DART-MS Data Interpretation Tool and Other Resources for Seized Drug Analysis

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&

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NIST

National Institute of Standards and Technology

Disclaimers

Certain commercial products are identified in order to adequately specify the procedure; this does not imply endorsement or recommendation by NIST, nor does it imply that such products are necessarily the best available for the purpose.

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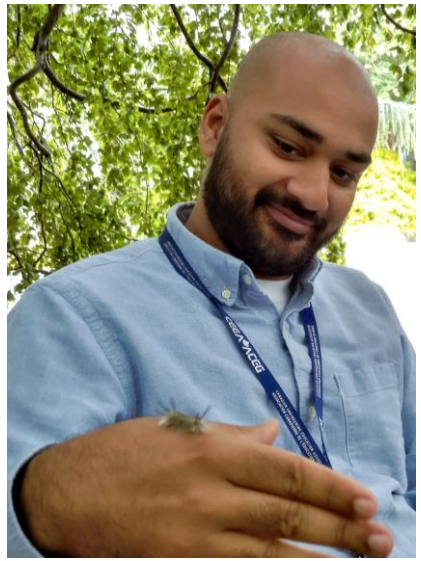
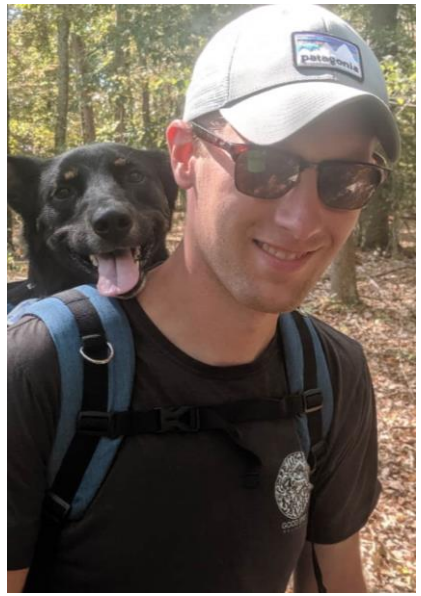
Who We Are / What We Do





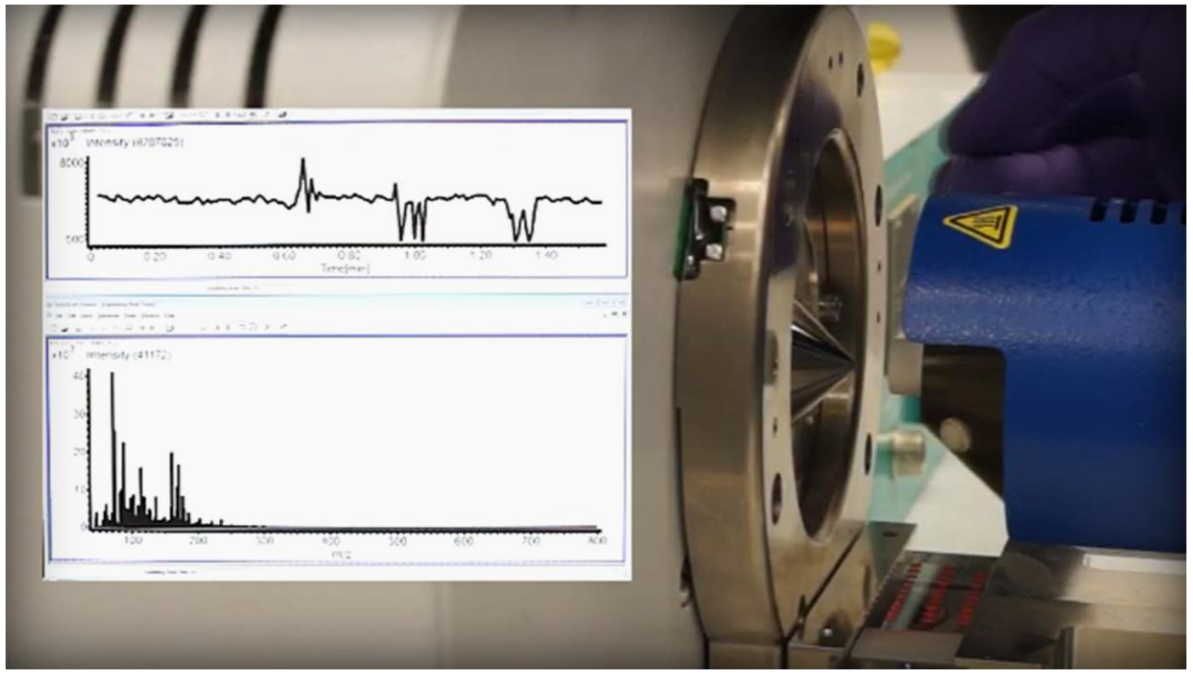
Support forensic chemistry disciplines by addressing measurement challenges through collaborative research.

Provide forensic practitioners at all levels (local, state, federal, and international) usable tools and resources.

Fundamentals of DART-MS

- One of many ambient ionization mass spectrometry sources
- Conventional DART-MS uses a heated helium metastable gas stream for sample desorption and ionization
- Allows for analysis of samples with minimal preparation or pre-treatment
- Analysis time 1 s to 5 s
- Typical LODs ng to pg
- Can be coupled to a range of mass spectrometers

DART-MS: Direct Analysis in Real Time Mass Spectrometry



DOI: 10.1016/j.forc.2020.100294

DART-MS Review Article

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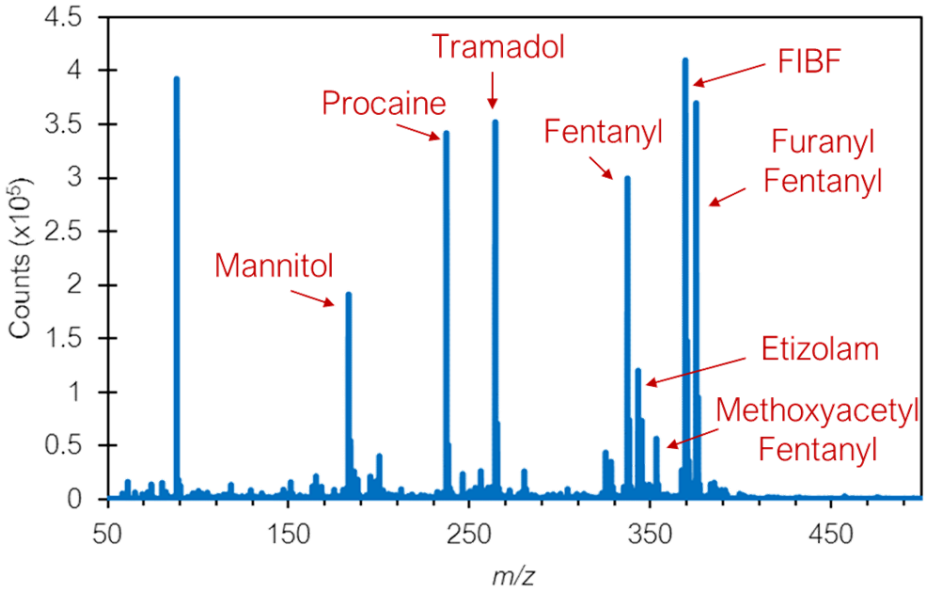
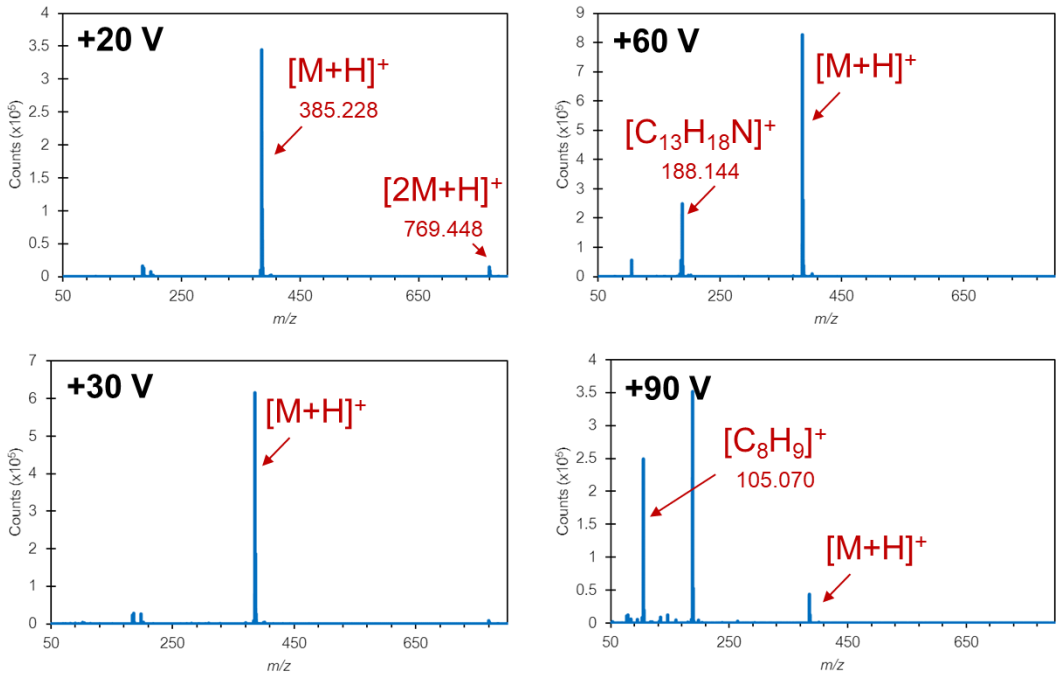
Fundamentals of DART-MS

One of the limitations of DART-MS is difficulty searching spectra due to lack of chromatography



Even with high resolution, assigning compounds can be difficult

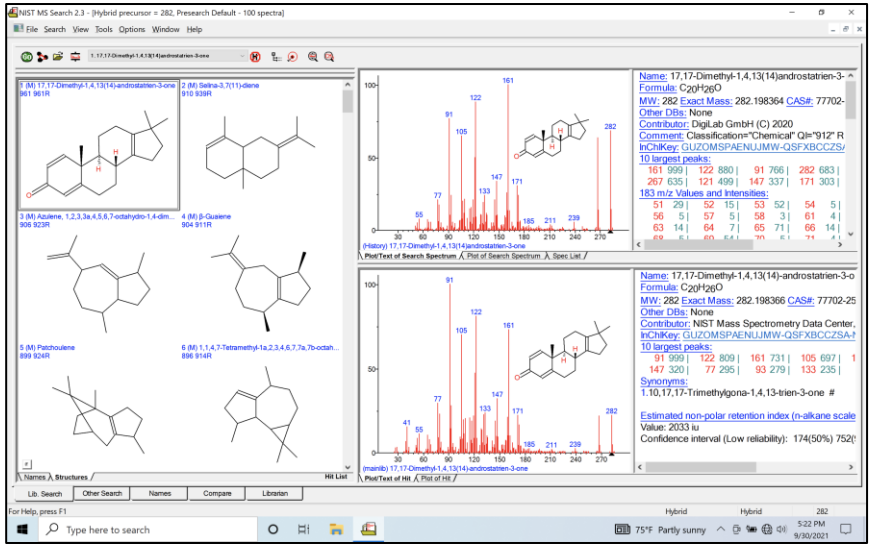


Can leverage is-CID to fragment compounds for more specific identification

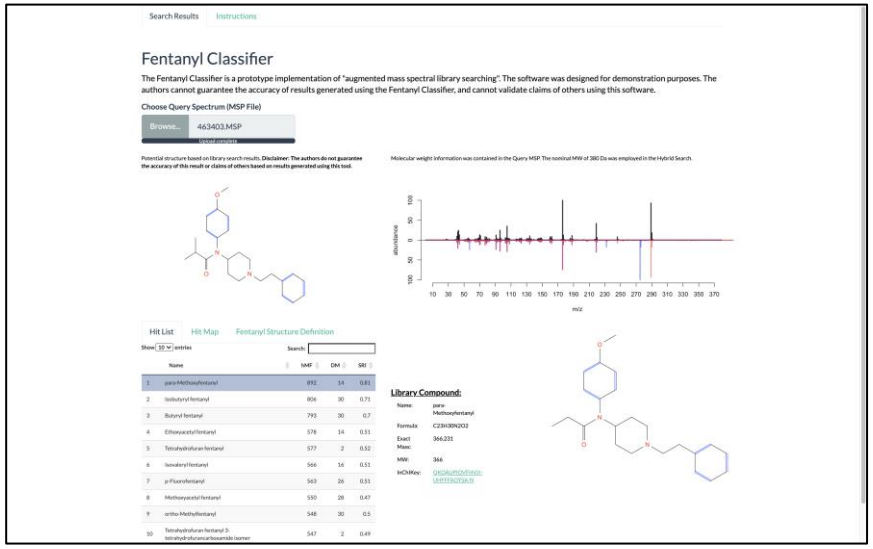
is-CID: In-Source Collision Induced Dissociation

Data Interpretation in Traditional MS

- NIST has several existing tools to help interpret traditional electron impact mass spectra (EI-MS):
  - **Automated Mass Spectral Deconvolution and Identification (AMDIS):** Automates extraction of GC/MS data files to generate consistent/reproducible mass spectra.
  - **Mass Spectral (MS) Search/Interpreter:** A comprehensive tool for interacting with mass spectral libraries, including a variety of useful search algorithms and data interpretation tools.
  - **Fentanyl Classifier:** A tool specifically for interacting with mass spectra of potential fentanyl analogs, attempting to localize the site of modification.
- To most effectively use these tools, a reference library is required



https://chemdata.nist.gov/



Two Key Challenges

1. Developing is-CID mass spectral libraries
   - Procuring and measuring relevant compounds
   - Determine whether spectra are appropriate measurements of compounds
   - Confirm all non-spectral data is correct (e.g. molecular formula, name, etc.)

Evaluating is-CID Mass Spectra

1. Developed a simple script with several filters and algorithms to assist in evaluating library mass spectra

```
You are welcome to redistribute it under certain conditions.
Type 'license()' or 'licence()' for distribution details.

  Natural language support but running in an English locale

R is a collaborative project with many contributors.
Type 'contributors()' for more information and
'citation()' on how to cite R or R packages in publications.

Type 'demo()' for some demos, 'help()' for on-line help, or
'help.start()' for an HTML browser interface to help.
Type 'q()' to quit R.

> source("asm_DARTMSDB-BuilderScript-1.07.R")
NIST DART-MS Database Builder v.1.07
Revised September 7th, 2021.

data.table 1.14.0 using 1 threads (see ?getDTthreads).  Latest news: r-datatable.com
**********
This installation of data.table has not detected OpenMP support. It should still work but in single-threaded mode.
This is a Mac. Please read https://mac.r-project.org/openmp/. Please engage with Apple and ask them for support. Check r-datatable.com for
updates, and our Mac instructions here: https://github.com/Rdatatable/data.table/wiki/Installation. After several years of many reports of
installation problems on Mac, it's time to gingerly point out that there have been no similar problems on Windows or Linux.
**********
Loading required package: grid


 Welcome to enviPat version 2.4
 Check www.envipat.eawag.ch for an interactive online version

Loaded all external packages.
Loaded all custom functions ('source/asm_Functions/')

There are 1 potential master files currently in the directory.

1: 210825_HeLibrary_Cicada_SmilesUpdate.xlsx

Click  to stop screen recording (integer value) for creating database:
```

Evaluating is-CID Mass Spectra

1. Developed a simple script with several filters and algorithms to assist in evaluating library mass spectra

2. Made the script and test files open-source and publicly available through github: https://github.com/asm3-nist/DART-MS-DBB

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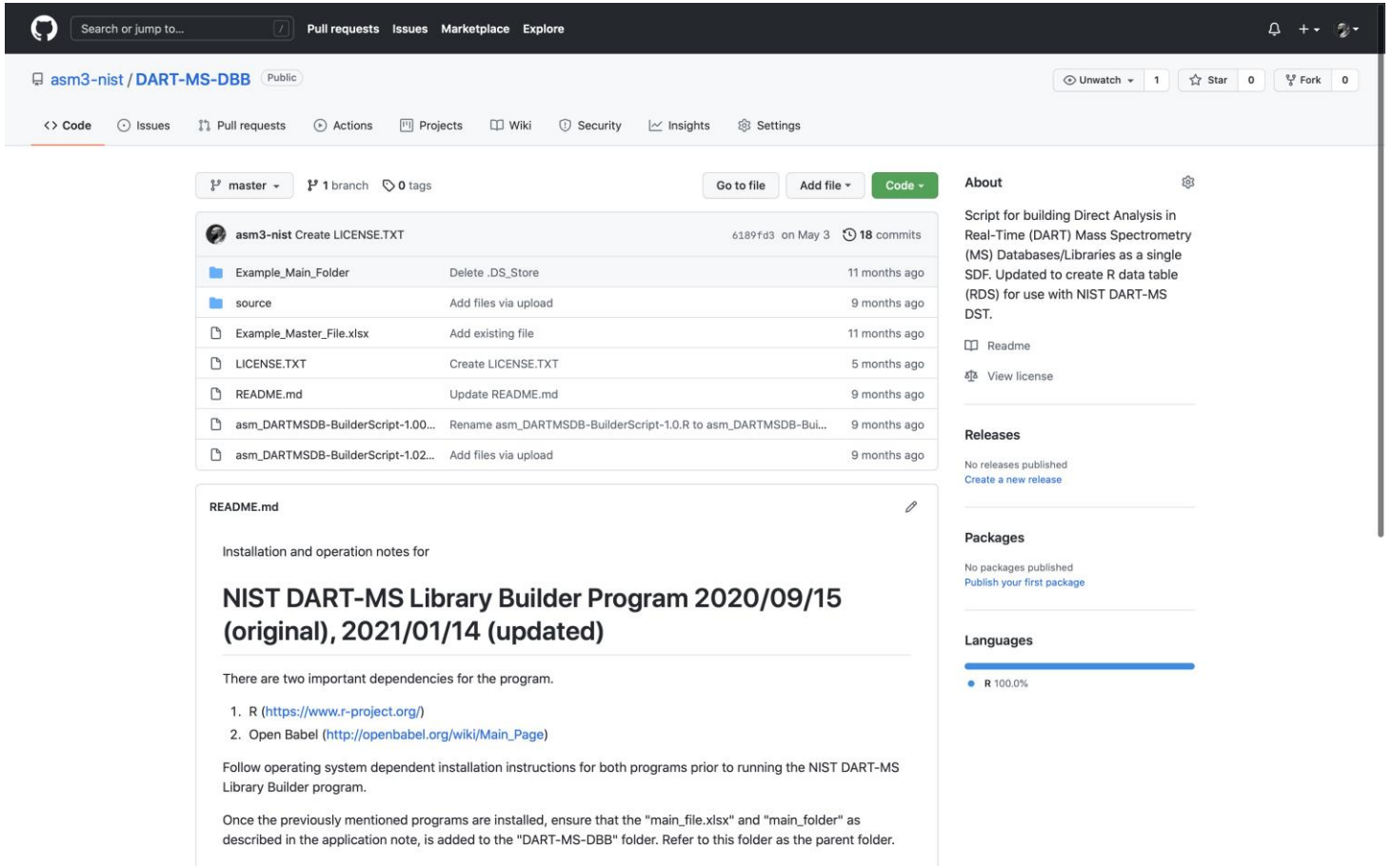

Evaluating is-CID Mass Spectra

1. Developed a simple script with several filters and algorithms to assist in evaluating library mass spectra

2. Made the script and test files open-source and publicly available through github: https://github.com/asm3-nist/DART-MS-DBB

3. Wrote a paper summarizing the methods:
   DOI: 10.1021/jasms.0c00416

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Creation and Release of an Updated NIST DART-MS Forensics Database

Edward Sisco*, Arun S. Moorthy, and Laura M. Watt

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SUBJECTS: Fragmentation, Reaction mechanisms, Molecules,

ACS Partner Journal
Journal of the American Society for Mass Spectrometry

Abstract

Facing increasing caseloads and an everchanging drug landscape, forensic laboratories have been implementing new analytical tools. Direct analysis in real time mass spectrometry (DART-MS) is often one of these tools because it provides a wealth of information from a rapid, simple analysis. The data produced by these systems, while extremely useful, can be difficult to interpret, especially in the case of complex mixtures, and therefore, mass spectral databases are often used to assist in interpretation of data. Development of these databases can be expensive and time-consuming and often relies on manual evaluation of the underlying data. The National Institute of Standards and Technology (NIST) released an initial DART-MS in-source collisional-induced dissociation mass spectral database for seized drugs in the early 2010s but it has not been updated to reflect the increasing prevalence of novel psychoactive substances. Recently, efforts to update the database have been undertaken. To assist in development of the database, an automated data evaluation process was also created. This manuscript describes the new NIST DART-MS Forensics Database and the steps taken to automate the data evaluation process.

KEYWORDS: DART-MS, database, library, seized drugs, data evaluation

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jasms.0c00416.

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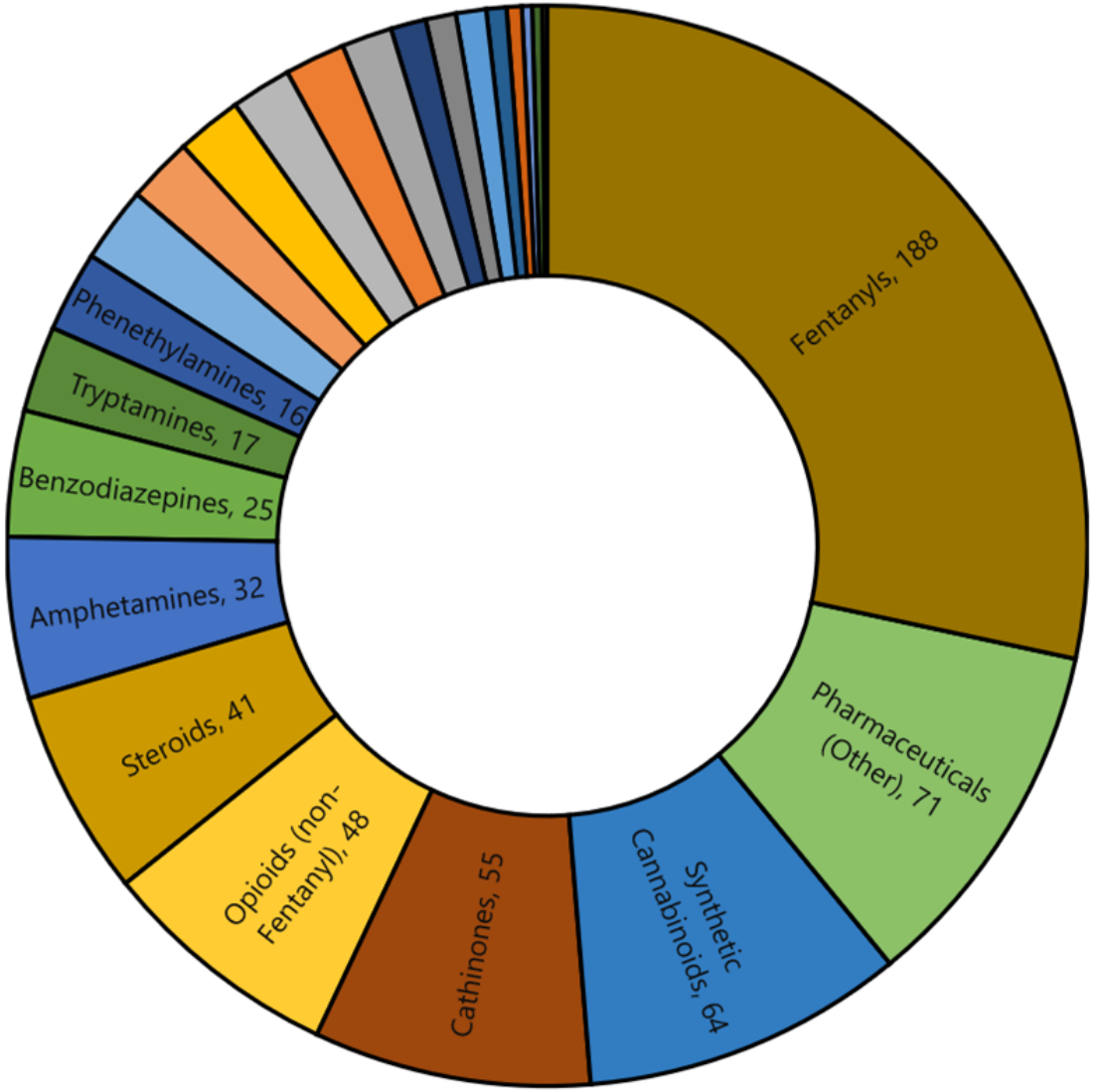
DART-MS Library

Over the last 24 months, significant efforts have been made to update the DART-MS database

- 895 compounds and growing
- 3 is-CID spectra per compound
- 131 entries were carried over from the original library

Update 4 (Dragonfly) recently released



https://doi.org/10.18434/mds2-2313

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Two Key Challenges

1. Developing is-CID mass spectral libraries
   - Procuring and measuring relevant compounds
   - Determine whether spectra are appropriate measurements of compounds
   - Confirm all non-spectral data is correct (e.g. molecular formula, name, etc.)

2. Searching is-CID mass spectra
   - Multiple (coupled) is-CID mass spectra collected per query
   - Query is rarely a pure compound in real-world analysis

Searching is-CID Mass Spectra

1. Developed the Inverted Library Search Algorithm (ILSA) for mixture analysis with multiple is-CID mass spectra

```
08444-1A.txt

Target m/z: 194.118821 (pm)
3,4-Methylenedioxymethamphetamine: FPIE-based Index: 0.835   RevMF-based Index: 0.883
Butamben: FPIE-based Index: 0.421   RevMF-based Index: 0.404
Methedrone: FPIE-based Index: 0.548   RevMF-based Index: 0.335
Target m/z: 163.075983 (pm)
Target m/z: 195.121086 (pm)
Target m/z: 423.205903 (pm)
Target m/z: 192.102651 (pm)
Target m/z: 164.07897 (pm)
Target m/z: 194.203044 (pm)
Target m/z: 206.11782 (pm)
Target m/z: 425.204212 (pm)
Target m/z: 208.132971 (pm)
3,4-Methylenedioxyethylamphetamine: FPIE-based Index: 0.916   RevMF-based Index: 0.778
Methamphetamine Methyl Carbamate: FPIE-based Index: 0.444   RevMF-based Index: 0.529
WARNING: An illegal reflective access operation has occurred
WARNING: Illegal reflective access by org.apache.poi.util.SAXHelper (file:/Library/Frameworks/R.framework/Versions/4.0/Resources/library/xl
sxjars/java/poi-ooxml-3.10.1-20140818.jar) to constructor com.sun.org.apache.xerces.internal.util.SecurityManager()
WARNING: Please consider reporting this to the maintainers of org.apache.poi.util.SAXHelper
WARNING: Use --illegal-access=warn to enable warnings of further illegal reflective access operations
WARNING: All illegal access operations will be denied in a future release
Target m/z: 194.281316 (pm)
Target m/z: 424.209288 (pm)
Target m/z: 385.213268 (pm)
Target m/z: 356.186154 (pm)
Target m/z: 312.124129 (pm)
Target m/z: 337.119564 (pm)
Target m/z: 196.12353 (pm)
Target m/z: 194.364582 (pm)
Target m/z: 468.145979 (pm)
Target m/z: 193.105379 (pm)
2-Fluorophenyl Cyclopentyl Ketone: FPIE-based Index: 0.278   RevMF-based Index: 0.353
Target m/z: 190.086991 (pm)
Target m/z: 387.226501 (pm)
4'-Fluoro, para-fluoro-trans-3-methyl Fentanyl: FPIE-based Index: 0.606   RevMF-based Ind
```

Searching is-CID Mass Spectra

1. Developed the Inverted Library Search Algorithm (ILSA) for mixture analysis with multiple is-CID mass spectra

2. Implemented the algorithm as a simple application and made it publicly available through github:

   https://github.com/asm3-nist/DART-MS-DST

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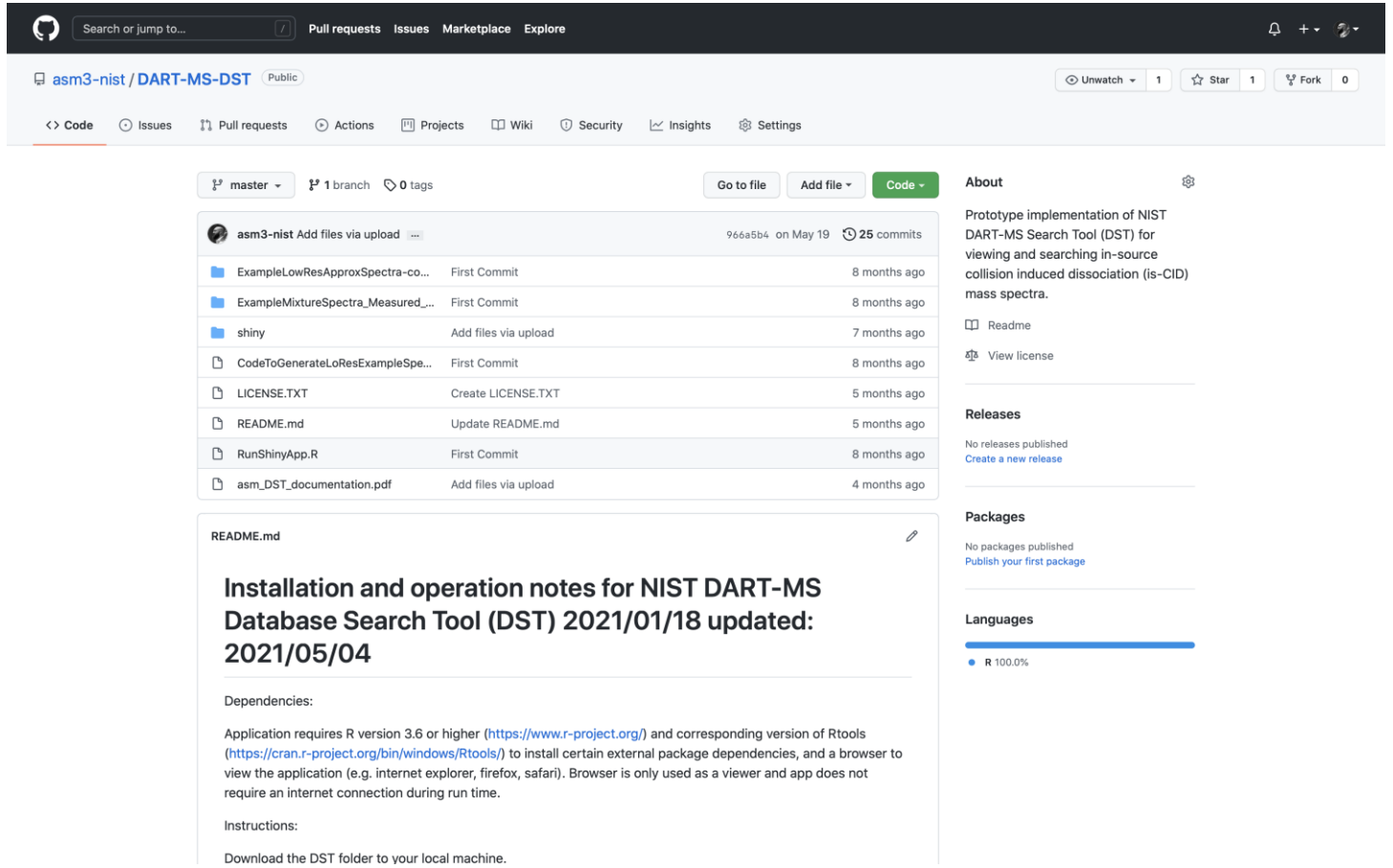

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   DOI: 10.1021/jasms.0c00416

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RESEARCH ARTICLE

A New Library-Search Algorithm for Mixture Analysis Using DART-MS

Arun S. Moorthy* and Edward Sisco

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SUBJECTS: Fragmentation, Algorithms, Reaction mechanisms,

ACS Partner Journal
Journal of the American Society for Mass Spectrometry

Abstract

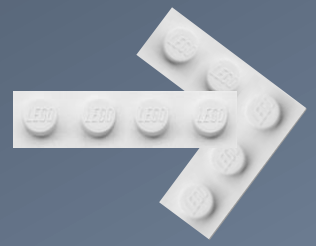
Forensic analysis of seized drug evidence often involves determining whether the components of an unknown mixture are illicit compounds. One approach to this task is to screen the evidence using direct analysis in real time mass spectrometry (DART-MS) to make presumptive identifications. This manuscript introduces a new library-search algorithm that enhances presumptive identifications of mixture components using a series of in-source collision-induced dissociation mass spectra collected through DART-MS. The multistage search, titled the Inverted Library-Search Algorithm (ILSA), identifies potential components in a mixture by first searching the lowest fragmentation mass spectrum for target peaks, assuming these peaks are protonated molecules, and then scoring each target peak with possible library matches. As a proof of concept, the ILSA is demonstrated through several example searches of model seized drug mixtures of acetyl fentanyl, benzyl fentanyl, amphetamine, and methamphetamine searched against a small library of select compounds and the freely available NIST DART-MS Forensics Database. Discussion of the search results and several open areas of research to further extend the method are provided. This new approach for presumptive identification provides analysts with refined information about mixture components and will be of immediate importance in forensic analysis using DART-MS. A prototype implementation of the ILSA is available at https://github.com/asm3-nist/DART-MS-DST.

KEYWORDS: algorithms, DART-MS, library searching, mass spectrometry, seized drug analysis

Supporting Information

Functional research

Functional research  Usable product

Functional research  Usable product

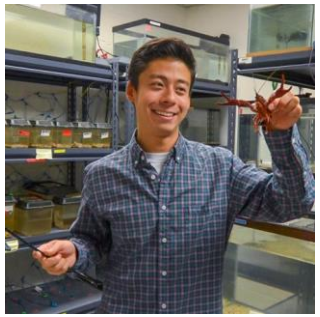
Funding

NIST

NIJ NATIONAL INSTITUTE of JUSTICE

Expertise

Ruthie Corzo



Stephen Tennyson

End-Users

Harris County Institute of Forensic Sciences (Texas)

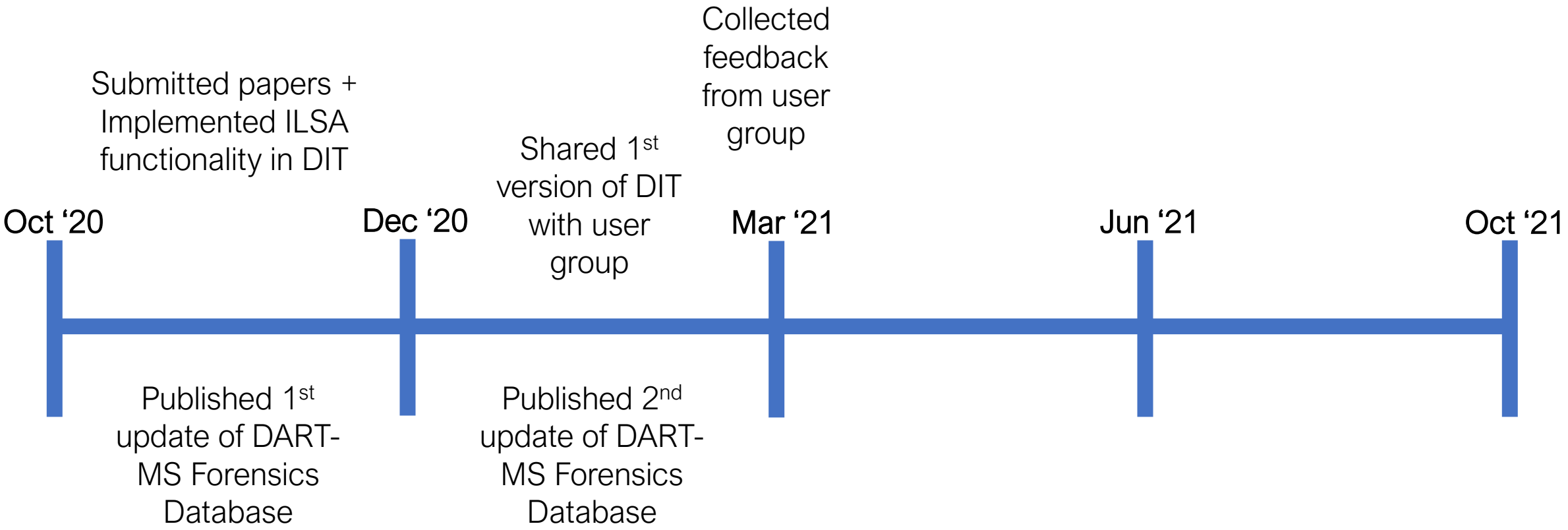
Maryland State Police Forensic Sciences Division

Virginia Department of Forensic Sciences

Food and Drug Administration Forensic Chemistry Center

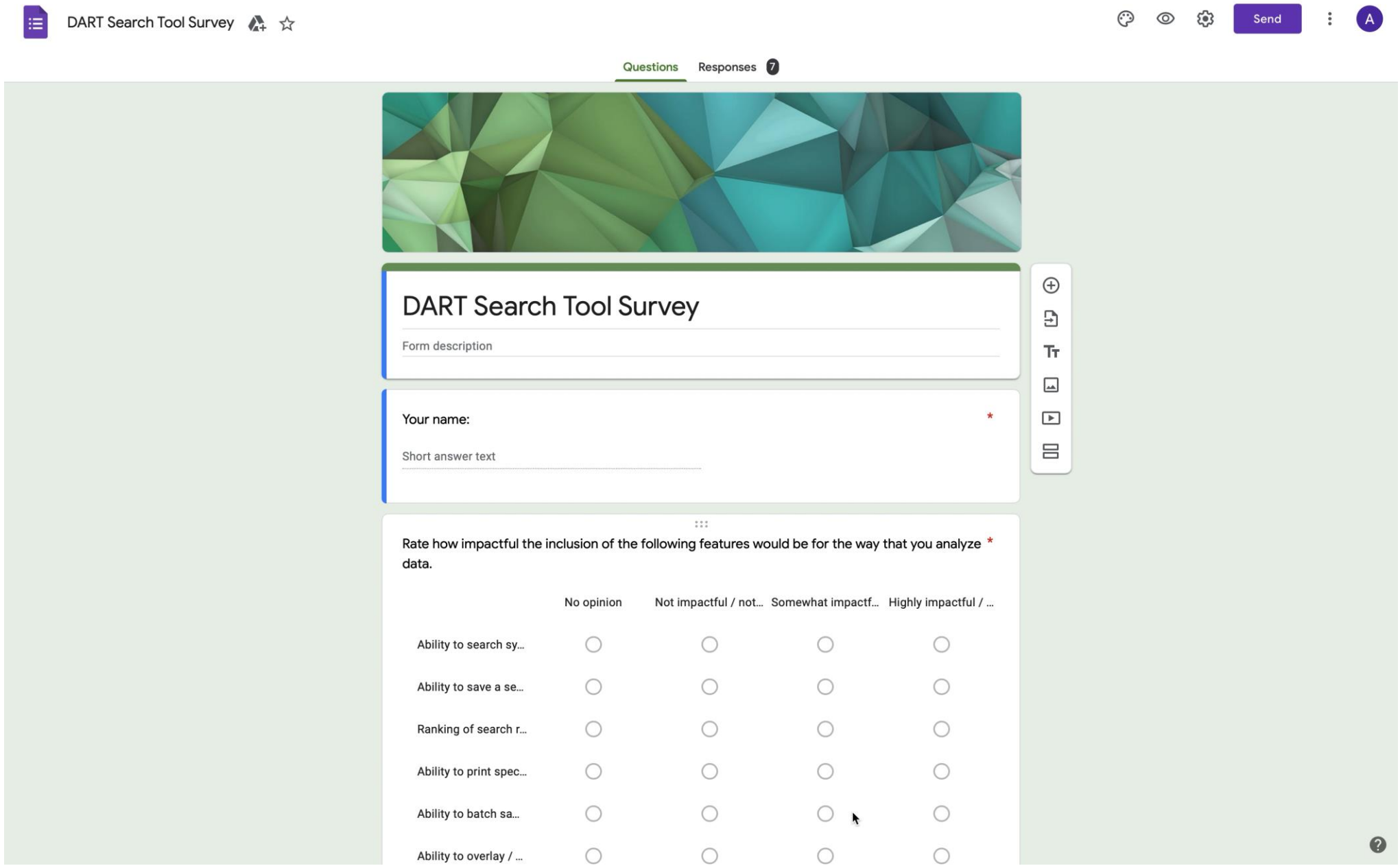
U.S. Customs and Border Protection INTERDICT Lab

Development of the Data Interpretation Tool (DIT)



DIT: *Data Interpretation Tool*

Survey 1 – Important Features & Bug Report



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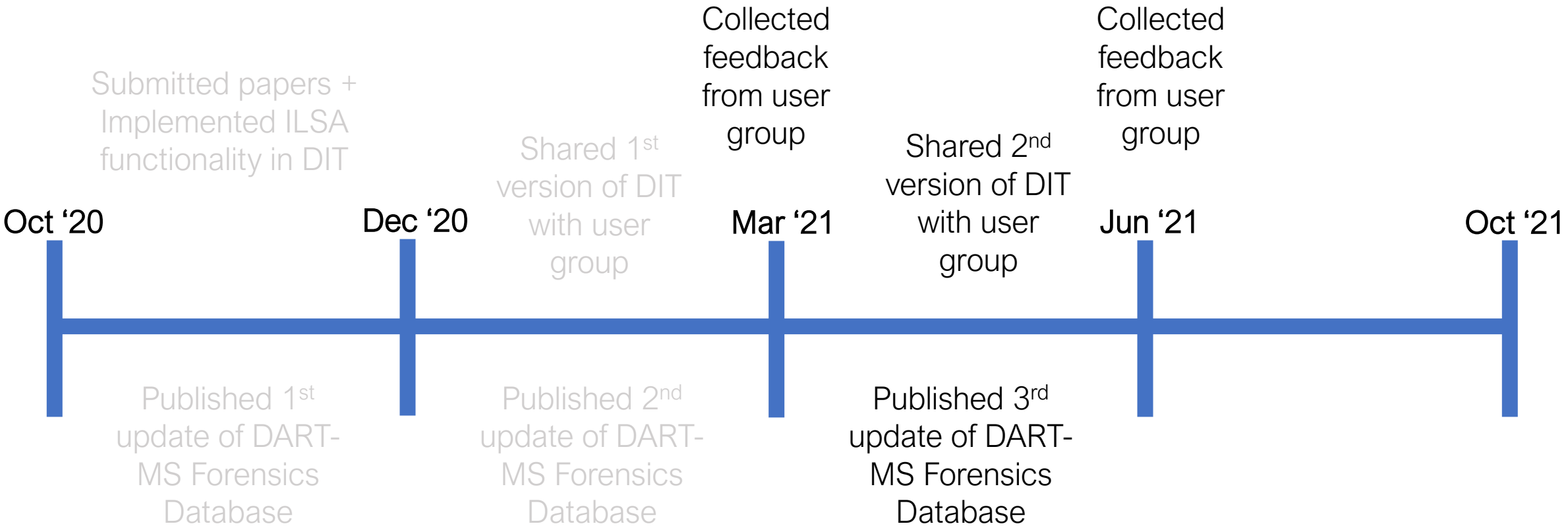
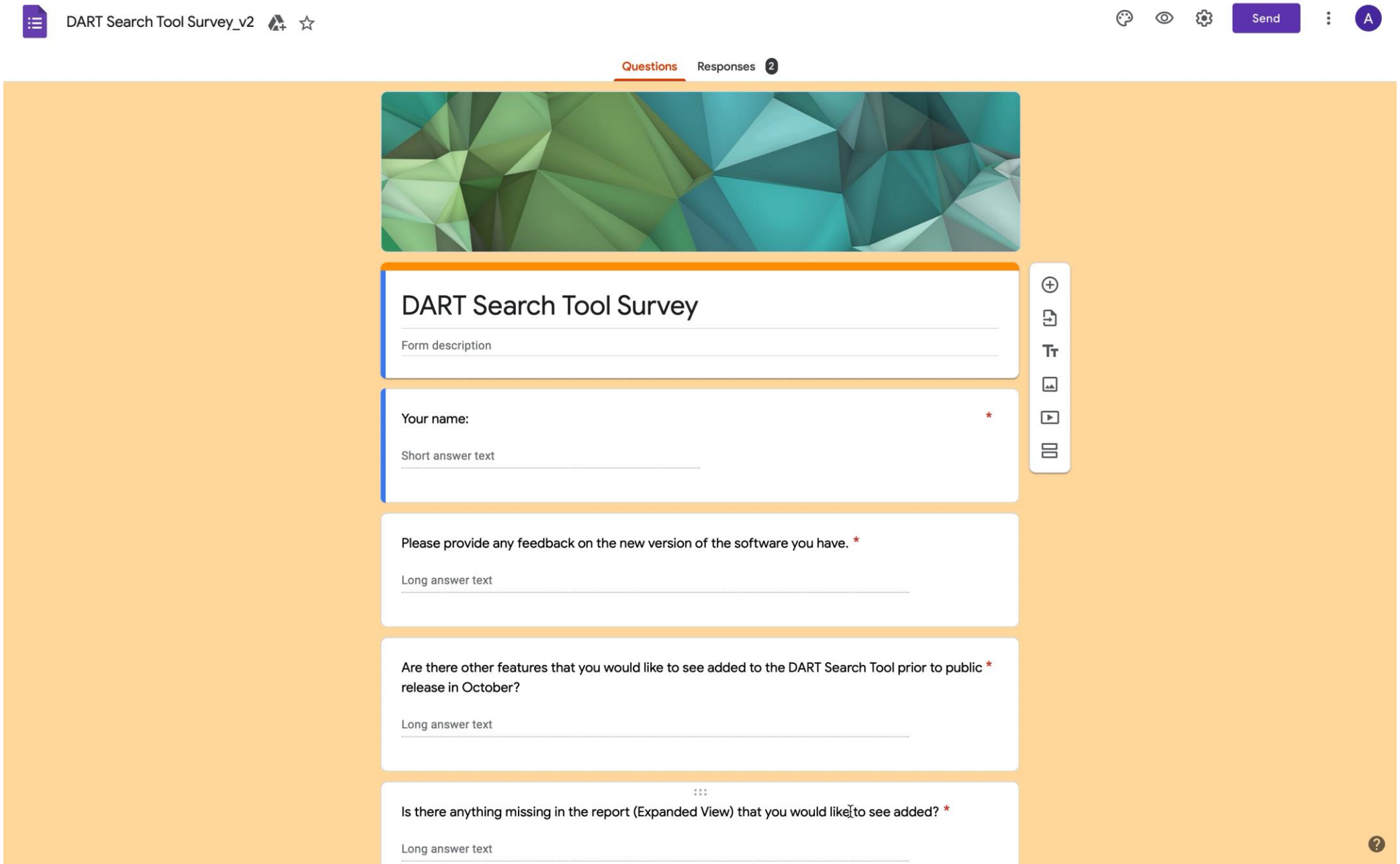
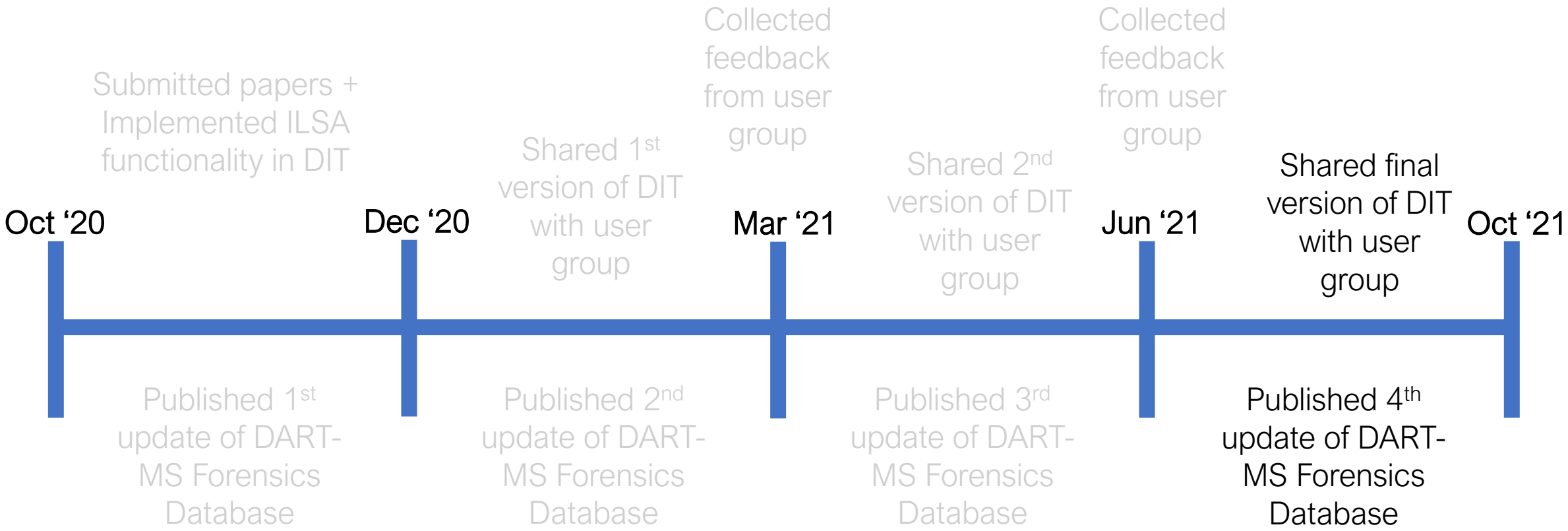


Survey 2 – General Comments & Bug Report



Development of the Data Interpretation Tool (DIT)



DIT

https://doi.org/10.18434/mds2-2448

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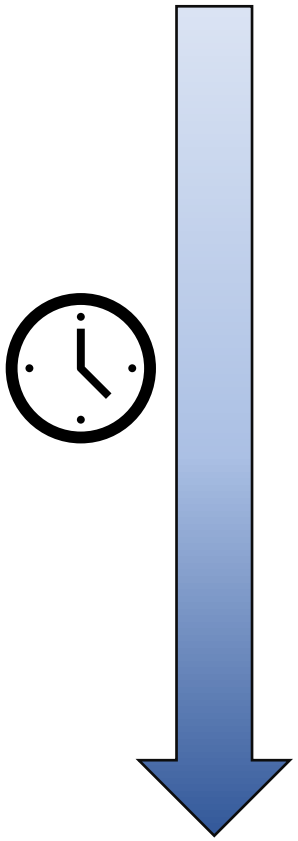
Future Features



- Negative mode library
- Database builder
- Batch processing
- Tools for identification of unknowns
- Datamining

FENTANYL

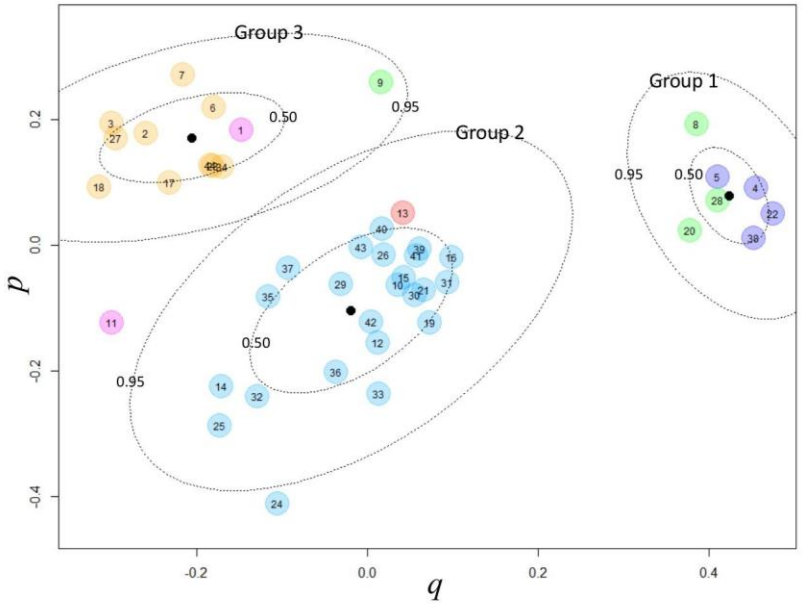
Mod site a

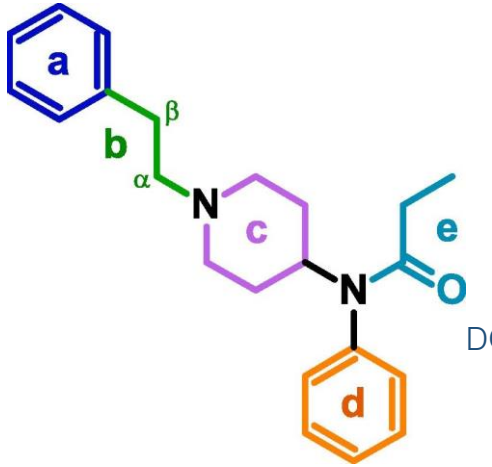
Mod site b

Mod site c

Mod site d

Mod site e





DOI: 10.1016/j.forc.2020.100237

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Other Resources – Landing Page

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PROJECTS/PROGRAMS

Methods, Software Tools, and Resources for Forensics Laboratories with DART-MS or other AI-MS Techniques

Summary

With increasing backlogs and more complex samples, forensic chemistry laboratories need new technologies that rapidly provide accurate analytical results. Many laboratories are adopting Direct Analysis in Real Time Mass Spectrometry (DART-MS) to meet this need. DART-MS enables laboratories to obtain mass spectra, or molecular "fingerprints," from samples in seconds instead of tens of minutes. Because this technique is highly sensitive, very little of the sample is handled or consumed during analysis. This reduces the risk of accidental exposure when analyzing highly toxic compounds such as fentanyl.

We are developing a suite of methods, software tools, and resources to help forensic laboratories adopt and implement DART-MS and other ambient ionization mass spectrometry (AI-MS) techniques. These include databases, mass spectral search tools, analytical methods, and example validation documents.

The NIST DART-MS Forensics Database 2020, an evaluated collection of mass spectra of seized drugs, cutting agents, and related compounds, is available for download from the NIST website.

UPDATE March 5, 2021: This database has been updated with spectra for an additional 100 compounds, mainly benzodiazepines, cathinones, synthetic cannabinoids, and tryptamines.

This project is part of NIST's ongoing effort to help labs detect and identify synthetic opioids and other drugs efficiently, reliably, and safely. If you have any questions, please contact %20DARTdata@nist.gov.

DESCRIPTION

The development of methods, software tools, and resources for forensic laboratories using DART-MS or other AI-MS techniques is a collaborative effort between the Surface and Trace Chemical Analysis

ORGANIZATIONS

Material Measurement Laboratory
Materials Measurement Science Division
Surface and Trace Chemical Analysis Group

NIST STAFF

Edward Sisco
Thomas P. Forbes
Elizabeth Robinson
Arun Moorthy

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edward.sisco@nist.gov
(301) 975-2093

PROJECT STATUS

Ongoing

https://bit.ly/3ry0Kyx

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Other Resources – Validation Package

Contains:

- Template SOP
- Template Validation Plan
- Validation Data Workup Sheets
- Validation Run Sheets
- Template Maintenance Plan
- Search Lists

Coming Soon: Training

Can help reduce validation time by up to 1-year

https://doi.org/10.18434/mds2-2424

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Pinterest.com

DIT

DARTdata@nist.gov

https://bit.ly/3ry0Kyx

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