HITS: A network to promote high-throughput (HT) approaches through inquiry-based case studies

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Abstract

Modern molecular biology techniques are increasingly utilizing automation and miniaturization to test numerous samples or conditions simultaneously. High-throughput (HT) approaches include massively parallel sequencing of DNA, synthesis of numerous nucleic acids and peptides, automated microscopy, microfluidics for single-cell analyses, small molecule screening using robotics, and genome-scale phenotypic characterization using CRISPR/Cas9 gene editing technologies. These approaches produce a wealth of results, often labeled 'big data.' However, there are limited educational case studies that address authentic high-throughput approaches using real data. We believe well-designed case studies focusing on HT approaches and using original datasets empower students to learn current approaches and exercise quantitative reasoning in data analyses.

We have created the NSF-funded High-throughput Discovery Science & Inquiry-based Case Studies for Today's Students (HITS) Research Coordination Network to address this gap. HITS brings together interdisciplinary groups of HT researchers and instructors to produce authentic HT case studies that can be implemented in a variety of courses, allowing students to analyze real data and learn valuable quantitative skills. The first cohort is developing new HT cases. As a pilot, we have designed and used four case studies in our upper-level undergraduate and graduate HT Discovery course, and the graduate students in the course each created case studies that highlight the applications of HT approaches and follow the NCCSTS guidelines. Together, these initiatives will increase the content available for teaching HT approaches.

HITS: A network to create high-throughput cases

A research and educational network that includes primarily undergraduate institutions, early career teaching faculty, and national and international researchers will create impactful educational materials to demonstrate the transformative power of high-throughput approaches and teach underlying quantitative skills.

Specific Objectives of HITS

- Provide workshops, a virtual community, and online resources to foster high-throughput research and its integration into the classroom
- Connect researchers and educators to design and assess quantitative biology case studies based on high-throughput discovery research
- Create a diverse consortium of institutions committed to implementing these quantitative educational tools in biology courses and curricula across the country and world

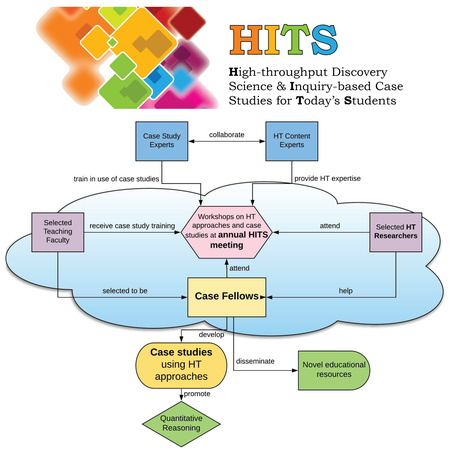

Figure 1. Logo and schematic of structure of the NSF RCN-UBE High-throughput Discovery Science & Inquiry-based Case Studies for Today's Students (HITS).

Summer HITS Workshops

Scientific Sessions	Case Study Sessions	Case Study Development
Speakers include HT experts from industry, government, and academia.	Speakers include experienced case study users who have created and implemented case studies in college classrooms.	NCSU Office of Faculty Development will present on rubrics and assessment. Groups will present updates at the end of this session.
Attendees include educators and Case Fellows, HT experts, and HT Researchers.	Attendees include case study experts, case study fellows, and selected HT Researchers.	Attendees include case study fellows and HT Researchers.
Attendees will learn about HT approaches. Collaborations are expected to emerge through interactions at this small but focused meeting.	Attendees will learn the value of well-designed educational case studies. Working groups will be formed by pairing HT Researchers with Case Fellows.	Groups will work to design and write novel case studies using HT approaches/datasets that can be readily implemented in college classrooms.

Figure 2: The 2018 Summer HITS Workshops were hosted by North Carolina State University and focused on raising awarness of novel high-throughput (HT) approaches and the use of educational case studies to engage students with authentic large datasets. Thirty participants attended the three-day event in which they learned about high-throughput approaches and available datasets, the design of educational case studies and problem-based learning, and the creation of rubrics for assessment of novel case studies. Participants included case study experts, faculty from numerous institutions, companies, and graduate students and postdoctoral fellows working on high-throughput research.

Case Studies Developed in Pilot Course

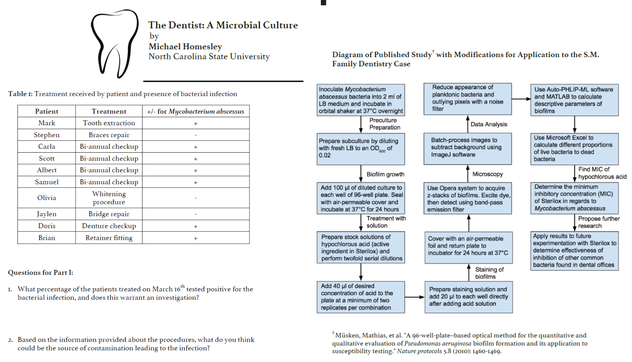
The Dentist: A Microbial Culture
by
Michael Homesley
North Carolina State University

Table 1: Treatment received by patient and presence of bacterial infection

Patient	Treatment	+/- for *Mycobacterium abscessus*
Mark	Tooth extraction	+
Stephen	Braces repair	-
Carla	Bi-annual checkup	+
Scott	Bi-annual checkup	+
Albert	Bi-annual checkup	+
Samuel	Bi-annual checkup	+
Olivia	Whitening procedure	-
Jaylen	Bridge repair	-
Doris	Denture checkup	+
Brian	Retainer fitting	+

Questions for Part I:

1. What percentage of the patients treated on March 16th tested positive for the bacterial infection, and does this warrant an investigation?
2. Based on the information provided about the procedures, what do you think could be the source of contamination leading to the infection?

Diagram of Published Study[1] with Modifications for Application to the S.M. Family Dentistry Case

Inoculate *Mycobacterium abscessus* bacteria into 2 ml of LB medium and incubate in orbital shaker at 37°C overnight
Precultre Preparation
Prepare subculture by diluting with fresh LB to an OD_{600} of 0.02
Biofilm growth
Add 100 µl of diluted culture to each well of 96-well plate. Seal with air-permeable cover and incubate at 37°C for 24 hours
Treatment with solution
Prepare stock solutions of hypochlorous acid (active ingredient in Sterilox) and perform twofold serial dilutions
Add 40 µl of desired concentration of acid to the plate at a minimum of two replicates per combination
Staining of biofilms
Prepare staining solution and add 20 µl to each well directly after adding acid solution
Cover with an air-permeable foil and return plate to incubator for 24 hours at 37°C
Reduce appearance of planktonic bacteria and outlying pixels with a noise filter
Data Analysis
Batch-process images to subtract background using ImageJ software
Microscopy
Use Opera system to acquire z-stacks of biofilms. Excite dye, then detect using band-pass emission filter
Use Auto-PHLIP-ML software and MATLAB to calculate descriptive parameters of biofilms
Use Microsoft Excel to calculate different proportions of live bacteria to dead bacteria
Find MIC of hypochlorous acid
Determine the minimum inhibitory concentration (MIC) of Sterilox in regards to *Mycobacterium abscessus*
Propose further research
Apply results to future experimentation with Sterilox to determine effectiveness of inhibition of other common bacteria found in dental offices

[1] Müsken, Mathias, et al. "A 96-well-plate–based optical method for the quantitative and qualitative evaluation of *Pseudomonas aeruginosa* biofilm formation and its application to susceptibility testing." *Nature protocols* 5.8 (2010): 1460-1469.

Figure 3: Excerpts of a graduate student project that was published through the NCCSTS. This pre-dental student focused on HT methods to screen for biofilm formation in dental equipment (UWDL's).

As a capstone project, graduate students in an upper-level *High-throughput Discovery* course at NC State University develop high-throughput (HT) related case studies. The course uses four new HT case studies, each focusing on a technology and using a different case type. Students are encouraged to submit their case studies to the National Center for Case Study Teaching in Science (NCCSTS) for peer review and publication. This trial serves as a model for the recently initiated HITS Research Coordination Network.

Interdisciplinary Groups Creating HT Cases

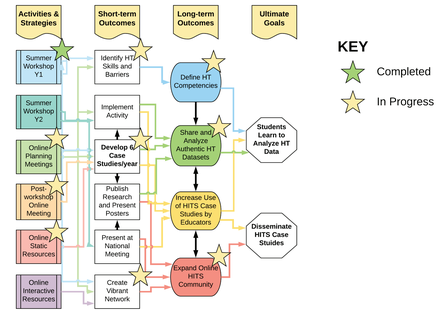

Figure 4: Logic model for the HITS network depicting the activities and outcomes of HITS. The network aims to produce 6-8 novel HT case studies per year for the next five years and train 50 faculty and 25 graduate students and postoctoral fellows. Interdisciplinary teams are formed during the workshop and HT experts and instructors work collaboratively to create new cases using authentic HT datasets.

HITS participants are developing new cases using novel datasets and cutting-edge approaches. Cases in production include the use of CRISPR screens, single-cell genomics, citizen science microbiome projects, and high-content microscopy datasets. By working collaboratively at the workshop and virtually through the QUBES online hub, participants are able to design exciting cases using authentic unexplored datasets that are adaptable to a variety of institutions and classrooms represented by the participants. Cases will be disseminated on the HITS webpage and through NCCSTS.

Expanding HITS

- Case studies are powerful tools to assist student learning of complex, technical material.
- HITS is filling a gap in available case studies involving high-throughput methodology to allow students to work directly with HT data to discover new approaches and findings.
- Students can contribute by generating case studies as part of courses and use resources developed by HITS.

References and Acknowledgements

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