A case study approach to high-containment laboratory workflows promoting sustainability, networking and innovation

This paper (No. 26082021-00183-EN) has been peer-reviewed, accepted, edited, and corrected by authors. It has not yet been formatted for printing. It will be published in issue **39** (3) of the *Scientific and Technical Review*, in 2021.

C.L. Hunt [(1)*], L. Yu [(2)], M. Cochran [(1)], J.-C. Liu [(3)], B. McCarl [(2)], C.D. Johnson [(4)], M. Brun [(4)] & M. Berquist [(1)]

(1) Institute for Infectious Animal Diseases, Texas A&M AgriLife Research, 1500 Research Parkway, Suite B270, College Station, TX 77843, United States of America

(2) Department of Agricultural Economics, Texas A&M University, 600 John Kimbrough Boulevard, College Station, TX 77843, United States of America

(3) Department of Computer Science and Engineering, Texas A&M University, 301 Harvey R. Bright Building, College Station, TX 77843, United States of America

(4) Genomics and Bioinformatics Service, Texas A&M AgriLife Research, 1500 Research Parkway, Suite 250, College Station, TX 77843, United States of America

*Corresponding author: carrie.hunt@tamu.edu

Summary

Advances in information technologies (IT) and operational technologies (OT) offer high-containment laboratories opportunities to evolve scientific and operational approaches, while increasing efficiency. Emerging technologies steadily introduce changes in data generation and management practices. United States (US) government agencies and partners operate high-containment laboratories that rely on IT/OT to provide critical scientific functions that support prevention, detection, response and recovery for catastrophic events.

These unique operating environments provide an opportunity for implementation of IT/OT that can facilitate both efficiency and deeper or parallel study of disease and associated biological phenomena. Operational study by subject matter experts can aid in identification of requirements and challenges pertaining to emerging IT/OT, examination of use cases, refinement of technical specifications and optimisation of workflows. The National Bio and Agro-Defense Facility (NBAF) in the United States of America (USA), slated to be fully operational by 2023, will be a state-of-the-art research and diagnostic facility with biosafety level 2, 3 and 4 laboratories for the study of high consequence transboundary animal pathogens and zoonotic diseases impacting public health. The NBAF will support the diagnosis of emerging diseases, development of countermeasures and transboundary animal disease training. Given the rapid emergence of IT/OT solutions, the authors utilised a case study approach to analyse and assess real-world, high-containment laboratory functions to help maximise efficiency in mission delivery for the NBAF and the broader high-containment laboratory network. The case study approach described here could be widely adapted to diverse situations characterised by a high rate of change to provide accurate, relevant workflow analyses and optimised recommendations.

Keywords

Blockchain – Genomics sequencing pipeline – Information technology – Laboratory networking – Operational technology – Workflow optimisation.

Introduction

High-containment laboratories operate in a unique environment, the analysis of which is well-suited to case studies of the impacts of information technologies (IT) and operational technologies (OT) on select laboratory workflows. A limited number of research institutions across the United States of America (USA) are equipped to facilitate work with pathogens of high consequence (Biosafety Level 3 or 4), which require certified containment laboratories. Even fewer include facilities for agricultural species: Biosafety Level 3 Agriculture (BSL-

3Ag). These facilities are dispersed geographically and operate largely in an independent manner. As there is no single entity providing comprehensive oversight, these issues and related biosecurity concerns were raised in a testimony before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives in October 2017 (1).

Biological agents identified as having the potential to pose a severe threat to human and animal health are classified as select agents. High-containment laboratories in the USA wishing to work with select agents must register with and be regulated by the Federal Select Agent Program, which is jointly overseen by divisions within the US Department of Health and Human Services' Centers for Disease Control and Prevention (HHS–CDC) and the US Department of Agriculture's Animal and Plant Health Inspection Service (USDA–APHIS). The Federal Select Agent Program regulates select agent and toxin possession, transfer and use, which includes permits for scientists (valid for five years) and CDC facility inspections at least once every three years. However, a review by the Government Accountability Office (GAO) in 2017 found that the Federal Select Agent Program failed to meet key elements of effective oversight related to independence, performing reviews, technical expertise, transparency and enforcement.

Research involving infectious agents potentially harmful to humans or animals (specifically those classified as Biosafety Levels 3 or 4) is inherently difficult owing to factors including complex facility requirements, regulatory issues, mandatory training/expertise, biosecurity control and high costs of operation. In the case of BSL-3Ag research, the requirement for large animals is an additional challenge that increases the need for specialised facilities and trained personnel. These studies are often limited by the availability of suitable animals and space (in contrast to studies involving rodent species) and it is more difficult to get approval for them because of strict regulatory and reporting requirements. An ever-increasing focus on animal welfare and transparency to the public adds another layer of complexity to this important type of research. Combined with the high operational costs associated with research under containment, there can be limitations to progress, with only a subset of researchers that are both able to attain the necessary funding and have the subject matter expertise to design high-containment studies.

For these reasons, coordinated studies that could serve multiple purposes and allow the sharing of animals, tissues or data among researchers in secure, transparent and trusted environments would be particularly advantageous. However, the status quo is that high-containment research facilities exist as digitally isolated, independent entities with associated limitations imposed on collaborative efforts within or across institutions, limitations that are regularly addressed in less critical settings by a myriad of technologies and tools available in today's marketplace.

The benefits of emergent IT and OT reach beyond increases in transaction quantity and speed. In this case study, networking concepts that included data aggregation and flows, spatio-temporal bridging and real-time awareness were utilised in order to propose solutions to some of these challenges. This approach facilitates examination of various resources within the laboratory environment, including sequencers, pipettes, robots, employees, bench space and time, with the introduction of novel technologies such as digital ledgers to facilitate transparency and trust. In addition, establishment of formal and informal networks as a mechanism to share these resources collaboratively facilitates the delivery of large quantities of complex laboratory activities that would otherwise be very difficult to achieve.

Important to this analysis is the inherent connectedness of emergent information and operational technologies. Nearly every new device, instrument or component of IT infrastructure is designed to enable network connectivity. As high-containment laboratories increasingly embrace emerging IT and OT strategies, the networked nature of infrastructure stands to change entire operational paradigms. The digitalisation of modern workflows transcends physical infrastructure. With the advancement of interconnectedness across high-containment facilities come increased challenges regarding cybersecurity. The protection of sensitive data and information from those with hostile intentions cannot be overemphasised. In these operations research case studies, the authors used a blended approach, leveraging economic methods, policy, procedure and capacity review of existing laboratories, as well as best practices in configuration of information technology infrastructure, all with the goal of prospective consideration and study of the implications of connectedness and how it can result in improved workflows and arrangements.

It is also important not to lose sight of the fundamental purpose of high-containment laboratories as controlled working spaces for pursuit of scientific solutions to high-risk biological threats to human, agricultural and environmental health. Such solutions are optimally derived from a community approach integrating emergent technologies and yielding new opportunities for implementing workflow optimisations at both the individual laboratory and high-containment community levels.

Approach

To address the task of workflow analysis with a focus on emergent IT/OT and resource optimisation in the high-containment laboratory setting, three case study topics were developed: *1)* an end-to-end genomics sequencing pipeline; *2)* conceptualisation of high-containment laboratories as a network; and *3)* the application of blockchain technology to the high-containment laboratory mission and environment. Careful consideration was given to developing a working group that included representation from all key stakeholder groups as well as crucial subject matter expertise. This included director-level membership from government and academic high-containment laboratory facilities across North America as well as European representation. Experts representing various IT/OT disciplines and key members of the Plum Island Animal Disease Center (PIADC) to NBAF transition team rounded out the group.

The working group was established in early 2019 and a two-day in-person workshop was held in Washington, DC to allow presentation of the case study topics as well as to provide a venue for networking of individuals from closely related disciplines and physically disparate locations. Considerable effort was made to keep these working group members engaged throughout the duration of the 24-month project. Feedback provided at the workshop and subsequent stakeholder interactions within and outside of the working group shaped the refinement of the case studies to ensure they would provide targeted, relevant content of maximal benefit to the stakeholders. A second working group meeting was held in mid-2020 which reconvened members for updates on the PIADC to NBAF transition as well as presentation and discussion of the case study findings.

Case study methods

High-containment laboratories facilitate crucial research on high consequence pathogens and are important resources at the intersection of human, environmental and animal health. To understand the impacts of networking and emerging technologies on the future of high-containment laboratory workflows and impacts, the following three case studies were conducted:

– Case study I is an examination of a genome sequencing laboratory. Using job-shop scheduling and inventory analysis, with a cost-centric focus, allows for a better understanding of laboratory processes and resource utilisation. The application of economic modelling to laboratory workflows can streamline decision-making for more efficient and cost-effective processes.

– Case study II consists of two parts, focused on a central theme of laboratory networking and the allocation of scientific resources. Part one consists of a compilation of notional containment laboratory attributes, referencing real-world limitations, for use in an econometric resource allocation model. Part two consists of a study of the European Research Infrastructure on Highly Pathogenic Agents (ERINHA), which is a European organisation that works to coordinate and distribute access to research across high-containment laboratory infrastructure in Europe.

– Case study III outlines a system for laboratory data handling, storage and secure dissemination. Emerging technologies such as blockchain and novel distributed computing and storage models can reduce network and collaborative barriers that currently exist in high-containment laboratories.

Methodology for Case study I: examination and model optimisation of low-cost whole genome sequencing

This analysis focuses on high throughput, lower cost whole genome sequencing that has been advanced, in part, by large increases in parallel sequencing capacity on sequencing machines. Economy of scale and standardisation have been employed for years in high-capacity human genome sequencing operations, but this case study focuses instead on varying densities of sample multiplexing for sequencing that can serve diverse research needs, in agricultural applications in particular, while still controlling cost. New modes of library preparation and DNA sequencing continue to be rolled out with ever-increasing capabilities. The latest Illumina sequencing system (NovaSeq 600 Sequencing System, Illumina, Inc. San Diego, CA, USA) includes four separate lanes in a flow cell and generates between 4,800 and 6,000 gigabases of information at maximum capacity; therefore, combining multiple samples from different sources is required to maximise utilisation of this massive single-run capacity. The demands of economy of scale require that these facilities optimise the amount of information required per sample, cost of library preparation and final cost of sequencing per sample. The flow cells used in sequencers can only be used once and are therefore consumable. This demands an exceptional quality control process for samples loaded into the flow cell. Once a run on the sequencer starts, it cannot be stopped or changed.

In this case study, application of this sequencing capacity and associated requirements was made across a wide array of samples on a run basis. Challenges regarding quality control and sample normalisation and timing were highlighted. With regard to timing, the amount of time it takes to accumulate enough samples from a variety of sources or to deliver the desired economy on a per sample basis may vary. Given these factors, thought needs to be applied to the operational needs and organisational structure of sequencing capacity. The scale of this work lends itself to centralisation of the sequencing function in a core facility, as opposed to maintenance of a sequencer in each laboratory. While Illumina, PacBio, Ion Torrent and Oxford Nanopore all offer various sequencers (operational technologies) with different features, a single industry-leading sequencer from one of these manufacturers was selected for this study and its parameters were used for model design (e.g. fidelity, cost per gigabase).

To better understand the genomics pipelining process from beginning to end, the authors partnered with a leading genomics sequencing core laboratory. They shadowed their scientists and observed their workflow from beginning (customer requests service) to end (data provided to customer), noting all decision-making processes along the way. A simplified diagram of this process, spanning initial quality control (iQC), library preparation, final quality control (FQC) and the sequencing process is shown in Figure 1.

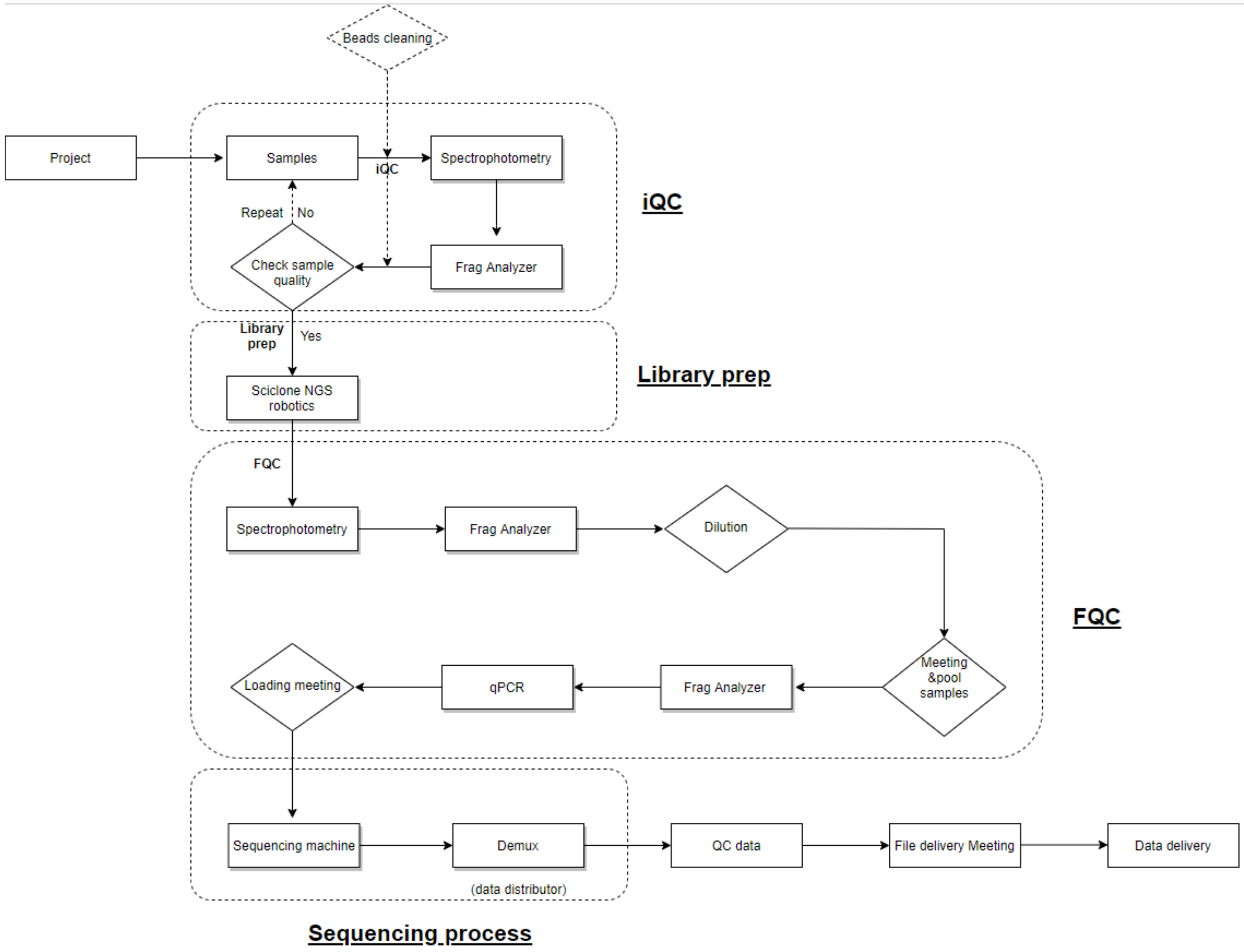

Fig. 1

Diagram of the end-to-end workflow for a genomics sequencing request

FQC: final quality control
Frag: fragment
iQC: initial quality control
NGS: next-generation sequencing
Prep: preparation
QC: quality control
qPCR: quantitative polymerase chain reaction

Inventory and job-shop scheduling models were developed to address inventory and scheduling in a high-throughput genetics sequencing laboratory. The inventory model developed ordering patterns for costly and highly perishable laboratory reagents. The job scheduling model constructed schedules on how to best assign jobs to alternative sequencing instruments as well as how to pool samples from multiple customers. The models were developed in the General Algebraic Modeling Systems (GAMS) coding language (GAMS Development Corp.; https://www.gams.com/). Both models were implemented using theoretical data as well as case study data from an existing laboratory.

The inventory model minimises the total costs of purchasing reagents, transporting supplies to the laboratory site, holding inventory on site and any affected production processes. The model is set up in a deterministic fashion using the following assumptions:

– lead time for filling orders is constant and known for all reagents

– each reagent is ordered from one and only one supplier

– demand is known and satisfied using a first-in/first-out (FIFO) inventory issuing policy

– shortages are allowed and, if they occur, production costs increase

– reagent shelf life is known and, at end of life, any unused reagents are subject to disposal.

The job-shop scheduling model is set up with the objective of minimising total cost of reagents and total cost of labour used in loading, unloading and operating the machines. A penalty cost is assigned to jobs that take longer to complete than the assigned due date. This model uses the following assumptions:

– machines use the same amount of reagents (kit-based) regardless of the number of samples being sequenced

– each process cannot start until the previous process for that job is finished

– each job is independent, and jobs have different numbers of samples to be processed

- only one batch of pooled jobs can be processed on an instrument at one time
- jobs can be pooled together to run on one instrument simultaneously as long as they do not exceed instrument capacity
- once the instrument starts, it cannot be stopped until the processing task is done
- instrument set-up time and the time taken to load and unload between operations are trivial.

Both models have been implemented, and the solutions demonstrated that mathematical modelling can be used as a tool to guide decision-making on inventory and workflow processes in a genomics laboratory context. Each model has integer variables that reflect choices, such as how many samples to pool for a sequencing run. The models represent an approach by which laboratories can standardise operations to improve efficiencies in the areas of cost, productivity and safety.

Methodology for Case study II: laboratory capacities and network allocation, and a study of the European Research Infrastructure on Highly Pathogenic Agents

The objectives of Case study II were twofold. The first was to create a questionnaire-based tool designed to capture operational and relational attributes of high-containment laboratories, which can serve to inform a resource allocation model. The signature attributes around which high-containment laboratory operation and networking can be defined will serve as categorical inputs for an econometric resource allocation model, which will be refined and run in a notional or representative fashion. The second part of Case study II is an in-depth case study on the ERINHA.

With improvements and rapid progress in IT/OT, networking between high-containment laboratories is technologically feasible. Strengthened connections between high-containment laboratories reduce the time required to achieve scientifically relevant milestones and conclusions. Time is only one potential criterion solved for across a network, but it is especially relevant in the context of the whole-of-industry and even whole-of-society solutions that high-containment laboratories are uniquely positioned to contribute to and develop. With diagnostics and surge capacity in the face of an outbreak or other disease emergency, network capacity is immediately tapped in an allocation problem that targets the time–cost trade-off, while delivering relatively uniform data across geographical areas. A systematic approach to data-intensive networking of everyday function and science is currently not as well structured or supported as emergency surge capacities. The scope of potential interaction is much wider in an 'everyday function' context. With the methods described below, operational research questions focused on data-intensive networking facilitated by current IT and OT solutions can be explored.

Laboratory capacities and network allocation

This approach is designed to investigate what is possible without immediately subscribing to the plethora of barriers to networking that are very real: funding competition, select agent regulations, sensitivities surrounding operational and scientific biosecurity parameters of a pathogen, scientific openness, difficult and sometimes outdated information security solutions, intellectual property vulnerabilities, lack of uniformity and documentation of many different environmental and situational experimental factors, and bureaucracy in general.

To begin population of an allocation model, an informational questionnaire was structured for both attribute aggregation and as a guide for engagement with partner laboratories that wished to participate. Key topic areas are outlined in Table I.

Table I

Laboratory features included in the questionnaire for inclusion in network allocation model

Category	Summary description
Personnel	Number, classification, contract work, guests, surge
Space and rooms	Space allocation for purpose (%)
Operational capacities	Operational capacities associated with function(s), surge
Disease/pathogen focus	Categories, types, mission
Information technology infrastructure	Key systems characterisation, cybersecurity
Key operational technologies	Characterisation, specialised OT
Funding, budget, governance structure	Cycle, source(s), goals, growth
Collaborations and partners	Model(s) and support for partnership/collaboration

OT: operational technologies

A simple conceptual model was designed to evaluate the impact of the presence of a designed laboratory network. This optimisation application involves choosing which laboratory in a network will be assigned new jobs for processing. The model assigns jobs to one of three laboratories, taking into consideration factors including laboratory capacities, the total cost to finish the jobs and completion time of the job that has the longest duration. To deal with multiple objectives in this model, a utility trade-off model is considered because there are no target levels. A set of underlying assumptions are defined for this model:

– each job is assigned to one and only one laboratory

– for a job to be assigned to a laboratory, it must be equipped with machines that can perform the tasks required to complete that job

– the assignment variables in the model are binary (‘1’ if a job is assigned to that laboratory, otherwise ‘0’).

Starting from this simple conceptual model with only three laboratories, the model can be extended with more laboratories and application complexity in order to assess the utility of distribution of research work across a network. This approach could help to determine the optimal site for performance of distinct work packages within and across a defined network of high-containment laboratories.

A study of the European Research Infrastructure on Highly Pathogenic Agents

The necessity for research on pathogens of high consequence and the challenges associated with this specialised work are a global issue. A Pan-European research infrastructure, designated ERINHA, has been developed to address research involving highly infectious emerging and re-emerging diseases classified as Risk Group 4, in order to contribute to the overarching mission of increasing the European Union's preparedness for and capability to respond to high consequence infectious disease threats. Their coordinated network approach to high-containment research is currently the only research infrastructure of its kind worldwide.

Therefore, a case study focused on this novel organisation was designed to provide a unique learning opportunity to understand the benefits, challenges and 'lessons learned' associated with this endeavour. To maximise the usefulness of this engagement, a list of relevant topics for discussion was developed and distributed prior to an in-person meeting with the Central Coordinating Unit at the ERINHA headquarters in Paris, France.

The following topics were discussed:

– current operational status: staffing, funding, membership, etc.

– plans for financial sustainability

– mechanisms for prioritisation and distribution of work

– approach for data storage, management and sharing

– organisational structure/regulatory bodies

– successes and challenges.

Information learned at this meeting and continued engagement with ERINHA leadership allowed the authors to use the knowledge gained to:

– assess the merit of initiating a similar research infrastructure in the USA

– extrapolate lessons learned and best practices to provide recommendations for the NBAF

– foster a collaborative relationship between ERINHA and North American high-containment laboratories.

Methodology for Case study III: blockchain and the future of laboratory networking

The emergent informational technology blockchain uses a distributed, peer-to-peer network to make a continuous, growing chain of records ('blocks') to form a digital ledger. Key features of this technology are that it is disintermediated, distributed and decentralised. Beyond its most prevalent use as the technology that powers Bitcoin cryptocurrency, blockchain is being tested and adopted by a broad range of industries to provide economic benefit in finance, banking, the Internet of Things (IoT), supply chain, manufacturing and healthcare. A number of blockchain's characteristics make it an attractive candidate for these diverse industries, including instantaneous transactions, transparency, immutability and traceability.

Key elements of blockchain make it useful in addressing many of the issues limiting progress in high-containment research. A permissioned blockchain would allow for control over what parties would have access to the blockchain, and different levels of access could be assigned. Information added to the chain could include metadata or other transactional records, approved Animal Use Protocols (AUP) and Standard Operating Procedures (SOPs), animal care and health activities, and daily research activity records. The decision-makers are often located outside the containment areas (entry to which requires substantial personnel training and biosecurity, personal protective equipment, showering out, etc.), thus creating a significant potential disadvantage to this research setting in delayed and sometimes faulty communication. Errors can be very costly in a high-containment setting, and the 'real-time' and immutable nature of blockchain technology would greatly benefit research efficiency and potentially personnel safety.

Providing those managing and performing research within high-containment facilities access to the blockchain would allow greater transparency as well as real-time auditing capabilities. For example, use of select agents (storage location and conditions, user, amount used) could be tracked more efficiently and effectively, capturing data with higher reliability. Blockchain access would allow the appropriate parties to have direct oversight of active research – whether these parties be sponsors, administrators or collaborators. This could increase trust among participants through transparency of records and could lessen the burden of facility inspections. Simplifying the process of reliably sharing information would encourage collaborative research efforts with the outcome of more efficient research, as well as accelerated development of new diagnostics, vaccines and treatments.

The identity of permissioned nodes and appropriate level of access to the blockchain would be determined based on parties' relationships to the study. These nodes could include:

– study sponsors/funding sources

– facility administration

– auditing agency

– principal and other investigators

– collaborating scientists

– institutional animal care committee/assigned veterinarians

– animal care staff

– laboratory scientists involved in diagnostic or basic research.

Knowing that most existing high-containment laboratories operate systems in isolation, (controlled) sharing of high-level resources would offer significant new opportunities to advance the field. Some examples include, but are not limited to, resource utilisation, data utilisation and protocol compliance. Auditable protocol compliance is a central tenet of high-containment laboratory operations, demonstrating a potential highly beneficial use case for network-wide auditable ledgers to identify the commonalities and differences of existing practices. Through orchestrated efforts, ledgers could be generalised into a joint auditing framework, which can then be used as a foundation for shared use of resources and data products, as well as shared best practices for experimental setup and technique.

Outcomes/Conclusions

Availability of high-containment laboratory space is expanding, likely due to focused federal funding for research and development on high-consequence pathogens and a greater focus on public health and diagnostic laboratory capacity in general (2). The total amount of planned or existent BSL-4 space in the USA increased by an estimated 12-fold between 2004 and 2007 (3). However, collaborative efforts within and across institutions have failed to keep pace with this proliferation of laboratory capacity. This is particularly evident in the international realm, in which some US scientists have made the decision to curb their international collaborations owing to differences in biosecurity regulation between countries (4). This phenomenon is worth further scrutiny, given that a recent review found that research collaboration in international networks enhances both the productivity of individual scientists and the quality of the research (5), a finding supported by the analysis performed via the ERINHA case study. If the USA wishes to be a global leader at the forefront of infectious disease research, innovation and disaster preparedness, novel approaches that promote laboratory networking and collaboration will be crucial to sustainability, durability and future success.

Figure 2 illustrates future potential for networking high-containment laboratories. These unique facilities have well established physical containment measures to protect laboratory staff, provide humane care for animals in studies and prevent accidental spillover of pathogens. While it can be costly and time consuming to carry out critical scientific investigations in these facilities, they are a cornerstone of biodefence against pathogens and vectors that can adversely affect large portions of the global population. As the world faces emerging biothreats, development and leveraging of technological approaches to data management and networking that can improve scientific productivity is a national security imperative. As demonstrated in the genomics case study, efficient deployment of these resources can benefit from the injection of outside disciplines, including the use of deterministic models that can be fitted to optimise functions of interest. In this way, connecting OT to rapidly advancing IT facilitates rapid advances in the outcomes and impacts of both individual research projects and overall high-containment activities.

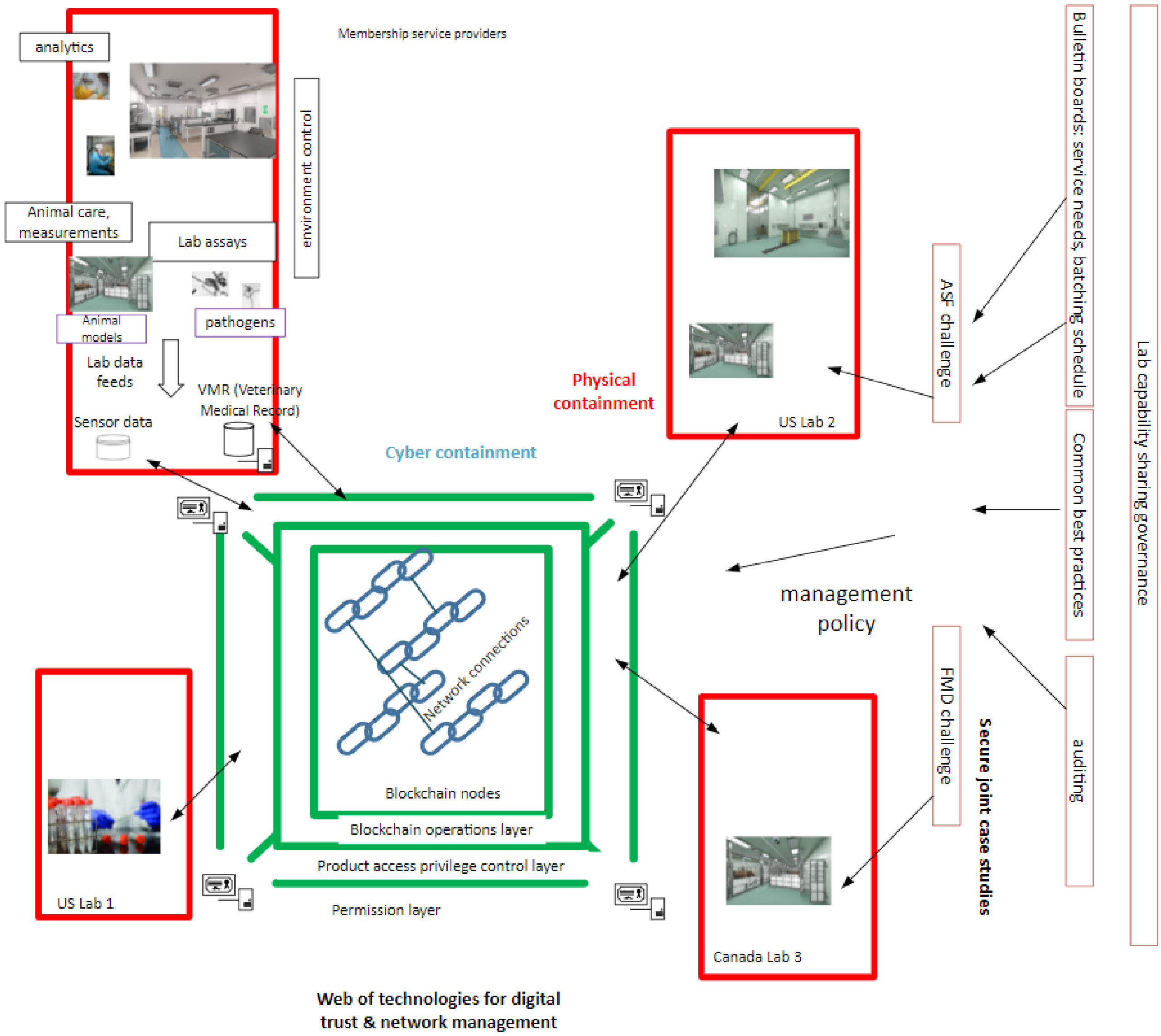

Fig. 2

Conceptualisation of a high-containment laboratory network

ASF: African swine fever
FMD: Foot and mouth disease
Lab: Laboratory
US: United States
VMR: Veterinary medical record

A laboratory space can be organised into mirrored physical and cyber domains, where the cyber domain includes various data acquisition systems, databases and laboratory management technologies. When properly managed, much of the cyber domain information can be shared among partner laboratories to serve specific purposes. Information sharing is the key to operational transparency and establishing trust and confidence among partners. It is also a powerful approach to demonstrating scientific credibility, accountability and compliance. Of course, the importance of cyber containment to protect the privacy and integrity of the interconnected laboratories cannot be overemphasised, as well as defence against malicious cyber adversaries. A potential barrier to the proposed collaborative approach is differing standards for cybersecurity, particularly in the case of international partnerships or those including both government and privately operated facilities. A host of mutually agreed upon cybersecurity tools will undoubtedly be required for defence against cyber-attacks or inappropriate system access, such as firewalls, anti-virus software, user authentication and other defences. These tools, combined with permissioned, distributed ledger technology, hold great promise for delivering networking solutions to the high-containment laboratory community that offer the utmost security, confidentiality and integrity for application on a global scale.

Incorporation of IT and OT advances can augment laboratory operations in innovative ways and, individually, the methods described here add great value to specific laboratory situations. In particular, laboratory networking and sharing resources geographically or across facilities with similar research and client-based activities can facilitate compounded increases in efficiency and effectiveness, including the ability to perform work that would otherwise not be possible on an individual level. Whether formal or informal, establishment of laboratory communities also enables improved adoption and adaptation of IT and OT to continue evolving scientific and administrative approaches, while increasing efficiency in meeting mission requirements. The case study approach described here could be widely applied to other highly variable situations to provide accurate, relevant workflow analyses and optimised recommendations.

Acknowledgements

This research was funded under contract with the United States Department of Homeland Security Science and Technology

Directorate (DHS-S&T) (contract no. 70RSAT18FR0000153). Any opinions expressed are those of the authors and do not necessarily reflect those of DHS-S&T, Texas A&M AgriLife Research or Texas A&M University.

References

1. Denigan-Macauley M. (2017). – High-containment laboratories: coordinated efforts needed to further strengthen oversight of select agents. GAO-18-197T. United States Government Accountability Office (GAO), Washington, DC, United States of America, 13 pp. Available at: www.gao.gov/assets/690/688087.pdf (accessed on 16 September 2020).

2. Gottron F. & Shea D.A. (2009). – Oversight of high-containment biological laboratories: issues for congress. Congressional Research Service (CRS), Washington, DC, United States of America, 34 pp. Available at: www.everycrsreport.com/reports/R40418.html (accessed on 19 August 2020).

3. Hammond E. (2007). – The Sunshine Project. *In* Germs, viruses, and secrets: the silent proliferation of bio-laboratories in the United States. Hearing before the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce, House of Representatives. 110th Congress, 4 October, Washington, DC, United States of America, 143–173. Available at: www.govinfo.gov/content/pkg/CHRG-110hhrg44948/html/CHRG-110hhrg44948.htm (accessed on 23 April 2020).

4. Fischer J.E. (2006). – Stewardship or censorship? Balancing biosecurity, the public's health, and benefits of scientific openness. The Henry L. Stimson Center, Washington, DC, United States of America, 93 pp. Available at: www.stimson.org/wp-content/files/file-attachments/Stewardship_1.pdf (accessed on 25 October 2019).

5. Kyvik S. & Reymert I. (2017). – Research collaboration in groups and networks: differences across academic fields. *Scientometrics*, **113** (2), 951–967. https://doi.org/10.1007/s11192-017-2497-5.