SAND2020-4584R

COVID-19 LDRD Project Summaries
April 22, 2020

Sandia National Laboratories currently has 27 COVID-related Laboratory Directed Research & Development (LDRD) projects focused on helping the nation during the pandemic. These LDRD projects cross many disciplines including bioscience, computing & information sciences, engineering science, materials science, nanodevices & microsystems, and radiation effects & high energy density science.

Bioscience

COVID-19 infection prevention through natural product molecules

This project evaluates natural product molecules with the potential to prevent 2019-nCOV infection. The molecules work by blocking the angiotensin-converting enzyme 2 (ACE2) protein active site in human airways. Previous work focused on modeling candidate natural compounds, but this work will examine three (baicalin, hesperetin, glycyrrhizin) in experimental in vitro studies, which include recombinant protein inhibition assays, cell culture virus inhibition assays and cytotoxicity assays. The project will deliver selectivity indices (ratio that measures the window between cytotoxicity and antiviral activity) of the three natural compounds that will help guide the direction of SARS-CoV-2 therapeutic development.

Rapid assessment for COVID-19

This project proposes to adapt Sandia's Rapid Syndromic Validation tool to collect syndromic-based patient information (e.g., mortality, morbidity, prevalence) to identify potential COVID-19 clusters and evaluate community spread. The novel R&D involves advanced modeling for high-resolution syndrome mapping and the differentiation of COVID-19 from flu, allergies, etc. Public health officials will be able to rapidly gather data to help prioritize testing and resources to specific regions and/or communities through a web interface. An additional public-facing web-interface will build on top of the tool, through which individuals can be screened and referred for test collection as appropriate. Only clinical symptoms and zip codes will be associated with the collected data.

Testing a novel peptide drug to treat COVID

There is growing evidence a 'cytokine storm' is a significant driver of COVID-19 mortality. The project hypothesis is that a patient's immune system becomes overactive causing white blood cells to over-produce small molecules called cytokines which further activate the immune system and cause the immune system to attack the infection as well as healthy tissue, resulting in organ failure. The heart and lungs are primary targets of SARS-CoV-2. When SARS-CoV-2 binds to enzyme 2 (ACE2) in heart and lung tissue, it decreases the inflammatory effect of ACE2 and allows the cytokine storm to grow. A novel

Sandia National Laboratories is a multimission laboratory managed and operated by National Technology & Engineering Solutions of Sandia, LLC, a wholly owned subsidiary of Honeywell International Inc., for the U.S. Department of Energy's National Nuclear Security Administration under contract DE-NA0003525.

peptide drug, donated by Novopyxis, will be tested in the lab and could potentially lead to increased survival and a reduction in the amount of hospital time for COVID-affected patients. The peptide, NP-6A4, is an anti-inflammatory, anti-fibrotic, and cardioprotective member of the renin-angiotensin system. Since NP-6A4 increases both expression and signaling of Angiotensin II receptor type 2 (AT2R), it is hypothesized that NP-6A4-induced increase in anti-inflammatory signaling can fill in the gap in the anti-inflammatory defense system of heart and lung cells caused the by loss of ACE2 due to SARS-CoV-2 binding and likely promote cell survival in these cell types.

Betacoronavirus sequence server

Monitoring changes in the SARS2 virus (COVID-19 agent) genomic and protein sequences over time will be essential for understanding clinical outcomes and predicting future impacts of the virus. This project focuses on developing a genome and protein sequence analysis tool as a fundamental enabling technology for monitoring SARS2. Analysis tool goals include supporting determination of 1) chains of transmission and 2) the functional consequences of sequence changes over outbreak progression, including effects on diagnostics. The tool will automatically extract and align protein sequences from the assembled data to obtain full genomic RNA sequences and then produce phylogenetic trees to monitor the progression of COVID-19 and be immediately useful to internal/external diagnostic work.

Handheld biosensor for COVID-19 screening

A Sandia surface acoustic wave (SAW) handheld biosensor will be developed to amplify and detect synthetic SARS-COV-2 RNA through DNA conversion. This biosensor will enable development of a rapid (<30 minutes), point-of-care diagnostic test for detection of COVID-19 from nasal swab samples. SAW devices are more robust in non-laboratory settings; theoretically more sensitive because they detect the mass of the sample (making it a promising approach for field-deployable sensors), and can be faster because they require smaller amounts of DNA to show a detectable signal. Sandia will develop/ integrate a 60C Peltier heater to enable amplification using the Loop-mediated isothermal amplification method. Amplifying DNA directly on the SAW is unique since it doesn't depend on having amplified DNA diffuse to the surface. The project will also design a sample cartridge for an existing Sandia-Sensor Kinesis Corporation platform, Optikus, that can handle samples from nasal and sputum swabs.

Development of novel medical countermeasures against COVID-19

Rapid development of effective antiviral diagnostics/therapeutics with a mechanism to respond quickly to emerging pathogens is needed. This project will focus on SARS-CoV-2 detection/diagnostics and quenching unincorporated amplification signal reporters (QUASR) with reverse-transcription loop-mediated isothermal amplification (RT-LAMP) chemistry requiring a simplified workflow and portable instrumentation controllable via smartphone. An immunoassays panel will detect viral and host antigens on Sandia's portable SpinDx platform and offer rapid detection without need for sample preparation.

Direct detection of viral ribonucleic acid (RNA) via QUASR RT-LAMP, combined with detection of host response to infection via SpinDx immunoassay, will diagnose all stages of COVID-19 and enable positive identification of SARS-CoV-2. Sandia's lipid nanoparticles will be leveraged in a COVID-19 mouse model to determine effectiveness at treating disease RNAs encoding 1) anti-SARS-CoV-2 neutralizing monoclonal antibodies with enhanced immune-protective characteristics, and 2) proteins to reduce lung inflammation without impeding viral clearance.

Pre-symptomatic COVID screening

Checking temperature is a preliminary screen for COVID-19 infection but is ineffective when a person is asymptomatic. Core body temperature fluctuates the least of all the vital signs, but skin temperature fluctuates rapidly. In recent work, unique temperature patterns were recorded up to three days before other signs of infection in septic patients. This project will use Sandia's existing transdermal microneedle platform to develop and test a transdermal temperature sensor able to continuously and accurately measure core body temperature to detect COVID-19 pre-symptomatically, predict severity, monitor disease progression, and improve treatment outcomes. The existing microneedle array needs minor modification to be converted into a temperature sensor. Commercially available fine wire gauge thermocouples were identified and tests of wires with similar dimensions show potential to be inserted into the needle bores of the existing array.

Computing & Information Sciences

Rapid response data science

This project focuses on the identification of key documents that allow analysts to rapidly arrive at useful advice for addressing COVID-19 through the application of unsupervised algorithms that will help organize the information space and assist subject matter experts (SMEs). This will be accomplished through existing data visualization, collection, processing, and indexing tools used in other research. Three tasks will be conducted in parallel and mutually inform each other. These include data collection and processing, adaptation of compression-based analytics, search, and visualization tools to develop a new capability to reveal the underlying shape of the information space, and the identification of questions our biomedical and public health SMEs need answered. The outcome will include the most useful machine learning algorithms, and the packaging of code such that it could apply to future work.

Modeling for epidemiology

This team seeks to employ state-of-the art optimization and resource allocation methods to model the COVID-19 pandemic and enable quantitative estimation of the effectiveness of different social and medical policies for containment. NM will be used as an exemplar to take advantage of the state's commitment to provide data to ground the R&D and to also provide a realistic case for model development, calibration, and testing. Partnership with the state will allow rapid access to diverse data types that can be incorporated into the model. A model of New Mexico's COVID-19 disease burden will

be developed and used to systematically investigate: (1) Incorporating unique behaviors of diverse populations across the state into the model; and (2) Evaluating testing and mitigation strategies in the current public health modeling framework. Project milestones include: (1) Completing model using initial public health data from New Mexico Department of Health (NMDOH), (2) Verifying model from initial outputs, (3) Calibrating in conjunction with NMDOH, (4) Sharing results with New Mexico and other government stakeholders.

Dynamic modeling value of rapid screening

This team will rapidly develop and apply a computational model of dynamics that impact COVID-19 transmission to and from first responders. The developed model will use the system dynamics modeling approach, which enables close attention to system structure and nonlinearities, while allowing for rapid development and effective results communication. This project will evaluate the daily movement and interaction of first responders, COVID-19 patients, and healthcare workers; the dynamics of epidemics (e.g. susceptible-exposed-infectious-recovered dynamics); and the dynamics of biosurveillance. Chosen interventions will be applied based on a range of response policy options to analyze whether to apply a given intervention, as well as when and how much (e.g. how long of a delay in application is acceptable). Initial results will be available after one week of activity, and further refinement will occur over the next month to ensure actionable results.

Forecasting COVID-19

This short-term forecasting project will develop a data-driven model with an inference technique, predicated on the observed time-series of people testing positive for COVID-19, to estimate the latent infection process (i.e., number of people infected every day), as a function of time, during the period when testing was not being performed. Once available, this rate of infection can be convolved with the incubation period to predict the time-series of people exhibiting symptoms. The project will adapt an existing method for estimating the latent process of infection to the peculiarities of COVID-19, the implementation of a faster, variational inference technique to enable quasi-real-time inferences. Bayesian estimation procedure to infer the infection rate curve and estimate the final size of the epidemic, and then the inferred infection rate will then be convolved with the incubation period to predict the epidemic curve. These can then be used within a resource allocation engine, such as the one being developed under the LDRD project focused on modeling for epidemiology.

Detect misinformation campaigns

Resurgent States are exploiting the COVID-19 pandemic to undermine disease response efforts, degrade social institutions, and subvert international management efforts. Sandia cybersecurity tools will be developed to identify/categorize COVID-19 misinformation and inform design of counter-misinformation campaigns. Sandia's Avondale web-crawler will search online social media and news streams to establish

labels and types of misinformation on viral origin, medical/non-medical countermeasures, public health and security sector capacity, and detection/surveillance messages. Next, data will be categorized/analyzed with Citrus and sticky-spready to define timeline, sources, message diffusion, type of misinformation related to disease emergence in China. This work will apply cybersecurity approaches to a naturally occurring infectious disease outbreak as it unfolds and develop a change detection algorithm for scientific data to identify temporal and directed-network movement into non-science networks and non-science networks influencing scientific data.

Robust estimation of transmission parameters for COVID-19 policy planning

Reliable and rapid estimation methods are needed to characterize COVID-19 transmission rates, predict resource needs, and assess the efficacy of mitigation policies. Data needed to estimate disease transmission are often limited or incomplete in early stages of an outbreak, and variations in testing can cause inconsistent bias. Government policies often do not immediately change individual behaviors. This project will develop novel inference capabilities to enable the rapid prediction of transmission parameters and transmission rate. This requires new methods that (1) integrate biased, limited data for reported cases, hospitalizations, and deaths, and (2) estimate temporal and spatial variation in transmission parameters. The project will develop a unique capability to perform rapid disease transmission parameter estimation at scale, including all counties in the United States, which can be used to assess the impact of state and national policies on the spread of COVID-19.

Engineering Science

Bioparticle transmission

This project addresses COVID-19 particle transmission and deposition through a computational investigation of particle trajectory, evaporation, and deposition that originates from coughing and sneezing events in typical crossflow configurations found in most social gathering spaces. The simulation effort will guide future social distance norms/rules and provide droplet lifetime estimates as a function of room humidity and deposition probability. The project plan includes initial plume dispersion configuration, the effect of crossflow in a typical space on particle transport and droplet lifetime originating from an idealized cough, determination of the lifetime of evaporating and depositing particles in a variety of complex flow configurations, analytical evaporating estimates of particles settling, and technical interaction with Stanford's Predictive Science Academic Alliance Program-II and III which has experience in post-Ebola particle dispersion simulation in aircraft spaces.

CFD modeling safe separation distances

The recommended six feet for social distancing to prevent COVID-19 spread is based on studies indicating larger water droplets or mucus discharged during a cough or other expiratory event only travel a

maximum of 1 – 2 meters, but recent studies indicate smaller more buoyant vapor droplets can be suspended/carried > 6 m. High-speed imaging shows the fluid dynamics of sneezing is complex, ranging from ejected mucosalivary fluid sheets to bag bursts to ligaments and finally to droplets. Detailed validated modeling is needed to explore a range of expiratory events, environmental conditions, and source/receptor factors to determine more accurate safe distancing requirements for COVID-19 and other infectious diseases. Computational fluid dynamics models will capture the transient, multiphase, turbulent processes of different expiratory events under different environmental and boundary conditions to determine ranges of safe separation distances. Modeling results will be validated with recent experimental data from Massachusetts Institute of Technology.

Science-based understanding of personal protective equipment degradation after sterilization for reuse
The U.S. needs an estimated 90 million masks for a 42-day outbreak. The ensuing shortage drives the need to develop sterilization techniques for re-useable hospital personal protective equipment (PPE). This study examines pore-level changes occurring when PPE is subjected to various sterilization protocols. The findings will help develop critical decontamination protocols and shed light on alternative materials for reusable masks. This project will perform pore-scale measurements on PPE sterilized by a variety of commercial methods including heating, sodium hypochlorite solution, hydrogen-peroxide vapor sterilization (in collaboration with University of New Mexico (UNM) Health Sciences Center (HSC), Department of Infectious Diseases), and gamma irradiation (in collaboration with the Gamma Irradiation Facility sterilization LDRD project). Sandia will analyze the micron-scale pore structure of new and decontaminated PPE, characterize micron scale pore-size distributions and tortuosity, and then correlate measured morphology changes in non-woven fabric masks with decontamination procedures and filtration performance. Matured methods will be applied to PPE provided by collaborators after confirmation of sterility through comprehensive testing at UNM HSC.

Direct Simulation Monte Carlo Model for COVID prediction
Individual-Level Models use commonly lagged/skewed data from early stages of past epidemics/pandemics and lead to predictions with significant margins of error. They are sensitive to a single, widely varying input parameter, the number of people infected by one person, leading to a large range of predicted outcomes. Sandia's simulation capabilities and High-Performance Computer resources can determine the current COVID-19 pandemic state and provide a platform to efficiently explore 'what if' scenarios on mechanisms affecting spread. Direct Simulation Monte-Carlo (DSMC) methods are computationally efficient, massively parallel, and run on state-of-the-art HPC platforms. They generate statistically accurate outcomes, excel at self-consistently tracking mobilities, and can consider additional factors. DSMC will reduce needed assumptions and increase predictive accuracy. This project will provide proof-of-concept visualization tools with immediate pandemic impact, lay a basis to model future

pandemic scenarios, and help comprehend the roles of asymptomatic cases and recovered individuals in the second round of the infection.

Aerosol transport through masks

Do-It-Yourself medical masks vary in pathogen filtration effectiveness based on materials used. This project will provide a deeper science-based understanding of aerosol transport mechanisms through commonly available alternative materials. Woven/non-woven materials used in filter-penetration studies will be compared with a modified *National Institute for Occupational Safety and Health* protocol utilized by the Sandia Filter Penetration Testbed. Flow condition testing will occur with varying aerosol size, charge, and phase (liquid versus solid), so dominant aerosol-transport mechanisms occurring for different types of aerosols can be determined. The micro-scale pore structure of each material will be analyzed to determine the pore-size distribution and tortuosity. Electret charge measurements will be made using techniques successfully applied to the Gamma Irradiation Facility sterilization LDRD project. Additional medical mask requirements, such as hydrophobic layers and a respiration pressure differential of a specific value, will also be tested.

Materials Science

PPE pipeline

The E-PiPEline project will address shortages of PPE for frontline U.S. health care providers to reduce exposure to COVID-19 by evaluating Emulated-PPE (E-PPE) design concepts for face masks and face shields using Commonly Available Materials (CAMs) with a fast time to market. The Sandia E-PiPEline project will evaluate existing referenced citations to select the best one-off methods for constructing an E-PPE face mask and shield while minimizing time to market, build difficulty, build cost, and maximizing qualitative effectiveness. To allow health care professionals to begin mass production of E-PPE face masks and E-PPE face shields, the project will develop and demonstrate an instruction template for an E-PPE face mask and face shield concept, define the trade space of cutting-edge E-PPE concepts for face masks and face shields using CAMs, develop relevant evaluation metrics, and defensibly evaluate E-PPE face mask and shield concepts.

Supercritical CO_2 for PPE

Supercritical CO_2 is a unique solvent that is becoming increasingly popular for industrial cleaning and chemical extraction processes through its ability to permeate into microporous materials and its performance as a solvent. The team hypothesizes that super critical CO_2 processing, with a suitable anti-viral additive, will allow for multi-reuse processing of N95 masks using the existing infrastructure in the U.S. and abroad in the dry-cleaning industry. The development and validation of a novel sterilization approach that leverages existing dry-cleaning processes would enable rapid deployment. Hospital

workers would fill a fabric bag with used N95 masks, add an anti-viral agent, and close it with a tie wrap before sending to a dry-cleaning service provider. Existing super-critical CO_2 dry cleaning cycle will be run, after which, the bags be returned to the hospital without being opened.

Spray-on active layer

This project will develop and demonstrate an active spray-on thin coating to improve PPE efficiency and extend their use time. The advantages of a spray include its ease of application to a number of surfaces (e.g., interior or edges of masks, frequently touched surfaces, masks), and that it can quickly improve or renew the surfaces it is applied to. The project will design and apply novel anti-viral formulations to deposit a renewable thin 'coating' via spray that provides an additional active disinfection functionality and demonstrate a proof-of principle showing that treated masks, filters, or similar PPE can more effectively prevent transfer of viral material and extend use time. This team will examine treated and reference surfaces for deposition and effectiveness in screening remaining viral activity.

Boronic acid-functionalized polymer

This team hypothesizes that boronic acid-modified polymers (BAMPs) can crosslink the spike glycoprotein of SARS-CoV-2 and thereby deactivate the virus. If true, BAMPs could potentially be deployed in several ways to inhibit the spread of COVID-19: as a protective coating incorporated into existing PPE such as N95 masks, as a functional element of air filtration devices, or in decontamination sprays. To test, they will acquire the SARS-CoV-2 spike glycoprotein, as well as ACE2 protein, which is identified as the key human cell receptor, perform a focused set of experiments to test the ability of BAMPs to crosslink the spike protein and to further inhibit binding of the spike protein to ACE2. If successful, they will provide to external researchers, who have access to SARS-CoV-2 and appropriate facilities for its handling, to initiate analogous testing of BAMPs on the actual virus.

Carboxylic acids as sanitizers

Food-grade short chain carboxylic acids (levulinic acid (LA)) are shown to improve the antiseptic effect of detergents, such as sodium dodecyl sulfate (SDS), and are used on food processing equipment. Its physical properties and effectiveness under organic load make the mixture a promising multi-purpose surface sanitizer. Since LA is not as widely produced as other carboxylic acids and to enable the rapid scale-up needed, this project will evaluate the effectiveness of mixtures of LA with readily available ingredients. The effectiveness of LA-SDS formulations will be evaluated against existing decontaminants and other readily available mixtures. If on-hand candidate materials are effective, the feasibility of deploying LA-SDS formulations will be evaluated based on their ability to be rapidly produced. The results will inform whether increased LA production is needed, and if it can be substituted for existing commodity carboxylic acids as a broad use surface sterilizer.

Self-cleaning coatings

This project will evaluate whether a polymer-based conformal system will be effective for the SARS-COV-2 virus and develop optimal disinfectant formulations. The base polymer, polyethyleneimines (PEIs) modified with polycationic hydrophobic alkyl chains, acts like a solid-state soap that punctures the lipid membrane of enveloped viruses rendering them inactive. A photosensitive antimicrobial compound known as zinc-tetra(4-N-methylpyridyl) porphine (ZnTMPyP4+) is doped into the PEI at 1 weight 24092% as a backup disinfectant. The backup mechanism is based on singlet oxygen generation on the material surface in the presence of visible light. This approach differs in that a single conformal coat is expected to supply enough material for 100% viricidal activity yet thin enough for discreet application on items such as PPE (masks, gloves, coats, etc.), medical equipment (e.g. ventilators, gowns, sheets), and high touch areas (e.g. door knobs/handles).

Continuous positive airway pressure ventilators for COVID-19 by modification of equipment

Ventilators are a critical resource for COVID-19 patients, but supply is limited. Continuous positive airway pressure (CPAP) equipment is produced in large quantities, provide some ventilator functionality, and use pressures in a similar range of 5-40 cm of H_2O. This work will modify CPAP equipment to provide basic ventilator support by tailoring the functions to provide variable pressure and handle higher oxygen concentrations. Work will begin with medical experts/pulmonologists to define therapeutic requirements for COVID-19 patients needing ventilator support, with the intent to make a CPAP ventilator to relieve demand and allow physicians to decide which patients need high-end machines, ultimately saving lives. A partnership with UNM's School of Medicine, Pulmonary Medicine Division, will define what is needed/practical. Engineers will begin parallel evaluation of modification approaches to obtain performance consistent with medical requirements. Then, a prototype will be constructed with the advanced manufacturing experts on our team; if successful, the manufacturing of parts will be distributed across the Department of Energy Complex.

Nanodevices & Microsystems

Catalytic materials for SAR-COV-2

The surface stability of SARS-CoV-2 has been shown to be up to 72 hours on plastic, 48 hours on stainless steel, and four hours on copper. Better material candidates are needed for high touch surfaces and PPE. Catalytic surfaces such as Ag/Al_2O_3 and Cu/Al_20_3 are shown to rapidly inactivate SARS Coronavirus in minutes. The team will study Ag/TiO_2 thin films shown to be 5x more efficient photocatalysts than previously studied material systems and investigate surface stability of coronavirus on Ag/TiO_2 under 365 nm UV-A light. Photocatalyst materials will be produced on silicon wafer targets in an ion assisted deposition process followed by thermal annealing in ambient conditions to control Ag nanoparticle size. Viral surface stability will be tested using human coronavirus strain NL-63 a BSL-2 safe surrogate for SARS-

COV-2, shown to have comparable surface stability, and measured with an infection assay and quantified with a plaque assay as compared to stainless steel control.

Radiation Effects & High Energy Density Science

Gamma Irradiation Facility sterilization

Ionizing radiation is known to cause atomic bond breaking and polymer cross-linking which, at high doses, can result in degradation of the structural/mechanical integrity of materials. Ionization radiation is also an effective way to neutralize pathogens. This rapid investigation will determine if crucial PPE has the appropriate integrity for re-use after gamma irradiation at levels consistent with neutralization of the SARS-CoV-2 virus. The initial focus is on the N95 mask since it is the PPE item in shortest supply. Uncontaminated masks will be irradiated at various ionizing dose levels using the Co60 gamma source at Sandia's Gamma Irradiation Facility and then checked for their fitting factor and structural integrity using industry standard tests. Doses are generated based on published viral sterilization data for a similar virus (SARS 2002). Other PPE, e.g. Tyvek suits, surgical masks, and face shields, supplied by collaborators at UNM Hospital, will also be irradiated and characterized, but these will not be tested against industrial standard tests for material integrity, so the characterization is qualitative. The utility of using gamma irradiation for sterilization of the N95 masks will be compared to published performance criteria on other commonly used sterilization methods.

Sandia National Laboratories is a multimission laboratory managed and operated by National Technology & Engineering Solutions of Sandia, LLC, a wholly owned subsidiary of Honeywell International Inc., for the U.S. Department of Energy's National Nuclear Security Administration under contract DE-NA0003525.

Sandia National Laboratories