JSTO in the News

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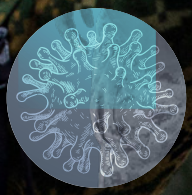
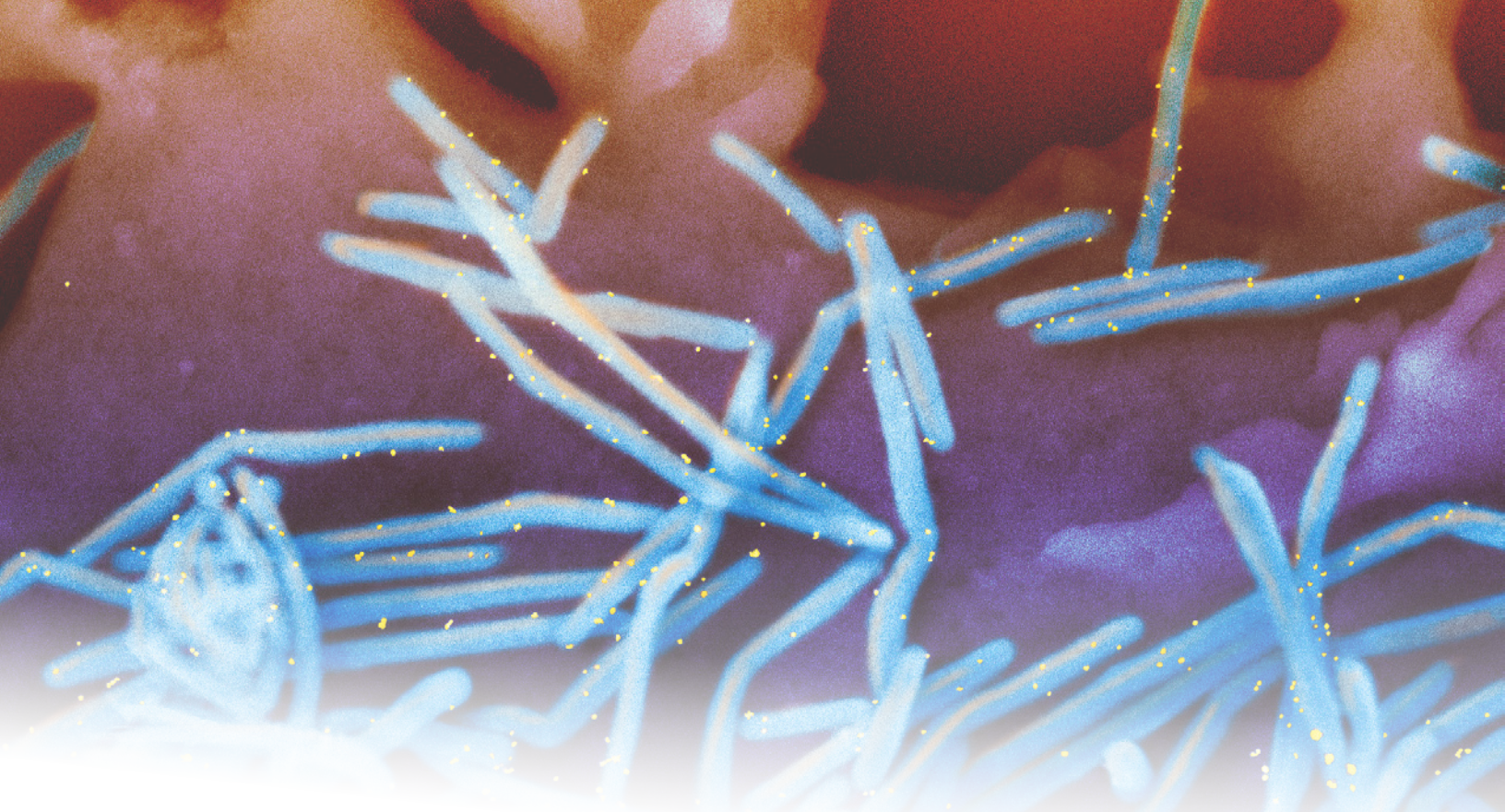


Body Language

Docking by Design



DTRA MISSION

DTRA provides cross-cutting solutions to enable the Department of Defense, the United States Government, and international partners to Deter strategic attack against the United States and its allies; Prevent, reduce, and counter Weapons of Mass Destruction (WMD) and emerging threats; and Prevail against WMD-armed adversaries in crisis and conflict.

CHEMICAL AND BIOLOGICAL TECHNOLOGIES DEPARTMENT MISSION

Lead DoD science and technology to enable the Joint Force, nation, and our allies to anticipate, safeguard, and defend against chemical and biological threats.

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Front cover: U.S. Navy Petty Officer 2nd Class Braden Johnson conducts a walking blood bank whole-blood transfusion on a simulated casualty during a Visit, Board, Search, and Seizure course at Fort Eustis, Virginia. (U.S. Marine Corps photo by Cpl. Matthew Romonoyske-Bean)

Inside cover: Scanning electron micrograph of human respiratory syncytial virus (RSV) virions (in blue) that are labeled with anti-RSV F protein/gold antibodies (in yellow) shedding from the surface of human lung epithelial A549 cells. RSV is a common contagious virus that infects the human respiratory tract. (National Institute of Allergy and Infectious Diseases photo)

Back cover: Sgt. Andrew Gardner, a medic with the 402nd Engineer Company in Des Moines, Iowa, administers an IV to Spc. Thomas Sill while Pfc. Peter Martin holds the IV bag during Sapper Stakes at Camp Dodge, Iowa. (U.S. Army photo by Catrina Francis)

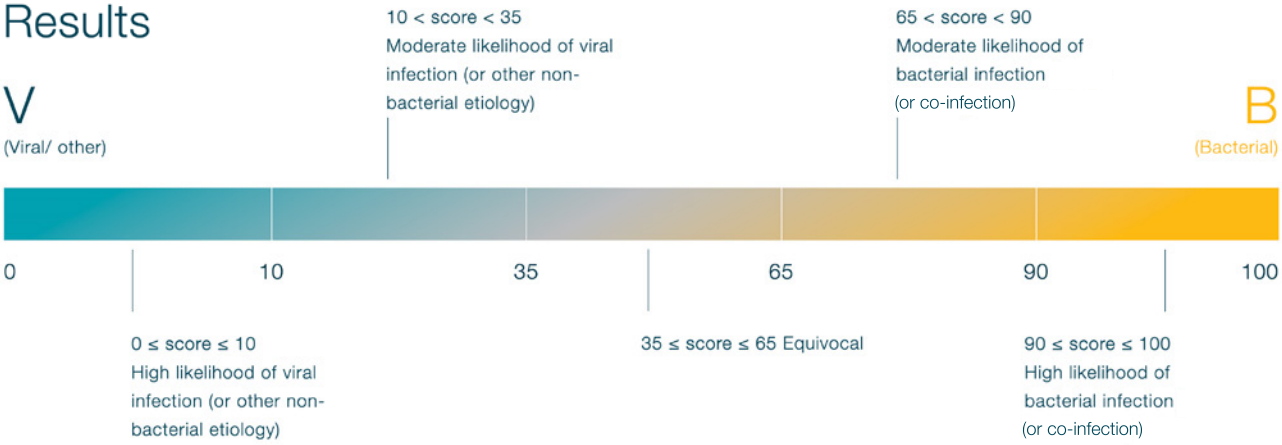
Body Language

Biomarkers of the body's natural responses indicate whether an infection is viral or bacterial. MeMed's Key is the latest way to listen to what the body is telling us.

A diagnostic test that quickly determines if an illness with a fever is caused by a bacterial versus a viral infection could speed up administering the appropriate treatment as well as help reduce the further emergence of antibiotic-resistant bacteria, which is a serious global health threat. A new analyzer by the Israel-based company MeMed called the Key is a host immune-response diagnostic tool that can distinguish between bacterial and viral infections.

The Defense Threat Reduction Agency's (DTRA) Chemical and Biological Technologies Department in its role as the Joint Science and Technology Office (JSTO) for Chemical and Biological Defense investment in MeMed supported the research team in looking for the body's response to the infection to identify it instead of looking for a specific bacterial or viral pathogen.

Interpreting Results



The new technology uses machine learning to integrate measurements of three key host-immune proteins into a score indicating the likelihood of bacterial or viral infections.

The Key analyzer and BV cartridge. (MeMed photo)

The new technology uses machine learning to integrate measurements of three key host-immune proteins into a score indicating the likelihood of bacterial or viral infections. This score, called BV, for bacterial vs. viral, has been measured and shown to be accurate in over 20,000 patients.

Prior to DTRA JSTO's investment, MeMed had already begun looking for biomarkers of infection to use in a rapid test. Through their preliminary work, the research team identified three biomarkers they could measure using a laboratory test called an Enzyme-Linked Immunosorbent Assay (ELISA) and an algorithm that combined these measurements into a score indicating bacterial versus viral infection—the BV score. The MeMed group validated the diagnostic accuracy of the BV score in various clinical studies with different populations and in different countries where the performance was compared to reference standards. While the ELISA test is sensitive, it takes up to three hours to complete and requires trained technicians to perform it.

The ELISA provided a proof of concept to measure the identified biomarkers, but MeMed wanted a faster and easier method to measure and report the results. With DTRA JSTO's investment, MeMed developed an analyzer that measures proteins using magnetic particles and a reagent to detect chemiluminescence, which is a robust method to get the precise and reproducible measurements they needed.

Other studies conducted on adults confirmed the pediatric studies and gave the team the confidence they had a BV score that MeMed could license for clinical use. Consequently, the team started another clinical study performed on American patients using MeMed's newly developed analyzer in several U.S. urgent care centers and emergency departments, and two Israeli emergency departments. After a thorough review, the Food and Drug Administration gave both the analyzer and the single-use, disposable BV cartridge full clearance.

This new diagnostic tool illustrates how DTRA JSTO can more quickly detect biologic threats against the Joint Force and administer effective treatments. Warfighters and civilians

A Global Crisis

Bacterial and Viral Infections Induce Similar Symptoms

40% of Prescribed Antibiotics are Unwarranted

U.S. AMR-related Deaths >35,000
U.S. AMR-related Illnesses >2,800,000
U.S. Annual Costs >$26 Billion

Growing Antimicrobial Resistance (AMR)

Limitations of Current Diagnostics

Poor Performance to Evolving Pathogens

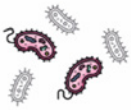
Pathogen Inaccessibility

False Alarms Due to Bystander Microorganisms

MeMed BV Blood Test Decodes the Immune Response to Infection

3-Biomarker Score Based on Machine Learning

Highly Accurate



Insensitive To Bystander Microorganisms

A Compact Point-Of-Need Device: MeMed Key

Rapid, Affordable and User Friendly

FDA Cleared and CE-IVD

Bacterial or Viral Diagnosis to Guide Antibiotic Decisions

Preparing The Stage For Global Impact

Massive Body of International Blinded Clinical Evidence

Score Already Applied in Real Life Settings

Worldwide Collaborations with Key Stakeholders

Planned Product Maturation

Expanding Sample Type to Include Whole Blood (Currently Serum)

Application for CLIA Waiver (Currently Moderately Complex)

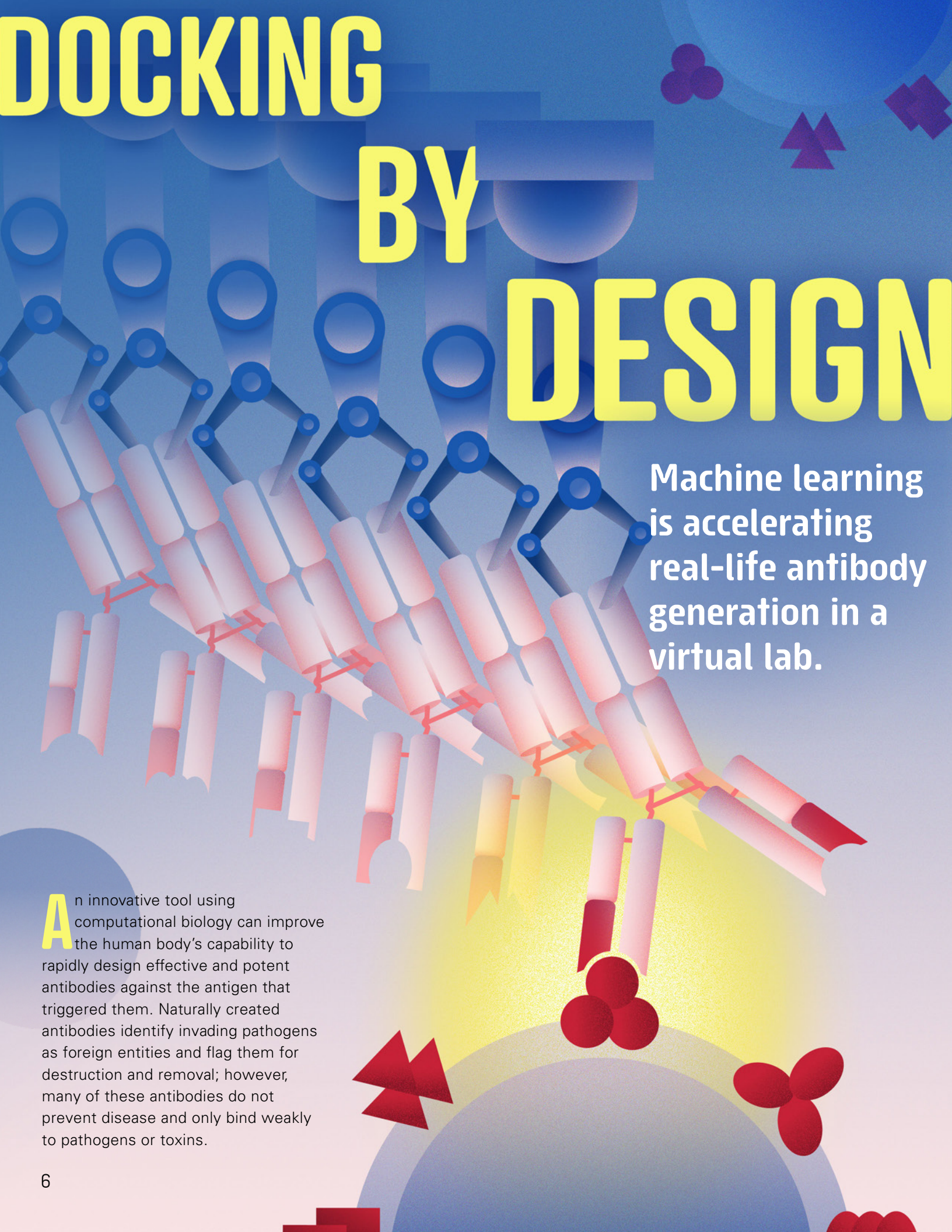
Expanding Test Menu (e.g., MeMed Universal Severity)

This chart illustrates the bacteria-virus dilemma with a proposed solution provided by DTRA JSTO's investment. (MeMed image)

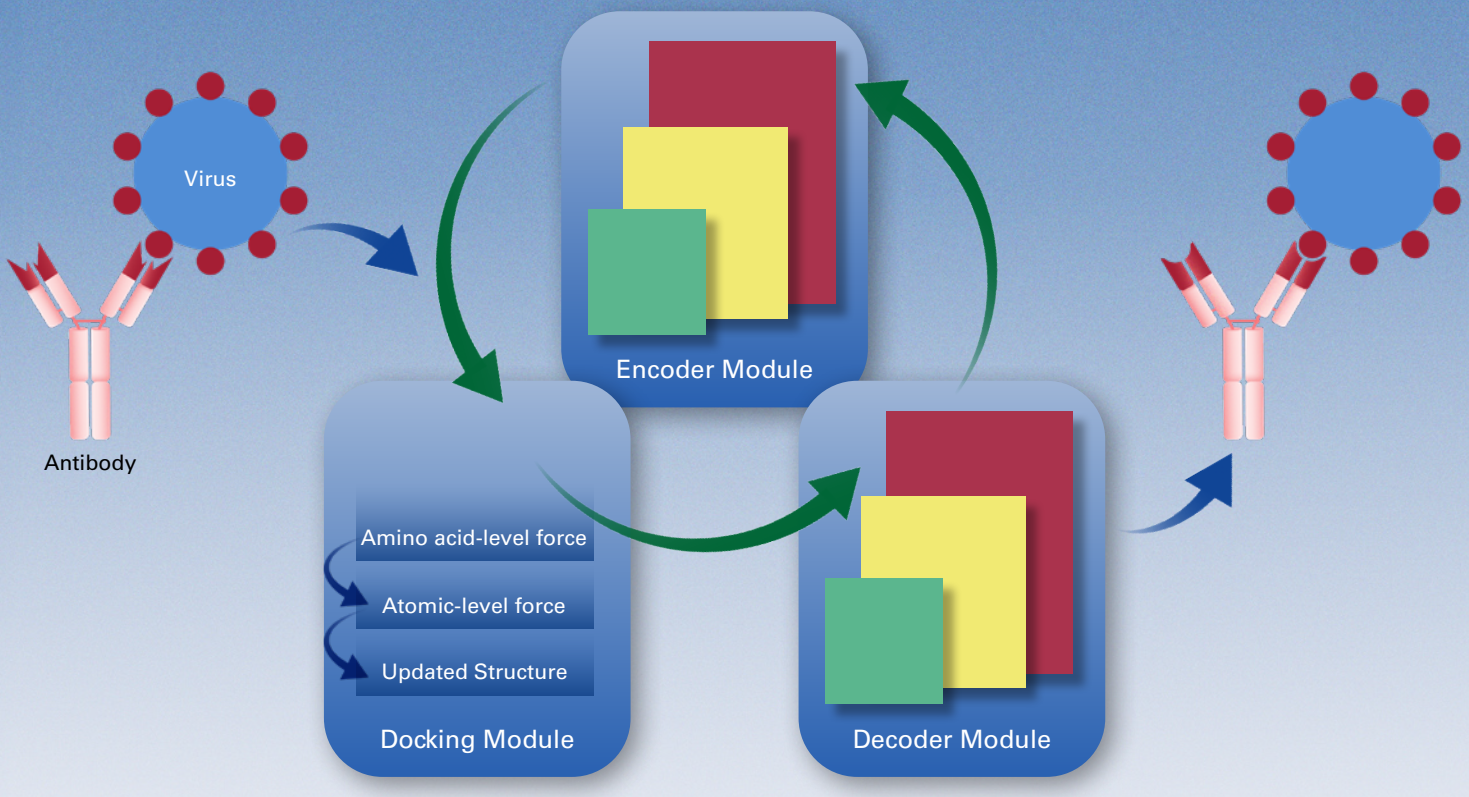
alike will be able to receive a quicker and more accurate diagnosis of their illnesses, leading to appropriate treatments, diminishing the administration of improper medications, and helping reduce the further emergence of antibiotic resistance. ●

DOCKING BY DESIGN

Machine learning is accelerating real-life antibody generation in a virtual lab.



An innovative tool using computational biology can improve the human body's capability to rapidly design effective and potent antibodies against the antigen that triggered them. Naturally created antibodies identify invading pathogens as foreign entities and flag them for destruction and removal; however, many of these antibodies do not prevent disease and only bind weakly to pathogens or toxins.



Hierarchical Structure Refinement Network (HSRN) to improve antibody affinity and function

To improve the body's immune reaction, high-affinity antibodies can be cloned and manufactured to provide short-term immunity in pre-exposure situations or to be used therapeutically during illness to help suppress tissue damage, allow the host defenses to catch up, and eventually overcome the infection. The Defense Threat Reduction Agency's (DTRA) Chemical and Biological Technologies Department in its role as the Joint Science and Technologies Office (JSTO) for Chemical and Biological Defense invested with researchers at the Massachusetts Institute of Technology (MIT) to design a technology capable of predicting antibody-antigen interactions and improving antibodies, which are an invaluable tool in DTRA JSTO's arsenal against biological weapons.

Antibody therapies are sometimes the first treatments available for new biological threats, as was the case in the beginning of the COVID-19 pandemic. However, antibody therapies developed from the blood of immune humans or animals take several months to produce, test, and formulate before beginning clinical trials. Typically, highly active human or animal antibodies are isolated and improved through laboratory experimentation to enhance efficacy by increasing binding affinity and functional activity. However, these efforts take a long time to develop; and in a nonemergency setting, such development often takes several years before clinical trials can start.

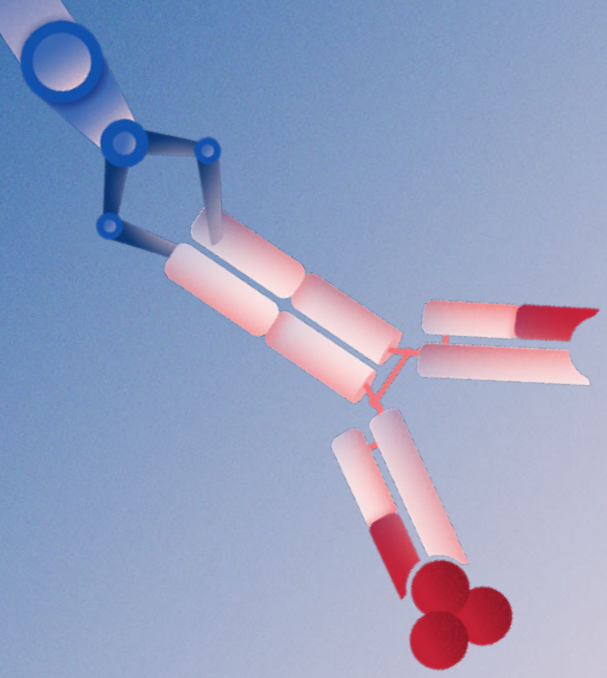
Hierarchical Structure Refinement Network (HSRN) to improve antibody affinity and function: HSRN consists of three modules (in the blue boxes) to improve the fit of an antibody (top left in pink) to its target antigen (upper right blue virus red spike protein). HSRN focuses on the portion of the antibody (red portion of the antibody), which binds its target.

The encoder module (top middle) defines the target-binding portion of the antibody as a point cloud, typically containing thousands of atoms, then encodes it at different resolutions for computational efficiency: antigen encoder (in red, finest resolution but higher computing cost and takes more time), atomic level encoder (yellow), and amino acid level encoder (green, crude resolution but least computing cost and time).

The docking module simultaneously folds the antibody and docks it to the target, using the two encoding level forces (dark blue boxes with blue arrows).

Cycling through the three modules, the HSRN uses an iterative refinement procedure (green circular arrows) to develop an improved lock-and-key tight fit between the updated antibody structure and target.

Finally, the decoder module translates the docking module output from a point cloud into an amino acid sequence. The result of HSRN is a complete amino acid sequence of an antibody with an improved affinity for its target (upper right, antibody bound to virus spike protein).



HSRN improved antibody docking success rates by 50% and out-performed both sequence- and structure-based models.

The best antibodies fit their targets tightly like a lock and key: the better the fit, the better the binding affinity, the more effective the response. Previously, an antibody's affinity was improved through antibody maturation experiments, but these assay-based laboratory experiments are costly, labor-intensive, and often do not adequately improve the binding affinity of a candidate antibody in a single round of experimentation. To overcome this constraint, researchers use computational biology for computer-based experiments to improve antibody binding affinity through mathematical modeling. Although these computational tools delivered improvements over previous methods, several limitations remained including reliance on pre-existing template features, sequences, or structures; systems capable of either designing or docking antibodies, but not both; and large computational times and costs.

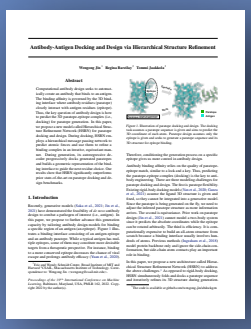
As a remedy, the MIT researchers created an innovative tool called Hierarchical Structure Refinement Network (HSRN) to improve the capability to rapidly design effective and potent antibodies. HSRN uses a multiscale, spatial representation of antibody-target interactions at the atomic level that enables it to:

- Predict antibody 3D structure from scratch
- Dock and design an antibody simultaneously
- Refine the antibody structure iteratively (i.e., through multiple cycles of test-evaluate-retest)
- Decrease computational cost and time

HSRN improved antibody docking success rates by 50% and out-performed both sequence- and structure-based models. Accordingly, HSRN and machine (ML) learning, when integrated into other capabilities being developed under DTRA JSTO's Discovery of Medical Countermeasures Against New and Emerging Threats (DOMANE) thrust area, will enable researchers to quickly design antibodies from scratch to combat existing and emerging biological pathogens.

Antibodies designed through HSRN and ML can also be developed in a shorter time with greater affinity and efficacy than was possible with previous computational and laboratory tools, which will result in delivering antibody-based medicines and treatments to the Joint Force faster and decreasing the impact of biological threats. ●

Free access to the research article is available on the *Proceedings of Machine Learning Research* website



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Within the Defense Threat Reduction Agency's Research and Development Directorate resides the Chemical and Biological Technologies Department performing the role of Joint Science and Technology Office for Chemical and Biological Defense. This publication highlights the department's advancements in protecting the Joint Force, our nation, and allies from chemical and biological threats through the innovative application of science and technology.

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