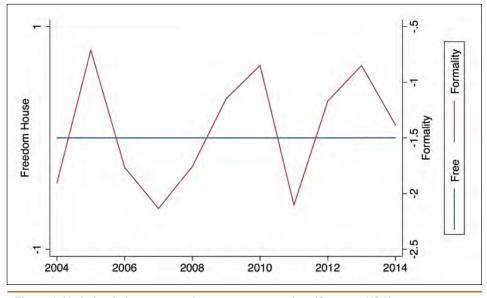


Figure 1. Variation in language and governance over time (Country: USA)

the political system that influence democratic leaders' freedom of speech. Legislatures and political advisors in open societies function as gatekeepers of policy change, vetting changes in foreign policy, tempering hasty and/or unilateral decisions, and encouraging consensus-building in the international community [22].

Democratic leaders also face more direct constraints from a trusted circle of advisors, confidants, and speechwriters. In democratic regimes, advisors should be less likely than in authoritarian regimes to blindly concur with leaders' proposed policies. Rather, they are more likely to offer candid and contrary opinions about the leader's foreign policy plans. Democratic leaders often solicit diverse opinions for policy speeches, which is especially useful given that they are accountable to a diverse constituency.

The role of audiences should also be considered when it comes to choices made by leaders. For example, democracies are likely to engage in consensus-building and diplomatic persuasion. In 2004, the Japanese delegation pronounced, "Peace and security, economic and social issues are increasingly intertwined. The response of the United Nations must be coordinated and comprehensive. UN agencies and organs must be effective and efficient [23]." Similarly, in 2012, the UK delegation declared: "The building blocks of democracy, fair economies and open societies are part of the solution, not part of the problem. And we in the United Nations must step up our efforts to support the people of these countries as they build their own democratic future [24]."

These features of democracies' language are in part due to the influence of the national leader's team of advisors and the extensive linguistic and ideological vetting that takes place before the speech is given. It is also partly due to the distribution of power between the branches of government; in other words, the leader generally does not make international claims, threats, or commitments without consulting and gaining approval from advisors and the legislature, and by extension, the general public, who can remove the leader from office for poor foreign policy performance.

Language in Non-democracies

Leaders from non-democratic countries generally face different and often fewer

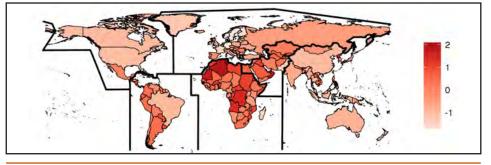


Figure 2. Syntactic Complexity in the World

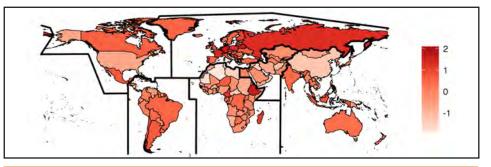


Figure 3. Word Abstractness in the World

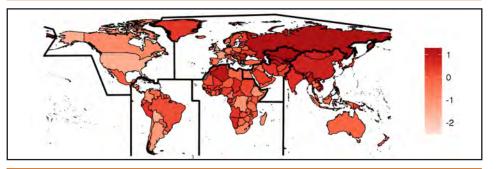


Figure 4. Expository Language in the World

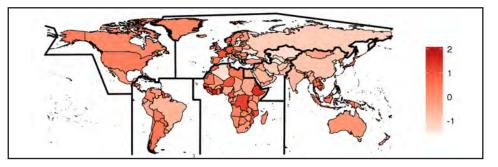


Figure 5. Deep Cohesion in the World

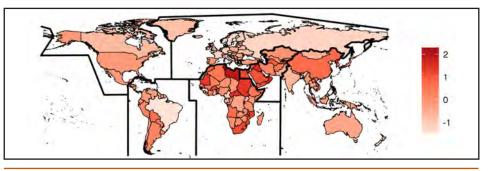


Figure 6. Referential Cohesion in the World

constraints than democratic leaders. Government types and governance can be compared in different ways and along varying schema, including the Polity IV scale [17], the Freedom House typology [25], and varying approaches to classifying types of non-democracies [26-29]. I map linguistic features onto institutional features to provide a context for interpreting language in the international system. The depth and robustness of public institutions characterizes the level of formality in public venues; of the non-democratic regimes, party-based ones have the most bureaucratic accountability. with personalist regimes having among the least [19, 26, 28, 30].

These institutional features are also used to explain other political phenomena, like compliance with international treaties and participation in conflict. Using the typology set out by Lai & Slater [28], political scientist Olga Chyzh evaluates authoritarian regimes' patterns of signing and complying with international treaties [31]. Of personalist regimes, Chyzh writes, "...personalist leaders are effectively not constrained (or almost so) by the need to seek approval on all except for very particular policy issues [31]."

Thus, in personalist and monarchical regimes, increased formality could be more easily attributed to specific individuals' contributions and should have language patterns least similar to democracies. In particular, leaders of authoritarian regimes tend to use distinctive linguistic approaches in their public addresses, including honorifics and more abstract and deferential language. We can see this in the words used in 2009 by the Ethiopian representative:

"Mr. President, It is indeed a great pleasure for me to extend my warmest congratulations to you on your election to preside over this 64th Session of the General Assembly of the United Nations. Permit me also to express my appreciation to the outgoing President for his effective leadership during the course of the last Session of the General Assembly [32]."

The 2004 speech by the Venezuelan representative illustrates the abstractness, referential cohesion, and tone in some authoritarian language (highlighted in bold):

"There are **moments** we can describe as historical turning points, **when nations** and **peoples** must decide where they stand. This is one of these moments, when history will judge us as leaders, and examine if we were democratic leaders that represented the will of our peoples. It is clear that the people of the world are taking a stand, against neoliberal economics and war. They are fighting against those who would impose their will by military and economic force [33]."

Notably, some authoritarian regimes, like party-based political systems, can display quasi-democratic traits that may make them more likely to speak and behave in a public forum like democracies. Chyzh provides further useful insight into how these regimes are constrained, writing that, "In contrast, authoritarian leaders with larger domestic bases oligarchic dictators—face decision-making constraints in more policy areas, as larger domestic bases have more diverse interests.

In addition, domestic institutions, such as cabinets, juntas or politburos, common to oligarchic regimes, tend to induce a status-quo bias, making policy change, such as entering into an international agreement, more difficult [31]." For example, the Chinese single-party political system has pseudo-democratic practices, such as elections and party member incentives for loyalty and participation.

Data, Methods, and Results

To explore the relationship between governance and language, I use text data from the UNGA general debate between 2004– 2018, analyzed with Coh-Metrix software

[18, 34]. Coh-Metrix is a computational linguistics tool used to analyze syntactic and semantic properties of natural language. At present, Coh-Metrix only operates on Englishlanguage corpora; however, an updated version called Coh-MetrixML will analyze syntax and semantics in five other languages: French, Spanish, German, Arabic, and Chinese. Linguistic features derived from Coh-Metrix include passive voice, latent semantic analysis, left-embeddedness, and age of lexical acquisition. Coh-Metrix and Coh-MetrixML analyze documents across more than 100 indices, and a principle components analysis reduces the language features to five dimensions: syntax simplicity; word concreteness; narrativity; deep cohesion: and referential cohesion. I discuss these features in more detail below.

The dependent variable from the empirical model comes from the Freedom House qualitative measurement of political rights and civil liberties, and categorizes countries as *Free* (0), *Partly Free* (1), and *Not Free* (2).

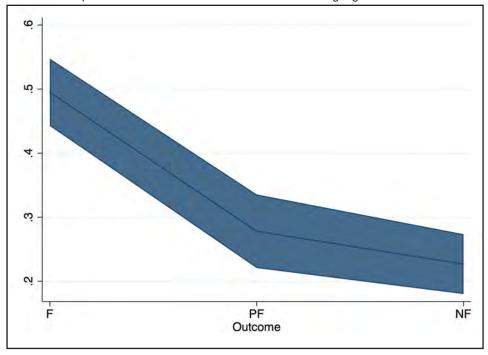
Figures 2 through 6 show maps of the five categories of syntax and semantics in the world, divided by DoD Geographic Combatant Commands. In Figure 2, we observe more complex syntax in countries with darker red color. In Figure 3, countries with darker shades of red use more abstract language, while those shaded lighter use more concrete terms. Figure 4 shows countries that use more list-like or enumerative language to convey their messages shaded in darker red, while those whose words follow the

| | Coef. | Std. err. | | |
|----------------------------------|--------------|-----------|--|--|
| Syntax Simplicity | 912819** | 0.2863679 | | |
| Word Concreteness | 0.0166279 | 0.2801613 | | |
| Narrativity | -0.3123128 | 0.3875027 | | |
| Deep Cohesion | 6078059** | 0.1862382 | | |
| Referential Cohesion | 0.1989457 | 0.292586 | | |
| Oceania | 0 | | | |
| Europe | -0.2363427 | 0.6653279 | | |
| Asia | 2.872868*** | 0.6175951 | | |
| Northern America | -14.71633*** | 0.9132589 | | |
| Latin America and Caribbean | -0.2186753 | 0.6762033 | | |
| Africa | 2.348479*** | 0.6147137 | | |
| cut1 | 1.735851* | 0.6806998 | | |
| cut2 | 3.733704*** | 0.6883903 | | |
| R-squared | 0.2621 | | | |
| N. of cases | 1689 | | | |
| * p<0.05, ** p<0.01, *** p<0.001 | | | | |

Table 1. Principle Components and Level of Freedom in the World

"narrative arc" more closely are shaded lighter. Figures 5 and 6 show deep and referential cohesion, respectively.

Countries whose language has more overall, or global, cohesion tend to speak along broader thematic tropes, whereas those with higher referential cohesion tend to be more locally repetitive in their concepts. We can observe clear differences between regions, governance types, and levels of development in these patterns. Table 1 shows the results of a generalized linear model with an ordered logit estimator, using Stata 15 software. Figure 7 shows the marginal effects of the covariates on the dependent variable, holding all covariates at their means. Countries that are more free use simpler syntax, whereas those that are less free tend to use more complex syntax. Similarly, countries that are rated more free tend to have higher levels of deep cohesion, and less free countries have less deep cohesion in their language.



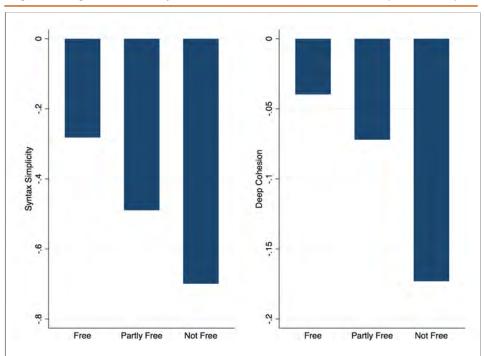


Figure 7. Marginal Effects of Syntax and Semantics on Level of Freedom (from Table 1)

This can be interpreted as follows: simpler syntax and deeper cohesion tend to suggest that there is a great deal of shared meaning and familiarity among countries using these language styles. On the other hand, countries that are highly repetitive and use more complex syntax may be trying to project or convey their authoritativeness, stature, or accomplish greater legitimacy in the international system by using more formal language styles. Extant research has established that individuals with genuine authority and power need not leverage their language to overcome perceptions about their legitimacy. Similarly, individuals who are members of an in-group tend to use more simple language, and in this way both syntax and semantics can provide clues to which members in the international system perceive themselves as members of the in-group, or the out-group.

Figure 8 shows syntax and semantics patterns by country type in the world according to the Freedom House Freedom in the World ratings. More free countries use simpler syntax and have higher levels of deep (or global) cohesion than do partly free or not free countries. Figure 9 represents these relationships geographically: darker blue indicates informal language, while greener colors indicate more formal language.

Other Applications

Studying syntax and semantics can help DoD and the IC better understand the consequences of online media influence over political events, such as elections and candidate behavior; the rise of new regional threats; the emergence and dissolution of allegiances and alliances between states and actors; and counterintelligence insight using words to infer latent qualities like status, hierarchy, and personality.

Analyzing the content and the style of language can help us make sense of complex "hard security" issues like nuclear aspirations and antagonism in North Korea, the effects of populist language on impressionable constituencies, the stability of authoritarian regimes and longevity of leaders, and the spread of terrorist propaganda for recruiting new participants. It can also enlighten us about "soft security" issues in the realm of human security, such as the spread of infectious diseases, the mobilization of radical domestic terrorist groups, and the effects of climate change on vulnerable and mobile populations.

Figure 8. Syntax Simplicity and Deep Cohesion in the World

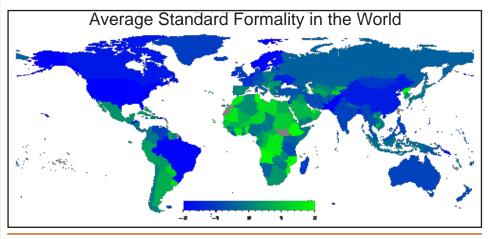


Figure 9. Average Standard Formality in the World

North Korean state media (KCNA) is another potentially valuable source of information about internal regime dynamics. Figure 10 shows differences in the amount of anger conveyed in articles about the Sony hack in 2014, and regarding potential military action against Guam. Interestingly, the level of anger was lower in the 2014 context where North Korea carried out their threat than in 2017 when the regime made threats against Guam. One possible interpretation of this could be that in contexts where an actor intends to follow through on the threat, less anger is conveyed as it is being "held in reserve" for carrying out the actual threat. On the other hand, in cases where a leader or regime is blustering or bluffing, they convey more anger as there is no immediate intent to follow through on the threats.

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Future Directions

Computational discourse analysis may also aid DoD in its efforts to develop automated technologies for the extraction of useful information from very large datasets for defense analysis. For example, in 2012, the Defense Advanced Research Projects Agency (DARPA) began work on a project called Deep Exploration and Filtering of Text (DEFT), which seeks to develop a deep natural-language processing architecture for text and audio analysis. According to DARPA, DEFT's purpose is to "find and represent key information, including information on entities, relations, events, sentiment, beliefs, and intentions" from multiple streams of data [35]. Developing a truly automated solution will require additional steps to

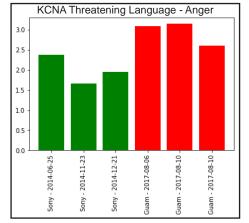


Figure 10. Threatening language in North Korean state media (KCNA)

move from data extraction to intelligence production, and computational discourse analysis can play a critical role in identifying key patterns in behavior, with human analysts playing central roles in interpreting results from computer-aided analysis [36]. Individual analysts remain the most important part of the analytical process. While computers excel at sorting and categorizing information, humans have the unique ability to contextualize, interpret, and communicate that information.

Acknowledgements

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TRANSFORMING MILITARY MEDICINE WITH 3D-PRINTED BIOELECTRONICS



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The advent of wearable or body-borne electronics is rapidly changing how the Department of Defense (DoD) provides diagnostic and therapeutic medical care to the warfighter [1].

Multiple DoD entities, from the U.S. Army Combat Capabilities Development Command's Chemical Biological Center, to the Defense Threat Reduction Agency [1], are seeking bioelectronics that can transform military medicine by providing medics with valuable information to improve acute care on the battlefield, and aiding military doctors providing prolonged care [2]. For instance, bioelectronics sensors that measure multiple signals, including heartbeat and the secretion of metabolites in perspiration [3], can provide remote monitoring of warfighter medical status during operations. Next-generation bioelectronics can be delivered by implantation [4, 5] or can be swallowed [6, 7] so as to deliver therapeutic medications.

A seamless integration of such bioelectronics with the soft, complex, and 3D shape of the human body is inherently challenging due to the geometrical, material, and mechanical dichotomies between the two. Conventional electronics are typically fabricated via planar, top-down processes on a rigid substrate. Conversely, the human body is an irregularly shaped and highly flexible, stretchable construct [5]. Significant research has been dedicated to overcoming this challenge, including the design of stretchable, flexible electronics, the development of electronic skin tattoos, and the manufacturing of electronic textile and bioelectronic implants [3, 5, 8].

Sp02

This article proposes and highlights the advancement of a multimaterial and multiscale 3D printing approach that can enable the fabrication of bioelectronics to better interface with the human body. Specifically, the article highlights the development of (a) a freeform electronics fabrication approach that allows for the creation of complex 3D systems [9, 10], and (b) the multimaterial-printing of an ingestible gastric resident system that allows for non-surgical and needle-free delivery of wireless electronics into the human body [7, 11].

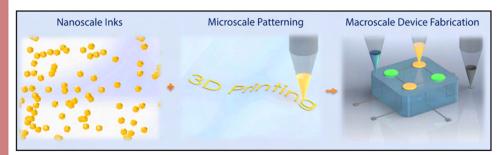


Figure 1. Multi-scale 3D printing of functional devices and bioelectronics [5]. Reproduced with permission. Copyright 2016 Elsevier.

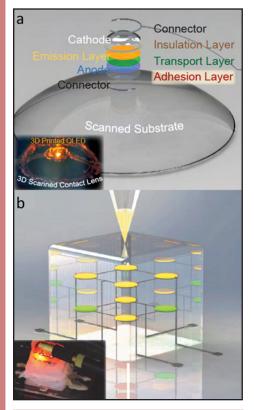


Figure 2. (a) 3D printed QD-LED on a 3D-scanned contact lens onto a curvilinear substrate. The inset shows the electroluminescence output from the printed QD-LED on a 3D scanned contact lens [12]. (b) 3D printed 2 × 2 × 2 multidimensional array of embedded QD-LEDs. The inset shows the electroluminescence output from the printed QD-LEDs within a 3D matrix [12]. Reproduced with permission. Copyright 2014 American Chemical Society.

Multiscale 3D Printing of Electronic Devices

3D printing is a broad class of manufacturing technologies, first invented in the 1980s. However, the majority of 3D printing capabilities remain somewhat limited to the use of specific plastics, passive conductors, and certain biological materials. A multiscale, extrusion-based 3D printing approach can enable the integration of diverse classes of materials to create a variety of electronics and functional devices

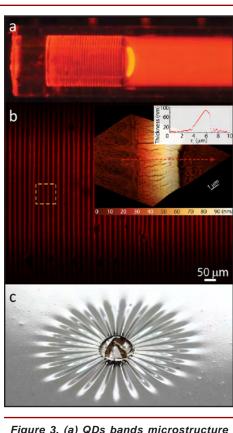


Figure 3. (a) QDs bands microstructure formed inside a capillary tube during a drying process. Fluorescence image of bands formed from the QDs as toluene evaporates from the open end on the left [18]. (b) Confocal microscopy image showing QD band arrays along the capillary tubes. Larger inset shows the Atomic Force Microscopy image of one of the bands. Smaller inset shows the profilometry measurement extracted along the path of the red arrow on the AFM image [18]. (c) Photograph of the deposition of silica nanoparticles on an elastomeric membrane to study the drying-induced stress by characterizing the wrinkles formation. Figure 3a and 3b reproduced with permission. Copyright 2015 American Chemical Society.

not easily achieved using standard microfabrication techniques [5, 9, 10, 12–16]. The ability to 3D print various classes of materials possessing distinct properties could enable the freeform generation of active electronics in unique, functional, interwoven architectures. For example, functional nanomaterials can be dispersed in solvents to form solution-processable inks, which can be integrated into micron-scale coating or printing processes, as illustrated in Figure 1.

Using a 3D-scanned topology and direct fabrication approach, electronics can be manufactured without complicated device design or transfer procedures. As a proof of concept, Figure 2a depicts a quantum dot light-emitting diode (QD-LED) on a 3D-scanned contact lens, and Figure 2b shows a 2x2x2 array of multicolored QD-LEDs embedded within a silicone cube. Both structures were created using a direct printing approach [12].

The multiscale 3D printing approach leverages the evaporative-assembly of functional nanomaterials during printing, which allows the sole execution of the deposition process with a desktop-sized microextrusion based printer. This can enable an easily deployable electronics 3D printing strategy, whereby small, portable printers can directly print highly customized functional devices, such as smart bandages, onto skin at the location needed.

The ability to govern the deposition of nanomaterials dictates the performance of advanced printed devices. However, nanomaterials typically do not spontaneously form a uniform and thin film during deposition. Instead, the process often results in a wide range of interesting features, such as the so-called "coffee rings" where most nanoparticles will be concentrated on the edge of a pinned contact line.

A variety of platforms have been proposed to better understand and ultimately control these dynamic and complex forces [17, 18]. For example, multiscale characterization of nanomaterials deposited in a confined construct can help elucidate the complex relationship between drying parameters (such as evaporation speed) and microstructure morphologies (see Figure 3a and Figure 3b) [18]. In another example, the drying-induced stress of a colloid can be characterized in real time by studying the formation of wrinkles that appear as a colloidal suspension deposited on a thin elastic membrane dries (see Figure 3c) [17].

Multimaterial 3D Printing of Ingestible Gastric Resident Electronics

As described above, multiscale 3D printing provides an opportunity to create biocompatible medical devices that can be used in regions that cannot be accessed by wearable,

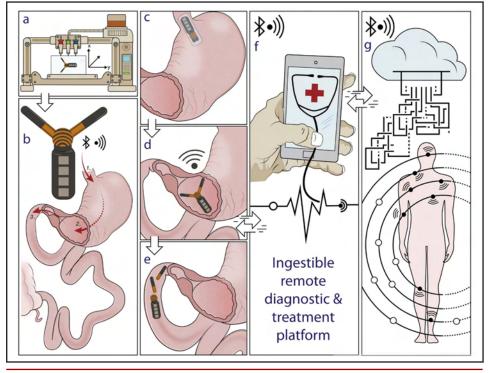


Figure 4. Illustration of 3D-printed gastric resident electronics (GRE) concept. (a–e): a desktop-sized multimaterial 3D printer can be used to fabricate a highly customized GRE which to be delivered orally, reside in the stomach for weeks, and finally break up to be excreted from the gastric space. (f–g): GRE can form bilateral communications with personal devices such as a smart phone directly for communications and controls. The seamless interconnection with other wireless wearable electronics and implants enables a real-time feedback-based automated diagnostic and responsive treatment. [7] Reproduced from Reference [7] under the terms of the Creative Commons Attribution License (CC BY). Copyright 2018 John Wiley and Sons.

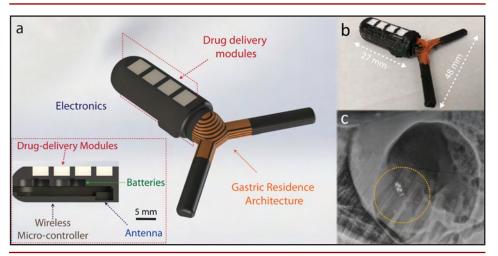


Figure 5. (a) 3D models of GRE device components, such as the gastric resident architecture, personalized drug delivery modules, electronics and power system for communications and control. (b) Optical photograph of the 3D printed GRE. (c) X-ray image of the deployed GRE in a porcine stomach. [7] Reproduced from Ref. [7] under the terms of the Creative Commons Attribution License (CC BY). Copyright 2018 John Wiley and Sons.

textile-based or epidermal electronics [8]. Nevertheless, continued research and development is needed to overcome the remaining challenges. Furthermore, direct implantation often requires surgical processes, and most surgically-placed medical implants carry an inherent risk of eliciting foreign body immune system responses [4]. Implanted devices can serve as a nidus for infection, which can require immediate operative intervention that is unavailable in remote locations.

Advancements in ingestible electronics can allow for the oral delivery of devices directly into the body, enabling a non-surgical, needle-free approach that obviates concerns of adverse

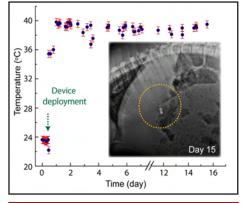


Figure 6. The in vivo result demonstrating the ability to achieve bilateral communications and control of GRE. A direct, real-time core-temperature measurement has been performed with a tablet attached on the wall of the cage over 17 days. Inset shows the X-ray images of the GRE on day 15, highlighting the robustness of the GRE to remain functional in the dynamic and hostile gastric environment for weeks. [7] Reproduced from Ref. [7] under the terms of the Creative Commons Attribution License (CC BY). Copyright 2018 John Wiley and Sons.

immune responses or infection [6]. Importantly, unlike most other organs, the stomach is a relatively immune privileged site in the human body; this enables the long-residence of devices without causing an immune response. However, despite decades of interest and research since its invention in the 1950s, ingestible electronics have yet to acquire the capability to reside in the hostile and dynamic gastric environment for a duration beyond just a few days [19, 20].

Multimaterial 3D printing can enable the creation of a wide range of multifunctional, robust, and transformable architecture [16]. For example, this enables the creation of "gastric resident architecture" (GRE) [7, 11], which is a structure that can be folded into the shape of a capsule, and upon ingestion and exposure to gastric fluid in the gastric space, expands into a mechanical configuration that prolongs its residence (see Figure 4a–e).

For the first time, this has enabled the gastric residence of electronics up to a month in duration, before disintegration of multimaterial interfaces that allow the excretion of the device. Indeed, the integration with various active electronics, wireless module and drug delivery components (see Figures 4f and 4g) via multimaterial 3D printing approaches can ultimately enable seamless interfaces with both personal electronics and the delivery of therapeutic agents, allowing a next-generation digital diagnosis and remote interventions. Figure 5a shows a computer-aided design model of the GRE device highlighting various key components, such as the gastric resident architecture, Bluetooth wireless-microcontroller and antenna, power system (batteries) for communications and control, and personalized drug delivery modules. The 3D-printed GRE device (see Figure 5b) can be folded into a capsule-size dosage form for oral delivery, as shown in the deployed device in a porcine stomach (see Figure 5c).

We also show the GRE's ability to perform long-term wireless bilateral communications and control of the ingested device with a personal device via Bluetooth connection. We acquired long-resident, real-time core temperature data directly from a GRE wirelessly transmitting to an Android device for up to 15 days. The receiver devices do not require an additional adaptor or communication device to function (see Figure 6).

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The connection strength is limited to the distance of an arm's length (<100 cm) to provide physical signal isolation. In future work, various gastric-tolerant drug delivery architectures (such as with a gold membrane) can be integrated to enable on-demand or programmable delivery of therapeutic agents [21].

Future works can also leverage the development of wireless powering and energy harvesting strategies, which can further extend the electronic functionalities in the dynamic and hostile gastric environment beyond a month. We envision that the freeform fabrication of ingestible wireless electronics from a desktop-sized 3D printer can enable a next-generation remote monitoring, diagnosis, and treatment platform for the warfighter.

Conclusion

This multiscale, multimaterial 3D printing electronics fabrication approach can enable the

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fabrication of bioelectronics that can better interface and integrate with the warfighter, and can realize a transformative remote diagnostic, monitoring, and treatment strategy. For example, this enables the freeform 3D fabrication of unique hybrid bioelectronics that cannot be created through conventional fabrication. We envision this approach can transform military medicine by enabling the seamless integration of electronics with the human body—ultimately enhancing the safety and well-being of service members before, during, and after training and operations.

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SILVER NANOWIRE-BASED WEARABLE SENSORS

FOR HEALTH ASSESSMENT AND PHYSIOLOGICAL ACTIVITY MONITORING

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Shanshan Yao & Yong Zhu

Driven by their growing usefulness for fitness tracking, medical surveillance, and physiological status monitoring, wearable devices have received significant interest from academia, industry, and the Department of Defense (DoD) [1]. As the underlying technology has improved, potential military applications for what is known as real-time physiological status monitoring (RT-PSM) have widened in scope [2].

Research conducted at the U.S. Army Research Institute of Environmental Medicine contends that RT-PSM can allow for military planners and commanders to prevent warfighter exhaustion through early detection of high stress loads (thermal work-strain), provide triage options by detecting warfighter injury during a mission, and improve the efficacy of warfighter training through energy expenditure monitoring during drills [2]. As Dr. Matt Coppock, chemist and team lead for the U.S. Army Combat Capabilities Development Command's Army Research Laboratory, noted in May 2019, "It can be envisioned that real-time health and performance monitoring" can help to optimize "individual to squad execution in multifaceted operational environments [3]."

Current wearables on the market are typically rigid—which is not ideal. Wearable sensors can achieve the best signal-to-noise ratio and achieve their maximum potential when constructed to maintain constant, conformal contact with the skin during body movements. A truly wearable device for health assessment and wireless physiological activity monitoring should be stretchable, mechanically robust and electrically stable under repeated loading, and mechanically unperceivable to the user. This is a difficult challenge, as human skin can be elastically stretched up to 15%, and the strain involved during daily motions can reach 100% for skin regions with wrinkles and creases (e.g., finger knuckles) [4]. It is particularly challenging when monitoring active warfighters, due to intensive body motions involved, and requirements for unobtrusiveness and comfortableness.

Wearable devices should be built upon stretchable substrates, such as elastomers or textiles, to achieve high levels of stretchability. There are two different, but complementary, approaches to developing stretchable electronics: top-down and bottom-up. In the topdown approach, thin films and ribbons are fabricated using conventional microfabrication techniques. Since elastomers are mostly incompatible with the microfabrication process, a transfer-printing step is required after patterning [5]. Geometrical designs are often required to introduce deformable structures to improve its stretchability [6].

Alternatively, the bottom-up approach uses synthesized nanomaterials to fabricate the stretchable devices due to their excellent mechanical compliance and large surface area. This approach is compatible with low-cost processes like solution-based methods and rollto-roll printing techniques. Wearable devices based on a variety of nanomaterials have been demonstrated, including metallic nanoparticles/ nanowires (e.g., silver nanoparticles [AgNPs], silver nanowires [AgNWs], gold nanoparticles [AuNPs]), carbon-based nanomaterials (e.g., carbon nanotubes [CNTs], graphene, graphene oxide [GO]), and transition-metal dichalcogenides [7–10].

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With these devices, it is now feasible to capture the physical parameters (e.g., strain, tactile, temperature, and biopotential) [11-13], and chemical parameters (e.g., glucose, lactates, ions, electrolytes, and pH) from the human body [14, 15], as well as environmental parameters (e.g., ultraviolet and gas) from its surroundings [7, 16]. Our group has been developing various wearable devices using solution-based fabrication processes, including sensors to measure strain [16, 17], pressure [18], touch [18, 19], temperature [20], hydration [21], and biopotential signals [21-23]; wearable heaters [22]; and stretchable antenna [24]. The building block common to each application is AgNWs, owing to their simple synthesis and processing methods, and high conductivity and ductility (i.e., large failure strain). These AgNW-based wearable devices can achieve robust performance and reliability under highstrain and high-repetition conditions-such as those experienced by warfighters in training or operations.

Silver Nanowire-based Wearable Strain Sensors

Strain sensing is necessary to enable several applications of wearable electronics, including activity tracking, sports performance monitoring, and human-machine interfaces [25]. For example, strain sensors can help quantify body motions (e.g., angle, speed, acceleration) during exercise in order to improve posture, evaluate athletic performance, prevent injuries, and facilitate rehabilitation.

Conventional strain gauges typically have a strain operating range of less than 5%, and can be used for stress analysis such as flight testing or structural integrity monitoring of critical infrastructure [26]. However, they cannot meet the large-strain requirement (> 50%) for wearable electronics.

Strain sensing techniques such as fiber Bragg grating, Raman shift, piezoelectricity, and triboelectricity are not practical for wearable applications largely due to their poor stretchability and need for sophisticated measurement equipment [27]. Both resistive and capacitive sensing mechanisms have been adopted to develop wearable strain sensors [7]. The resistive sensing method is advantageous in terms of its sensitivity and simplicity of data acquisition, but it suffers from poor linearity and large hysteresis.

On the other hand, capacitive strain sensing offers excellent stretchability, linearity, and low hysteresis. A wide range of stretchable and conductive materials can serve as the electrodes, including CNTs, AgNPs, graphene, and metallic nanowires—among which AgNWs exhibit the best conductivity for a given density [8].

As illustrated in Figure 1A, the strain sensor is essentially a stretchable capacitor, where the top and bottom electrodes were fabricated by embedding AgNWs just below the surface of an elastomer (polydimethylsiloxane (PDMS) [18] or Ecoflex [17]). To serve as the dielectric, a thin layer of highly stretchable Ecoflex was sandwiched between the two electrodes. Under a tensile strain, the length of the capacitor increases as the width and the distance between the two electrodes decrease, resulting in a capacitance increase (see Figure 1B). The gauge factor (relative capacitance divided by the mechanical strain) for the strain sensor with AgNW/Ecoflex electrodes is close to 1 for strain of up to 150%, which is sufficient for monitoring human motions [17]. In addition to a constant gauge factor over a wide strain range, our strain sensor demonstrated a fast response time. low hysteresis, and skin-like mechanical properties (Young's modulus of 96 kPa).

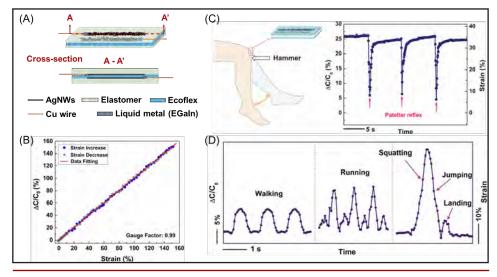


Figure 1. (A) Schematic illustration of the fabricated capacitive strain sensor. (B) Relative capacitance change as a function of tensile strain for stretching and releasing. Reproduced with permission [15]. Copyright 2018, IEEE. (C) Capacitance change and strain associated with knee motions in patellar reflex. (D) Relative capacitance change and strain associated with various human motions. (C, D) Reproduced with permission [16]. Copyright 2013, The Royal Society of Chemistry.

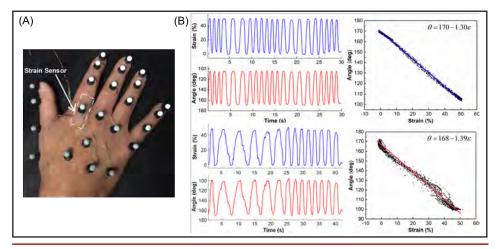


Figure 2. (A) A skin-like strain sensor and reflective markers attached onto the hand of a stroke patient. (B) Comparisons between the strain measured from the strain sensors (blue) and the angle measured from the IR cameras (red) for a healthy control (top panel) and a stroke patient (bottom panel). (A, B) Reproduced with permission [15]. Copyright 2018, IEEE.

Preliminary experiments have revealed good wearability and large-deformation sensing capabilities. These results came from mounting the capacitive strain sensors onto a human body to monitor skin deformations associated with finger flexing (Figure 2), knee motions in the patellar reflex (Figure 1C), and other motions, such as walking, running, and jumping from squatting (Figure 1D) [18].

Recently, our group cross-validated the accuracy of our strain sensors by comparing them against conventional optical motion tracking systems using reflective markers and infrared (IR) cameras.

Figure 2A shows the experimental setup, where both the strain sensors and reflective

markers were attached to the hand of a stroke patient. The strain associated with finger flexing was monitored using the attached strain sensor, and the finger bending angle was captured by the IR cameras simultaneously. Figure 2B shows excellent correlation between the two methods for tracking the joint motions of a stroke survivor and a healthy control. In addition, it shows that the strain sensor possesses excellent resolution to capture the details of the jerky motions of the stroke patient.

Silver Nanowire-based Wearable Hydration Sensors

Hydration levels regulate key body functions such as core temperature, blood pressure, and heart rate. Dehydration can be a serious

risk factor for warfighters, as well as a symptom of potential ailments like skin disease, kidney stones, and gastroenteritis [28, 29]. Real-time tracking of hydration levels can benefit those working in extreme conditions, and help evaluate the effectiveness of medical therapies [30]. Most portal hydration monitors on the market place electrodes onto the skin to measure changes in the skin's conductance, capacitance, and impedance. However, such planar electrodes are rigid and need to be manually pressed against the skin for reliable reading. The Rogers research group has made recent progress in this area, demonstrating a series of photolithographically patterned epidermal devices in serpentine layouts for skin-attachable hydration sensing [30, 31].

To enable a conformal electrical and mechanical interface to the skin, we based our hydration sensors on AgNW/PDMS conductors, where AgNWs were inlaid under the surface of PDMS [32]. The AgNW/PDMS conductors combine the superior conductivity of silver with the enhanced stretchability of nanomaterials and polymers to achieve highly conductive electrodes which can maintain good conductivity up to 50% tensile strain [33]. The AgNW/ PDMS conductors were patterned into interdigitated electrodes to facilitate the impedance measurement (see Figure 3A).

Upon placing the hydration sensor onto the skin, impedance (which is dependent on hydration levels) can be measured from the two terminals. The AgNW hydration sensor was calibrated against a commercial hydration monitor (Moisture Meter D (MMD), Delfin Tech). As shown in Figure 3B, when the hydration level (MMD reading) increases, the impedance measured from the AgNW sensor decreases.

To achieve a better wearability form factor, the AgNW sensor was combined with a network analyzer chip, button cell battery, ultralow power microprocessor, and Bluetooth transmitter, and integrated into a flexible wristband as a watch-type hydration monitor (see Figure 3C). The resulting wearable hydration monitor is compliant, wireless, and can be continuously worn on the skin for long periods of time without degrading its performance.

Silver Nanowire-based Dry Biopotential Electrodes

Biopotential electrodes capture bioelectric variations and electrophysiological signals in tissues. Representative electrophysiological

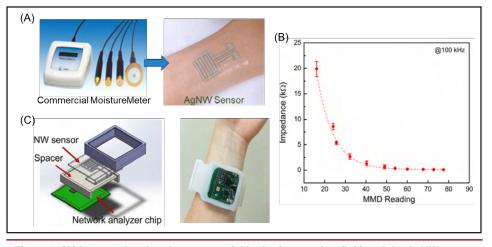


Figure 3. (A) Images showing the commercial hydration monitor (left) and the AgNW sensor worn on the wrist (right). (B) Skin impedance measured from the AgNW hydration sensor as a function of the hydration level measured from the commercial hydration monitor. (C) Schematics showing the PCB, 3D printed spacer, AgNW skin hydration sensor, and encasing (left). The hydration monitor worn on the wrist like a watch (right). (A–C) Reproduced with permission [19]. Copyright 2017, John Wiley and Sons.

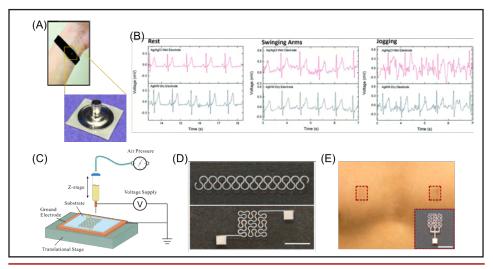


Figure 4. (A) AgNW/PDMS based dry electrode attached on the wrist using a Velcro strap. (B) Comparison of the ECG signals between the AgNW/PDMS electrodes and the commercial Ag/AgCl wet electrodes. (A, B) Reproduced with permission [21]. Copyright 2015, The Royal Society of Chemistry. (C) Schematic illustration of a EHD printing system. (D) Two printed AgNW patterns with high resolution. Scale bar, 5 mm. (E) EHD printed AgNW dry ECG electrodes attached on chest. The inset shows the magnified image of the printed electrode. Scale bar, 5 mm. (C–E) Reproduced with permission [20]. Copyright 2018, The Royal Society of Chemistry.

signals include electrocardiogram (ECG), electromyogram (EMG), electroencephalogram, and electrooculogram, which reflect the electrical activity of the heart, muscle, brain, and eyes, respectively. Conventionally pre-gelled Ag/AgCI wet electrodes are used to capture the electrical signals, where conductive gel is used to establish a reliable electrode-skin interface.

Wet electrodes are flexible and wearable; however, the gel dries over time, leading to degraded signal quality. The dehydration of the conductive gel requires the gel to be re-applied, which is inconvenient and sometimes infeasible. Moreover, the gel and adhesive can potentially trigger skin irritations [32, 34]. Therefore, gel-free (dry) electrodes are greatly needed. Metal thin films and nanomaterials, including metallic nanomaterials and carbon-based nanomaterials, have been used to develop biocompatible and compliant dry electrodes for long-term monitoring [32].

Highly conductive and stretchable conductors made of AgNWs embedded in PDMS matrix were used for electrophysiological sensing without the use of conductive gel [23]. The positive and negative electrodes were placed on the left and right arms using Velcro straps (see Figure 4A), and the ground electrode was placed on the right leg. Reliable electrode-skin impedance is crucial for acquiring a high signal-to-noise ratio and low motion artifact. Here, the good compliance of the AgNW/PDMS electrode allows for low electrode-skin impedance without the gel and good contact with skin during body motions. As shown in Figure 4B, the AgNW/PDMS dry electrode performed as well as the pre-gelled Ag/AgCl electrodes when the subject was resting, swinging their arms, and jogging. Each wave of the ECG signal (i.e., the P wave, QRS complex, and T wave) can be clearly identified from the ECG waveforms.

Heart rate can also be readily extracted from the R-R interval of ECG signals. As cardiovascular disease is the leading cause of death in the U.S., continuous ECG monitoring in wearable form factors could significantly improve public health outcomes and decrease overall health care costs. In addition to ECG, the electrodes can also be used for surface EMG measurements. For example, AgNW/PDMS electrodes were placed on the right extensor digitorum communis and used to capture muscle activities during wrist extension-contractions [23].

The strain sensors, hydration sensors, and dry electrodes discussed above were fabricated via solution-based coating methods (i.e., drop casting), with the use of a mask to generate patterns. Additionally, we have demonstrated the electrohydrodynamic (EHD) printing of Ag-NWs onto flexible and stretchable substrates [22]. As illustrated in Figure 4C, EHD printing systems typically include a pneumatic dispensing system, a voltage supplier, and a precision three-axis translation stage. To make the ink for EHD printing, 4 wt% poly(ethylene oxide) (PEO) was added to a 15 mg/ml AgNW/water solution to adjust the viscosity of the ink. To enable the best printing results, the inner diameter of the nozzle was set at 150 µm, and the outer diameter of the nozzle at 250 µm. The printing voltage was set at 1500 V, with a standoff distance (distance between printing head and substrate) of 75 µm, and back pressure of 0.4 psi.

With EHD printing, AgNW inks can be printed onto various substrates without masks, including PDMS (dopamine treated), PET, glass, letter paper, nanofiber paper, polycarbonate filter, and nature rubber latex (i.e, lab-use gloves). The smallest linewidth was ~45 μ m. After removing PEO with water and heat treatment, high conductivity of ~5.6×10⁶S/m was achieved. AgNWs were printed onto PDMS

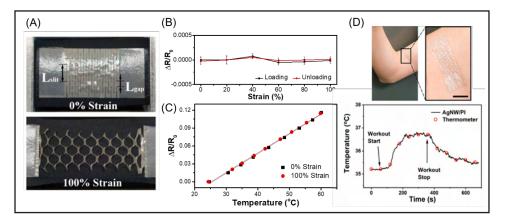


Figure 5. (A) Photographs of the AgNW/PI temperature sensor without strain (top) and with 100% tensile strain (bottom). (B) Relative resistance change of the temperature sensor under tensile loading/unloading. (C) Relative resistance change of the temperature sensor as a function of temperature, characterized under 0% strain and 100% strain. (D) Photographs showing the AgNW/PI temperature sensor attached to the skin near biceps (top). Scale bar, 10 mm. Comparison between temperature recorded by the AgNW/PI temperature sensor and IR thermometer during biceps workout (bottom). (A–D) Reproduced with permission [18]. Copyright 2019, American Chemical Society.

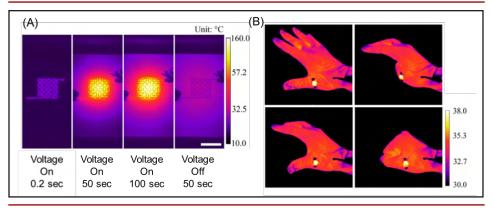


Figure 6. IR images showing the temperature distribution of (A) a AgNW heater when the voltage was on and off (scale bar, 5 mm) and (B) a AgNW heater printed onto a glove during hand motions. (A, B) Reproduced with permission [20]. Copyright 2018, The Royal Society of Chemistry.

substrate following a Greece Cross pattern for ECG sensing (see Figure 4E). This fractal inspired pattern ensures good mechanical stretchability and large area coverage [35]. ECG recordings were successfully acquired by placing two AgNW/PDMS fractal electrodes on the chest. Comparable signal quality with commercial pre-gelled electrodes has been demonstrated.

Silver Nanowire-based Wearable Temperature Sensors

Body temperature is one of the most important vital signals, and it correlates with illnesses such as fever, heat stroke, and infection [7]. Wearable temperature monitoring requires good stretchability, fast response, a wide sensing range (25–50 °C), and high precision (±0.1 °C in the range of 37–39 °C and ±0.2 °C for below 37 °C and above 39 °C) [6, 35]. The main challenge associated with wearable temperature sensors is the crosstalk between temperature and strain during body movements. It is difficult to differentiate the relative contributions of temperature and strain to the overall change in electrical signals. To overcome this problem, a stretchable temperature sensor that is insensitive to strain is required.

Our group developed a stretchable thermoresistive temperature sensor based on AgNW/ polyimide (PI) composite [20]. The temperature sensor was patterned with a Kirigami structure, where cuts were introduced to enable out-ofplane deformations during stretching to minimize the local strain in the AgNW/PI thin film (see Figure 5A). The Kirigami structure also makes the temperature sensor vapor-permeable to prevent heat and sweat accumulation, improving the comfort for long-term wear.

Figure 5B shows the relative resistance change of the AgNW/PI temperature sensor during loading and unloading, up to 100% strain. Owing to the introduction of the Kirigami

structure, the variation of the resistance was within 0.05%, indicating negligible sensitivity to strain. Temperature coefficient of resistance (TCR), defined as follows, is commonly used to describe the sensitivity of a thermoresistive temperature sensor:

$$TCR = \frac{1}{R(T_0)} \frac{R(T) - R(T_0)}{T - T_0}$$

where $R(T_o)$ and R(T) are the resistance at temperatures T_o and T, respectively.

The TCR of the AgNW/PI temperature sensors increases with NW density (from 0.26 to 2.05 nanowires per µm²) and annealing temperature (up to 200 °C). As shown in Figure 5C, for the AgNW network density of 2.05 per µm² after 200 °C annealing, the calculated TCR was 3.32×10^{-3} °C and the sensitivity was 0.47Ω °C over the temperature range from 25 °C to 60 °C. Negligible difference in the TCR and sensitivity was observed with 100% tensile strain and without strain. To demonstrate practical wearable applications, the AgNW/PI temperature sensor was attached onto the skin near the biceps to monitor the temperature change during exercise (see Figure 5D). The temperature change was also monitored using a commercial IR thermometer for comparison. Good correlation was achieved for temperature variations recorded from the wearable AgNW/PI temperature sensor and the IR thermometer.

Silver Nanowire-based Wearable Heaters

Our group has also worked to develop improved, highly flexible wearable heaters. Wearable heaters can protect warfighters from extreme cold-weather climates and facilitate the recovery of joint fatigue and injuries. Heat improves blood flow, alleviates pain, relieves muscle spasms, decreases joint stiffness, and reduces inflammation [37, 38]. Conventional wearable heating elements include heat packs and resistive heating wraps. Heat packs are typically bulky and thick, and the temperature is noncontrollable and nonuniform, causing

 Majidi, C. (2018). Electronic stickers for wireless physiological monitoring in a tactical environment. *Journal of the Homeland Defense & Security Information Analysis Center, 5*(4). Retrieved from <u>https://www. hdiac.org/wp-content/uploads/Electronic</u> <u>Stickers for Wireless Physiological Monitoring V5l4.pdf</u>

 Friedl, K. E. (2018). Military applications of soldier physiological monitoring. *Journal of Science and Medicine in Sport, 21*, 1147– 153. doi:10.1016/j.jsams.2018.06.004 discomfort [39, 40]. Joule-heating wraps offer well-controlled heating temperature; however, due to their low flexibility, they fail to conform to the curvilinear surface of the skin. Commercially-used electrothermal materials, such as ferro chromium-based alloys, are challenged by high rigidity and low heating efficiency [41]. Indium tin oxide (ITO) has been the dominant electrode material due to its good electrical conductivity. With rising indium costs and other limitations in mind-including slow thermal response, harsh processing conditions, and dramatically deteriorated conductivity under strain-alternative conductive materials are in demand to replace ITO for heating applications [8].

AgNWs were adopted to develop wearable heaters. Their conductivity guarantees a low actuation voltage, and mechanical compliance enables good robustness against mechanical deformations. AgNWs were directly printed by EHD onto flexible substrate with Peano curve fractal patterns [35]. As depicted in the IR thermal images of Figure 6A, the 6×6 mm heater can provide a temperature up to ~160 °C at the voltage of 25 V, with maximum heating and cooling rate of 21 and 29 °C s⁻¹, respectively.

To demonstrate wearability, the heater was mounted onto the thumb area (see Figure 6B). The heater maintained stable temperature under deformations caused by finger movements, illustrating its reliable performance during body motions. Besides applications for thermotherapy, wearable heaters can be further integrated with thermo-responsive drug release systems for wearable drug delivery, as demonstrated by the Kim research group [42, 43]. When RT-PSM monitors detect an injury or other medical emergency, wearable heaters can potentially be used to administrator therapeutic therapies through thermotherapy or thermo-responsive drug delivery.

Wearable heaters can actively protect warfighters from extreme cold environments while maintaining their body temperature for good performance. The integrated wearable therapy components, together with the wearable sensors, can provide timely and closed-loop healthcare, which is especially beneficial in life-threatening situations.

Conclusion

Wearable, wireless, and multimodal sensors provide real-time physiological parameters (e.g., temperature, hydration, ECG, and motions) and environmental data (e.g., temperature, humidity, and pressure) for activity monitoring, performance tracking, warfighter fatigue detection, and strategic planning [1].

As discussed in this article, our group developed a variety of AgNW-enabled wearable devices-all fabricated through low-cost, solution-based processes. As these technologies continue to improve, the data collected by RT-PSM sensors could be used to develop what the U.S. Army Research Institute of Environmental Medicine calls a "soldier readiness score"-an index comprised of musculoskeletal fatigue limits, thermal work-strain loads, and mission-specific physiological status parameters (e.g., pulmonary threats, hypoxia) [2]. Active analysis of such readiness scores improves unit readiness and aids commanders in matching individual operators to the needs and capabilities required by specific missions [2].

The unprecedented combination of mechanical stretchability and electrical conductivity of AgNW/elastomer nanocomposites allows for excellent wearability and robust performance, even under repeated body movements. To promote the practical applications of AgNW based wearable devices, it is important to scale up the fabrication of wearable devices and improve reliability over long periods of use, where ongoing efforts are currently underway [21, 43, 44].

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ENERGING TECHNOLOGIES FOR DISRUPTIVE EFFECTS IN NON-KINETIC ENGAGEMENTS

Joseph DeFranco, Diane DiEuliis, CPT L. R. Bremseth (USN SEAL ret), LtCol J.J. Snow, & James Giordano

Over the past decade, China's increasing activities in media and industrial acquisition, soft power messaging, development, and exploitation of international laws has made it starkly apparent that the U.S. is engaged in an innovative form of multi-dimensional competition. China's commitment to the scientific and technological (S&T) enterprises as specific components of current and future Five-Year Plans emphasize an increasing reliance on-and investment in-convergent S&T approaches (e.g., cyber, nano, media, and economic) to effect dominance on the world stage [1]. This use of multiple technological pathways, coupled with pre-bellicose, non-kinetic actions and subtle yet potent influence operations demonstrates a strategic paradigm to threaten, if not suppress, U.S. global power [2]. During 2018, the Department of Defense (DoD) pressed forward on garnering both internal and external expertise to increase technology-focused efforts necessary to inform policy, acquisitions, and security strategy [3-6]. Over the past four years, the authors were tasked by the Department of Energy's Lawrence Livermore National Laboratory and the Donovan Group and the SOFWERX Innovation Center at United States Special Operations Command (USSOCOM) with studying the use and advantages of current and emerging technologies (ETs) by near-peer adversaries. Toward that end, an exploration of these non-kinetic, technology-enabled engagements was conducted by the group to best define the current evolution in tactics and strategy challenging U.S. national security.

Non-kinetic Engagements

Considerable and expanding aspects of political and military actions directed at adversely impacting (or defeating) an opponent often involve clandestine operations that can be articulated across a spectrum. These operations are frequently augmented by supporting missions that range from overt warfare to far more subtle engagements, which do not meet current criteria for explicit acts of war. Routinely, nations and actors have employed clandestine tactics and operations across kinetic and non-kinetic domains. Arguably, the execution of clandestine kinetic operations is employed more readily, as these collective activities often occur after the initiation of conflict (i.e., "Right of Bang"), and their effects may be observed and/ or measured to various degrees. Given that clandestine non-kinetic activities are less visible, they may be particularly effective because they are often unrecognized and occur "Left of Bang." Other nations, especially adversaries, understand the relative economy of force that non-kinetic engagements enable, and are increasingly focused on developing and articulating advanced methods for their operations.

Much has been written about the fog of war [7]. Non-kinetic engagements can create unique uncertainties before and/or outside of traditional warfare, precisely because they have qualitatively and quantitatively "fuzzy boundaries" as blatant acts of aggression [8]. The intentionally-induced ambiguity of non-kinetic engagements can establish plus-sum advantages for the executor(s), and zero-sum dilemmas for the target(s). For example, a limited scale non-kinetic action, which exerts demonstrably significant effects, but does not meet defined criteria for an act of war, places the targeted recipient(s) at a disadvantage. First, in that the criteria for response (and proportionality) are vague and therefore any response could be seen as questionable. Second, in that if the targeted recipient(s) responds with bellicose actions, there is considerable likelihood that

THE SUPREME ART OF WAR IS TO SUBDUE THE ENEMY WITHOUT FIGHTING.

they may be viewed as (or provoked to be) the aggressor(s), and therefore susceptible to some form of retaliation that may be regarded as justified.

Bitcoin

Non-kinetic engagements often utilize non-military means to expand the effect-space beyond the conventional battlefield. The DoD and Joint Chiefs of Staff do not have a well agreed-upon lexicon to define and to express the full spectrum of current and potential activities that constitute non-kinetic engagements. It is unfamiliar—and can be politically uncomfortable—to use non-military terms and means to describe non-kinetic engagements. And as previously noted, it can be politically difficult, if not precarious, to militarily define and respond to non-kinetic activities.

Disruptive Effects

Non-kinetic engagements are best employed to incur disruptive effects in and across various dimensions (e.g., biological, psychological, social) that can lead to intermediate and longterm destructive manifestations (in a number of possible domains, ranging from the economic to the geo-political). The latent disruptive and destructive effects should be framed and regarded as "Grand Strategy" approaches that "Rapid advances in biotechnology, including gene editing, synthetic biology, and neuroscience, are likely to present new economic, military, ethical, and regulatory challenges worldwide as governments struggle to keep pace..."

2019 Worldwide Threat Assessment of the U.S. Intelligence Community to the Senate Select Committee on Intelligence [11]

evoke outcomes in a "long engagement/long war" context, rather than merely in more short-term tactical situations [9].

Thus, non-kinetic operations should be regarded as tools of mass disruption, designed to sustain compounding results that can evoke both direct and indirect de-stabilizing effects. These effects can occur and spread from a) the cellular (e.g., affecting physiological function of a targeted individual) to the socio-political scales (e.g., to manifest effects in response to threats, burdens, and harms incurred by individuals and/or groups), and b) the personal (e.g., affecting a specific individual or particular group of individuals) to the public dimensions in effect and outcome (e.g., by incurring broad scale reactions and responses to key non-kinetic events) [10].

It is important to recognize various nations' dedicated enterprises in developing methods of non-kinetic operations (e.g., China, Russia), and that such endeavors may not comport with ethical systems, principles, and restrictions of the U.S. and its allies [12, 13]. These differing

ethical standards and practices, when coupled to states' highly centralized abilities to coordinate and synchronize activity of the so-called "triple helix" of government, academia, and the commercial sector, can create synergistic force-multiplying effects to mobilize resources and services that can be non-kinetically engaged [14].

Virtual Currencies and Nations

Attention should also be paid to the activities, roles, and viability of virtual currencies and virtual nations as capabilities to exercise disruptive effects and power. The first internet currency, Flooz, was initiated in 1999 [15]. However, it wasn't until 2009 that virtual currencies were actually recognized, and the first blockchain-based cryptocurrency was established [16]. But the true power of virtual currency is in its ability to support smart contracts via the blockchain algorithm.

This strength has allowed legal and medical documents to be uniquely produced and secured while controlling access in a "permissionful" manner. By 2014, virtual nations like BitNation and Asgardia, and countries like Estonia and Bulgaria, began to offer e-residency programs for corporations and digital transients. These new entities offer services and specific benefits to "digital citizens" that may pose unique challenges to traditional governance structures and rules [17–21].

A virtual nation is defined as "an individual, group, community, or corporate entity which derives power from access to high capital resources or high data resources allowing for the influence and successful massing of decentralized digital power to achieve physical effects at the state, national or regional level [22]." A virtual nation may be state- or non-statesponsored, it may form from collectives, or it may even be a single powerful individual. It is possible that virtual nations may revolutionize how diplomatic, information, military, and economic tools could be used in the future by both state- and non-state actors who are seeking to achieve national- to regional-level effects without being encumbered by traditional laws governing existing nation states [22, 23]. Table 1 provides a comparison of how virtual nations and virtual currencies may enable new mechanisms for the exercise of both power and effect, either in concert or competition with existing nation states, non-state actors, and traditional financial structures.

Blockchain can drive new forms of governance, business, and security by providing a cheap and effective automated mechanism that significantly saves on transaction costs while providing a digital means to formalize relationships

Actor Type **Traditional Financial** Virtual Currency Governance Structures Nation State Five traditional models: mon-Primary reliance on Initial forays traditional financial include movement archy, democracy, oligarchy, structures and internatoward digital cash authoritarianism, totalitariantional markets for daily in Asia and smart ism; highly centralized, internaeconomic operations contracts for legal tional law derives from Peace and medical of Westphalia and associated treaties Non-State/State May relay on traditional Movement by Centralized or decentralized Sponsored financial structures for certain groups organizations, ideological or funding towards alterpolitically focused, may or may native financial not comply with existing goverstructures which nance and/or legal structures; operate within gray zones cannot be frozen or sanctioned by nation states and can be hidden to protect operational security Virtual Nations Will only use traditional Establish and rely Decentralized, borderless, financial structures on alternative voluntary, self-selecting for as necessary; tend financial, commucode of law, governance type, to avoid reliance on nication, legal, and services provided to citizens decision-making and decision-making processnational governance es; designed to operate outside and services in favor structures freof independent and quently based on of existing Westphalian and unregulated action existing blockchain international law algorithms, such as Ethereum

Table 1. Characteristics of Real and Virtual Nations and Currencies [23]

between assets, people, and organizations. As well, blockchain can also serve as the foundation for virtual nations. Taken together, virtual currencies and nations can establish bases for multi-dimensional smart contracts [24]. Decentralized Autonomous Organizations are the most complex manifestation of a smart contract. Other features of smart contracts include the ability to self-verify and self-execute; provide improved security; and reduce the need for intermediaries (like existing state governments) to regulate and approve transactions.

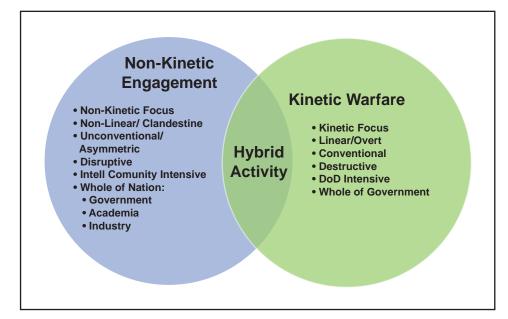
This has resulted in the recent revolution of supply chain efficiency by IBM (15% increase in global trade volume, 5% increase in global gross domestic product); secure medical records and real time internal hospital infectious disease detection and tracking by Spiritus Partners; and the successful creation of alternative governance mechanisms that are beginning to rival existing nation state processes and institutions in places like Cyprus, Estonia, and the United Arab Emirates [23]. Such developments can be viewed as economically evolutionary, if not revolutionary, with each and all pushing the boundaries of industry, finance, and governance to significantly change the basis of transactions across domains and dimensions of society [23].

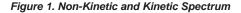
Technologies as Enabling Tools in Non-kinetic Engagements

Nation states, virtual nations, and state- and non-state actors' abilities to exert change are enhanced both by: a) radical leveling technologies (RLTs)-extant technologies that can be employed in novel ways to exert disruptive effects in certain contingencies (e.g., changes in social economic markets, vulnerabilities, and volatilities); and b) ETs (i.e., as threats, [ETTs]) that can be utilized for their novel properties and capabilities to exercise multi-focal and multi-scalar disruptions to produce transformative and de-stabilizing effects in support of non-kinetic engagements (see Figure 1). ETs can be particularly problematic given that they are new and may not be viewed or defined as threats, and can evoke effects which, while potent, may not be easily recognizable or attributable to the technology or the actor(s).

Emerging Technologies as Threats

To date, the threat of existing radiological, nuclear, and (high-yield) explosive technologies has been and remains generally well-surveilled and controlled. However, new and convergent





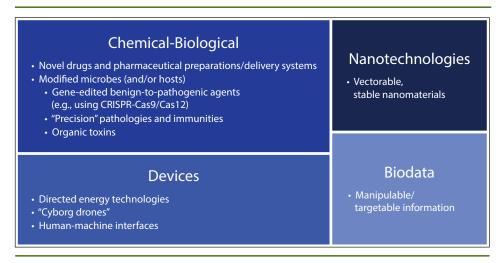


Table 2. Emerging Technologies as Threats to International/National Security

innovations in the chemical, biological, cybersciences, and engineering fields yield tools and methods that, at present, are not completely or effectively addressed by the Biological Toxin and Weapons Convention (BTWC) or Chemical Weapons Convention (CWC) [25, 1–6]. An overview of these ETs is provided in Table 2.

Our ongoing work focuses primarily upon the brain sciences [10, 13, 25–32]. As recently noted in the *Worldwide Threat Assessment* of the US Intelligence Community to the Senate Select Committee on Intelligence [11], the brain sciences entail and obtain new technologies that can be applied to affect chemical and biological systems in both kinetic (e.g., chemical and biological "warfare" that may sidestep definition—and governance—by the BTWC and/or CWC), or non-kinetic ways (which fall outside of, and, therefore, are not explicitly constrained by the scope and auspices of the BTWC, CWC, or code(s) of conventional warfare) [26–28, 33–34].

Gene Editing

Apropos current events, the use of gene editing technologies and techniques to modify existing microorganisms [35], and/or selectively alter human susceptibility to disease [36], reveals the ongoing and iterative multi-national interest in and weaponizable use(s) of emerging biotechnologies as instruments to produce "precision pathologies" and incur "immaculate destruction" of selected targets. The advent of CRISPR/Cas-based gene editing methods has enabled a more facile approach and has re-enthused interest and capabilities rendered by such techniques. Thousands of guide RNA sequences are broadly available and foster research uses in a variety of health and scientific disciplines [26]. Pairing this new capability to target and study genetic material with other ETs (e.g., neuroscience) could engender the development of potentially hazardous genetic modifications.

Of course, gene editing has limitations. Designing genetically active molecules that can target and affect the DNA in the nucleus of a cell can be arduous. Constructing molecules that are permeable to natural barriers (e.g., the blood-brain barrier, cell membranes, etc.) can be difficult if they are large or chemically inapt. In some cases, these constraints can be overcome both by using ETs or other/older gene editing techniques [37], and as CRISPR/Cas systems continue to increase in utility (i.e., with recent discoveries of additional endonuclease types and subtypes). For example, the Cas12 RNA-guided nuclease effector is a smaller and, in some cases, more functional version of Cas9, which increases the efficacy of CRISPR systems [38].

Indeed, older/alternate gene editing techniques may be used in conjunction with CRISPR/Cas systems to enable more precise genetic targeting. Zinc finger nuclease (ZFN) was one of the first archetypes of enzymatic DNA programing [39]. However, due to difficulties with ZFN design and application, methods like transcription activator-like effector (TALE) and CRISPR/Cas systems were developed for their simplicity and effectiveness [40, 41]. Like CRISPR/Cas systems, TALEs were found to exist in situ within bacteria [42]. The TALE gene editing system has the ability to cleave specific, desirable DNA sequences in various organisms and cell types [43, 44]. Although the technique lacks ease and speed, its high targeting capacity affords various in vivo uses. Recent research dedicated to reducing the time required to generate TALE systems may render these applications more facile and viable for use either alone and/ or with CRISPR-based approaches in the future [45].

CRISPR/Cas nucleases can be easily programmed to target a DNA segment of interest by pairing them with guide RNA [46]. Currently, CRISPR/Cas-systems are widely recognized as a superior gene editing technology. But like any molecular technique, CRISPR/Cas-based methods can be unsuccessful *in vivo* for numerous reasons. For instance, modifying genetic material can invoke cellular defense mechanisms to repair altered genes (sometimes rendering the modification null) or induce apoptosis (i.e., cell death). Additionally, limited cellular uptake of CRISPR can constrain effects and outcomes. These restrictions have been overcome in recent studies that have inhibited DNA damage caused by CRISPR/Cas9 [47], or have used gene delivery vectors to enhance uptake and optimize results [48, 49].

Extant unknowns of genomics, proteomics, and neuroscience can both limit CRISPR utility and/or lead to a host of unanticipated (but not necessarily unusable) effects that can be leveraged to influence public health and national security. For example, controlling (if not suppressing) off-target effects is necessary for a successful gene editing system. However, while off-target mutations may be a problem for therapeutics or the enhancement of organisms, such off-target manifestations might not be problematic (or in some cases may be desirable) when using gene editing technology to design a weapon to induce broad-ranging effects.

To be sure, if intended objectives of morbidity or lethality were obtained, it is likely that other (non-morbid or non-lethal) off-target effects would be viewed as less important or disregarded altogether. Further, the use of a combinatory approach (i.e., examining all gene editing systems and/or technologies for their utility) may increase the ease of genetically modifying benign microbes and proteins to be pathogenic, and altering extant pathogens so as to make them more dangerous. These methods could possibly be used to engineer bioagents that evade detection or attribution.

Biodata

CRISPR may also be used to perform rapid, comprehensive screens of specific genes and the phenotypes they produce [50]. This information could be utilized to reveal ways that certain individuals and/or groups could be specifically targeted. We have referred to these various categories of information as "biodata," noting that ETs such as CRISPR, taken with multi-modal information from other forms of assessment (e.g., neuroimaging, biomarkers) have broadened the scope of potential variables that may be identified, accessed, assessed, and, perhaps, ultimately affected [51].

The "digitization of biology" (i.e., information about the genetic code, translated proteins, and/or related metadata) is an unexploited quarry of opportunity for any actor who wishes to specifically target an organism. To be sure, there are concerns about breaches of individual privacy and how such biodata might be interpreted and used to incur certain biases in the ways that individuals or groups are viewed

| Country | Major Research Institutions or Companies | Example Research Projects and Themes | |
|----------------|--|--|--|
| China | National Center for Nanoscience and Technology EPRUI Nanoparticles & Microspheres Company Hongwu International Group | Biological effects of nanomaterials and nanosafety Nanodevices, nanomanufacture and applications Development of nanomaterials and microspheres Nano-sized powders | |
| Germany | University of Freiburg Dresden University of Technology BASF Frauenhofer-Gesellschaft | Bionanotechnology and suprmolecular bioaggregates Nanoelectronics Nanoanalyses Nanostructured materials | |
| Russia | Moscow Institute of Physics and Technology RUSNANO Selecta Biosciences OCSiAL | Nanobiopharmaceurtics Nanooptics and plasmonics Nanomaterials and quantum nanostructures Nanoelectronics and photonics | |
| United Kingdom | University of Cambridge London Centre for Nanotechnology ATDBio Owlstone | Nanoporous materials Modifying oligonucleotide scaffolding for nanoengineering Development of nano-scale structures Nanofabrication | |

Table 3. Selected International Nanoengineering Research Programs [55]

and/or treated. But additional considerations must now be afforded to the risk and threat of physical harms that could be incurred through access to such information.

In this light, biodata may be of even greater concern if and when neuropsychiatrically relevant. Such information could be used to identify individual and group susceptibilities and vulnerabilities to particular agents and effects, which may be instrumental in gene-edited production of novel and more precise microbes, toxins, antigens, or drugs. Moreover, (neuro) biodata can be manipulated to change individual and group medical records in ways that can influence the tenor and scope of clinical care, if not social, legal, and political regard.

Nano-engineering

Nanotechnology is a relatively new science that examines and engineers particles and devices at an atomic or molecular level (1–100 nm). Nanoscience and engineering have been, and are increasingly viewed for their viability to create neurotoxic/neuropathologic agents [34].

A recent review has raised concerns about incomplete effectiveness of protective barriers against the penetrance of nanomaterials to the brain, and this may afford an opportunity for vectoring these substances to the cerebral space to exert a variety of uses [52]. Specifically, attention was focused upon the potential of nanomaterials to induce neuroinflammation, oxidative stress, neuronal cell death, and to alter production of various neuroactive chemicals and affect network properties of the brain.

Evidence shows that nanoparticles can access the central nervous system via a number of routes. Uptake of nanoparticles through the nasal cavity can directly reach the brain through the olfactory tract, and because neurons have the capability to assimilate nanoparticles, the effect can spread throughout the brain. Pulmonary intake involves nanoparticles first crossing the lung-blood barrier, and subsequently the blood-brain barrier, to affect the nervous system. Translocation of nanoparticles from the gut and/or skin to the brain have also been documented, but the efficiency and potency of those routes are less understood [52].

Current applications of nanotechnology include: a) the insertion of nanodevices to remotely control organisms; b) creation of nanocarriers/capsules which could be used to transport molecules (carrying chemicals, proteins, or DNA/RNA) across membranes and the blood-brain barrier to target specific tissues or organs; and c) development of novel neurological molecules that are less (or not) susceptible to current countermeasures and/or therapeutics [53]. Nanomaterials can also be employed to enhance other ETs. As stated above, natural barriers can inhibit or reduce the penetrance and action of CRISPR molecules in the brain, and nanocarriers have been developed to increase the assimilation of

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CRISPR molecules into targeted cells [54–56]. Although still under-exploited for its kinetic and non-kinetic potential, nanotechnology is being explored for its dual or direct military use by a number of nations—including the U.S. (see Table 3).

Toward Address, Mitigation, and Prevention

Without philosophical understanding of, and technical insight to, the ways that non-kinetic engagements entail and affect civilian, political, and military domains, coordinated assessment and response to any such engagement(s) becomes procedurally complicated and politically difficult. Therefore, we propose and advocate increasingly dedicated efforts to enable sustained, successful surveillance, assessment, mitigation, and prevention of development and use of RLTs and ETTs to national security.

We posit that implementing these goals will require coordinated focal activities to: a) increase awareness of radical leveraging and ETs that can be utilized as non-kinetic threats; b) quantify the likelihood and extent of threat(s) posed; c) counter identified threats; and d) prevent or delay adversarial development of future threats (see Figure 2).

Indubitably, there are novel risks associated with misuse of the information and capabilities conferred by RLTs and ETTs. It should be presumed that access to such information and tools by bad actors is high, as many databases are openly shared, and those that are not shared have been, or may be vulnerable to hacking [51]. Access to this information and capability increasingly enables non-kinetic engagements, thereby fortifying the need to identify, meet, assess, and counter novel threats.

Exemplary of such enterprise is the development and growth of a relatively new discipline, "cyber biosecurity," which focuses upon evaluation, mitigation, and prevention of unwanted surveillance, intrusions, and malicious action(s) within cyber systems of the biomedical sciences [57]. However, for cyber biosecurity—or any program of coordinated assessment, mitigation, and prevention—to exert a sustained and iterative effect, it must exist within and be synergized by a larger infrastructure of dedicated effort.

Toward this end, we pronounce the need for a Whole of Nation approach to mobilize the organizations, resources, and personnel required to meet other nations' synergistic triple helix capa-

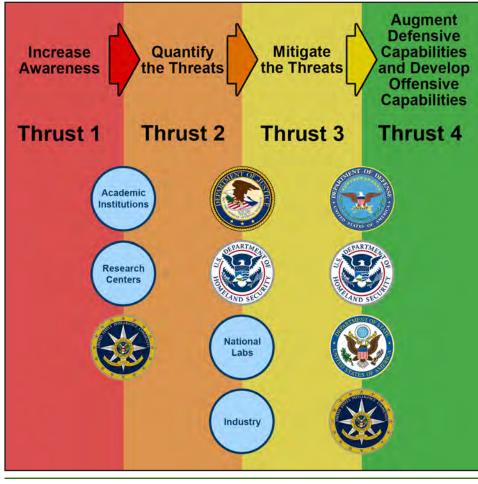


Figure 2. Four-Thrust Whole-of-Nation Approach

bilities to develop and non-kinetically engage RLTs and ETTs (see Figure 2).

Utilizing this approach will necessitate establishment of:

1. An office (or network of offices) to coordinate academic and governmental research centers to study and evaluate current and near-future non-kinetic threats

2. Methods to qualitatively and quantitatively identify threats and the potential timeline and extent of their development

3. A variety of means for protecting the U.S. and allied interests from these emerging threats

4. Computational approaches to create and support analytic assessments of threats across a wide range of ETs that may be leveraged and afford purchase in non-kinetic engagements

In light of other nations' activities in this domain, we view non-kinetic deployment of ETs as a clear and viable future threat [11, 58]. Therefore, as previously stated [28, 33, 34], and reiterated here, we believe actions should not focus on whether such methods will be utilized, but rather when, to what extent, and by which group(s) will such use be possible, and most importantly, ensuring the U.S. and its allies will be prepared for these threats when they are rendered.

Disclaimer

The opinions expressed in this article are those of the authors, and do not necessarily reflect those of the United States Department of Defense, United States Special Operations Command, and/or the organizations with which the authors are involved.

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Calendar of Events

| UUIY | | | | | |
|---|--|--|---|---------------|--|
| July 11 • Laurel, MD HDS 10th Annual Integrated Air and | | July 23 • HDS | July 23 • Washington, D.C. HDS Arctic Day 2019 | | |
| | Missile Defense Symposium | | | | |
| July 23 – 24 • Wilmington, DE CBRN CBRN Defense Conference & Exhibition | | July 30 – August 1 • West Lafayette, IN HDS 2019 Hypersonics Capabilities Conference | | | |
| Augu | st 2019 ——— | | | | |
| August 6 HDS | - 8 • Bethesda, MD 2019 Global Explosive Ordnance Disposal (EOD) Symposium & Exhibit | August 19 – 23 • Augusta, GA CIP TechNet Augusta 2019 | | | |
| August 20 CIP | 6 – 28 • Alexandria, VA iFest 2019 | | | | |
| Septe | ember 2019 — | | | • | |
| September 10 - 12 • Novi, MIAEThe Battery Show | | September 16 – 18 • Groton, CT HDS 2019 Undersea Warfare Technology Fall Conference | | | |
| Septembe HDS | er 17 – 19 • Quantico, VA Modern Day Marine | Septemb HDS | er 23 – 26 • Tam Federal Identity | ipa, FL | |
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