High-throughput Element Purification

Upscaled applications of isotope analyses in medicine, ore exploration and beyond

Dr. Brandon Mahan, James Cook University*

Triskem vUGM, November 24, 2020

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Prelude:
Who am I?

Visiting Associate Fellow, University of Wollongong (Wollongong)

Purpose: Development of automated IEC protocols
Host: Tony Dosseto

Visiting Research Fellow, Monash University (Melbourne)

Purpose: Interlab calibration of isotope solutions and rock standards
Host: Oliver Nebel

Visiting Fellow, Macquarie University (Sydney)

Purpose: Isotope Metallomics collaboration including Centre for MND
Host: Simon Turner

TRISKEM

IEC Research & Development

Purpose: Development of pan-applicable rapid IEC protocols

ThermoFisher SCIENTIFIC

Automated Systems Partnership, Isotope Metallomics Initiative

Purpose: Technique development; community and partnerships

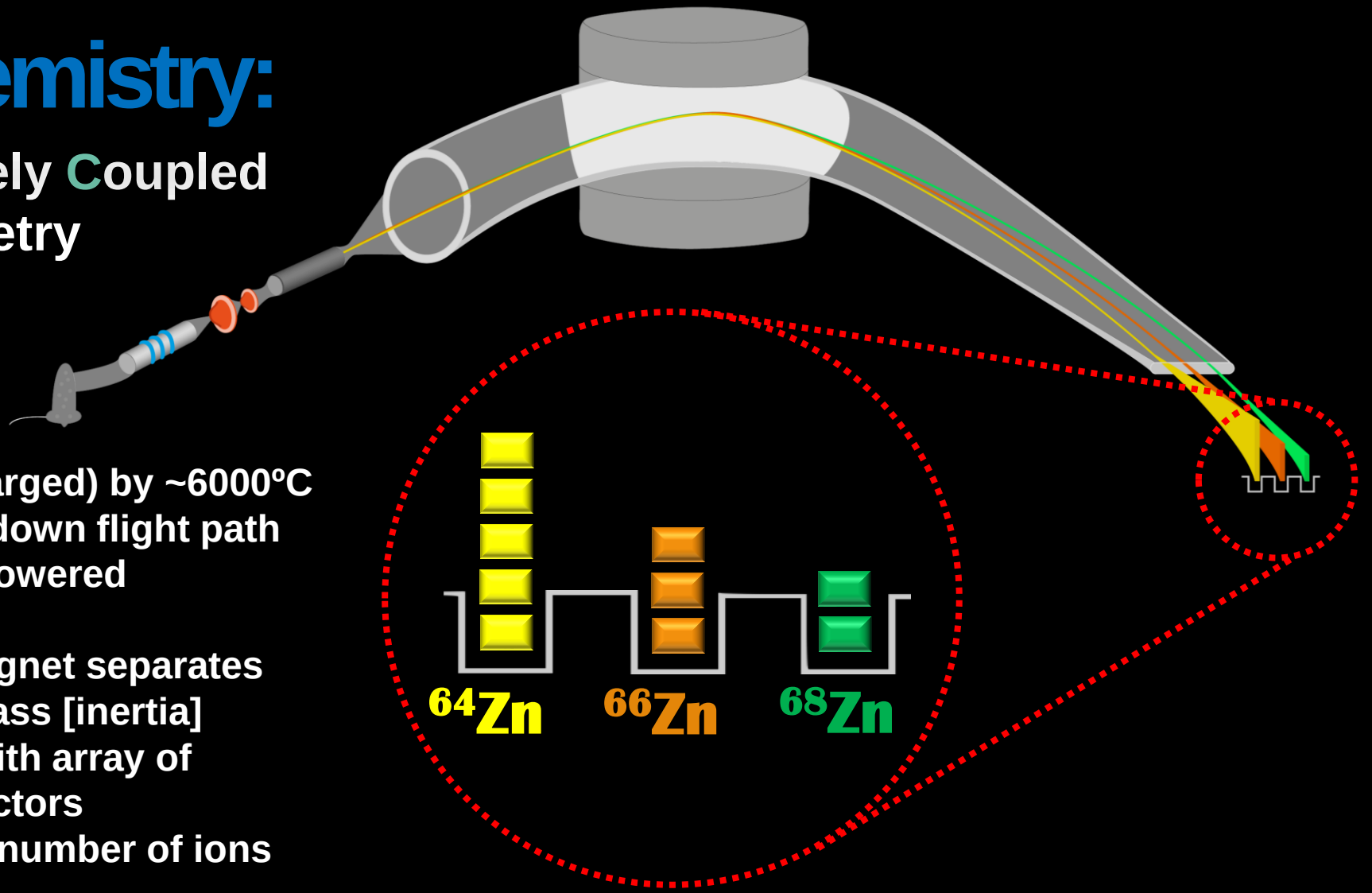
Longitudinal AD Collaboration

Purpose: Create comprehensive, longitudinal AD database

Act 1:
Introduction of Characters

The workhorse of isotope geochemistry:

Multi Collector Inductively Coupled Plasma Mass Spectrometry (MC-ICP-MS)



- Isotopes ionized (single-charged) by ~6000ºC Ar plasma and accelerated down flight path
- Cations deflected by high-powered electromagnet
  - Given same charge, magnet separates ions solely based on mass [inertia]
- Cations terminally collide with array of electrically conductive detectors
  - Voltage proportional to number of ions

The workhorse of isotope geochemistry:

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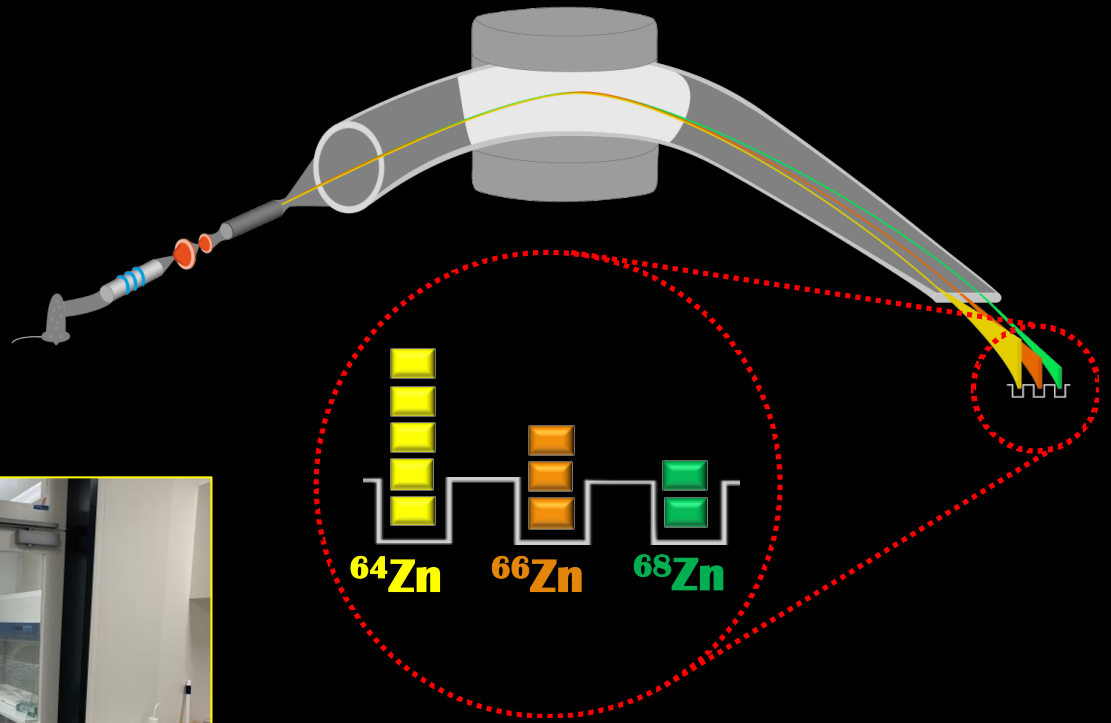
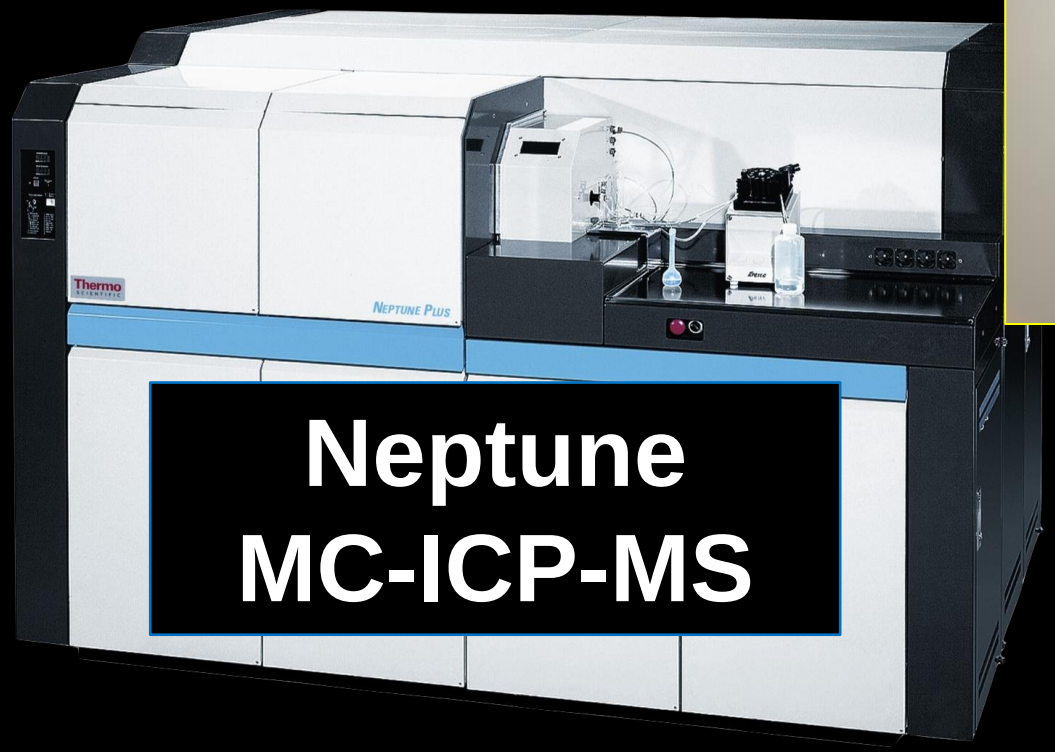
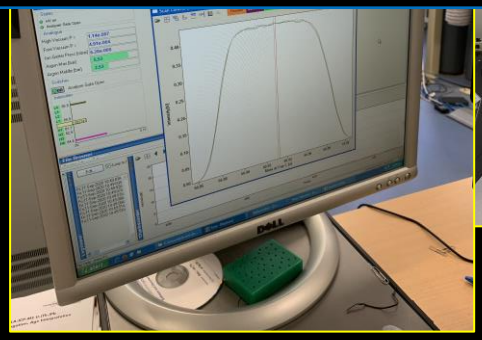




Neptune MC-ICP-MS

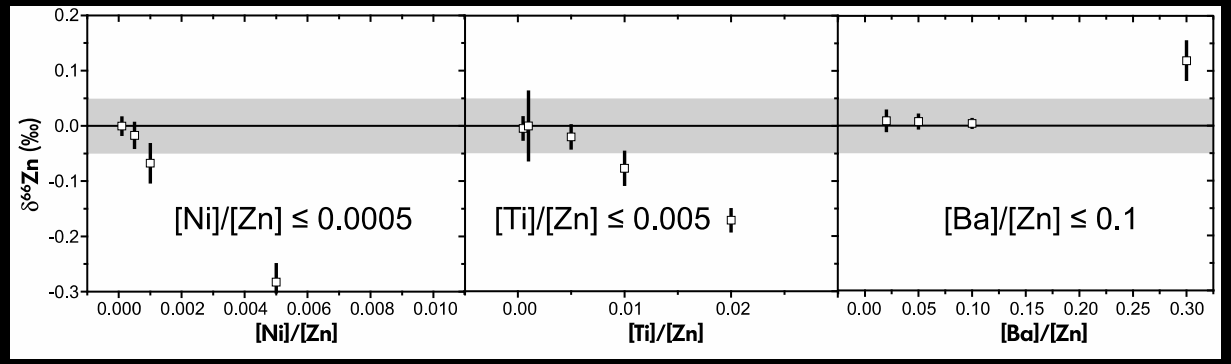
JCU Laboratories

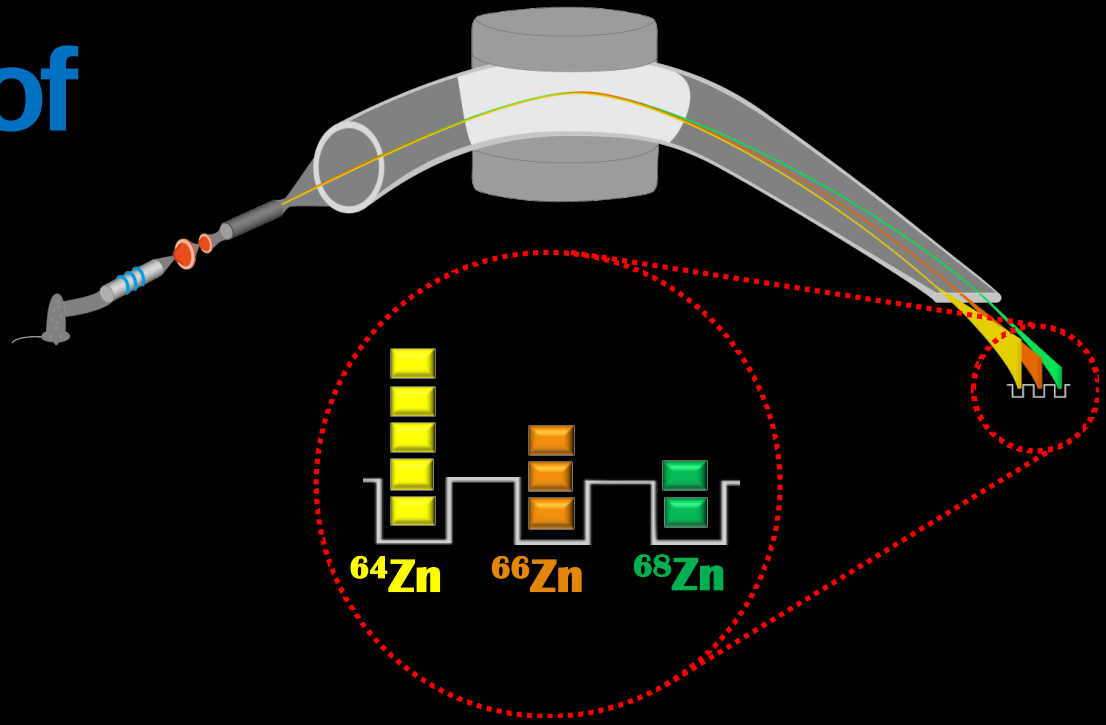


The ghosts in the machine of isotope geochemistry:

Spectral Interferences

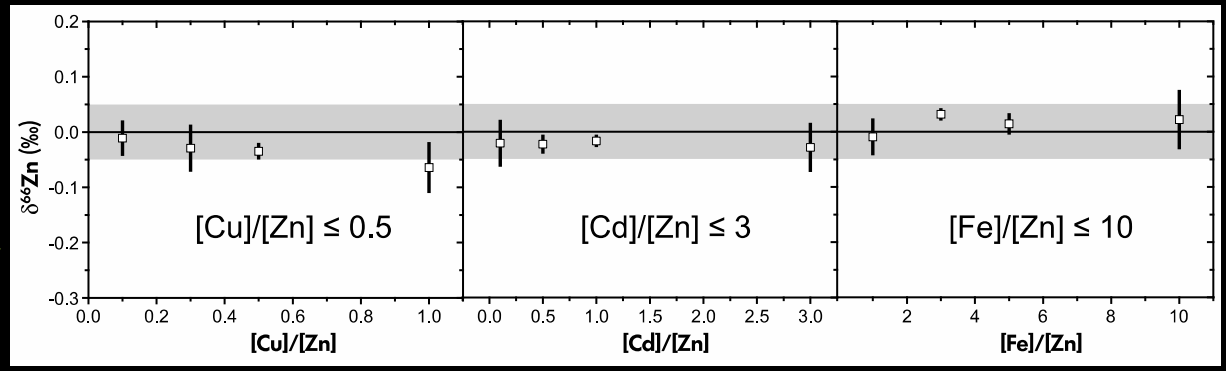
e.g. Zinc





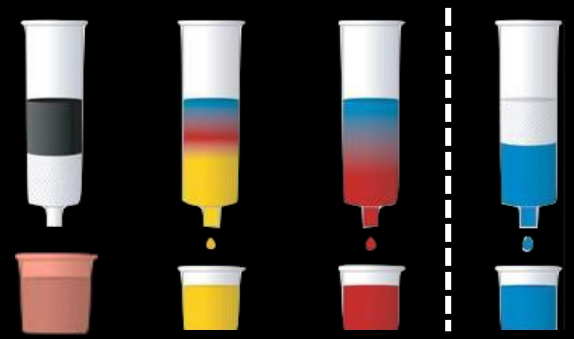
^{64}Zn	48.89	$^{32}S^{16}O_2^+$, $^{48}Ti^{16}O^+$, $^{31}P^{16}O_2{}^1H^+$, $^{48}Ca^{16}O^+$, $^{32}S_2^+$, $^{31}P^{16}O^{17}O^+$ $^{34}S^{16}O_2^+$, $^{36}Ar^{14}N_2^+$
^{66}Zn	27.81	$^{50}Ti^{16}O^+$, $^{34}S^{16}O_2^+$, $^{33}S^{16}O_2{}^1H^+$, $^{32}S^{16}O^{18}O^+$, $^{32}S^{17}O_2^+$, $^{33}S^{16}O^{17}O^+$, $^{32}S^{34}S^+$, $^{33}S_2^+$
^{67}Zn	4.11	$^{35}Cl^{16}O_2^+$, $^{33}S^{34}S^+$, $^{34}S^{16}O_2{}^1H^+$, $^{32}S^{16}O^{18}O^1H^+$, $^{33}S^{34}S^+$, $^{34}S^{16}O^{17}O^+$, $^{33}S^{16}O^{18}O^+$, $^{32}S^{17}O^{18}O^+$, $^{33}S^{17}O_2^+$, $^{35}Cl^{16}O_2^+$
^{68}Zn	18.57	$^{36}S^{16}O_2^+$, $^{34}S^{16}O^{18}O^+$, $^{40}Ar^{14}N_2^+$, $^{35}Cl^{16}O^{17}O^+$, $^{34}S_2^+$, $^{36}Ar^{32}S^+$, $^{34}S^{17}O_2^+$, $^{33}S^{17}O^{18}O^+$, $^{32}S^{18}O_2^+$, $^{32}S^{36}S^+$

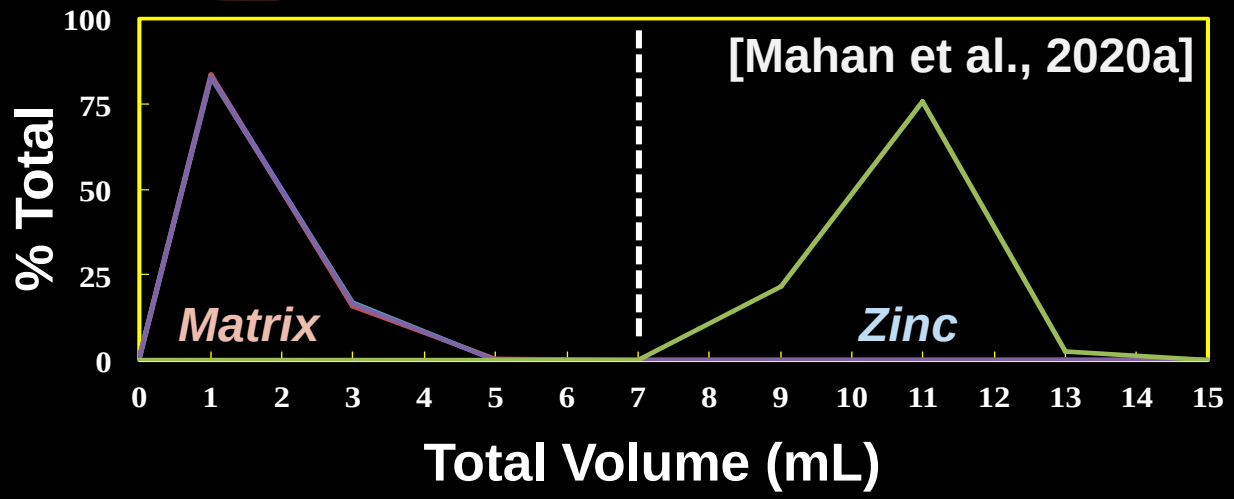
[Chen et al., 2015]

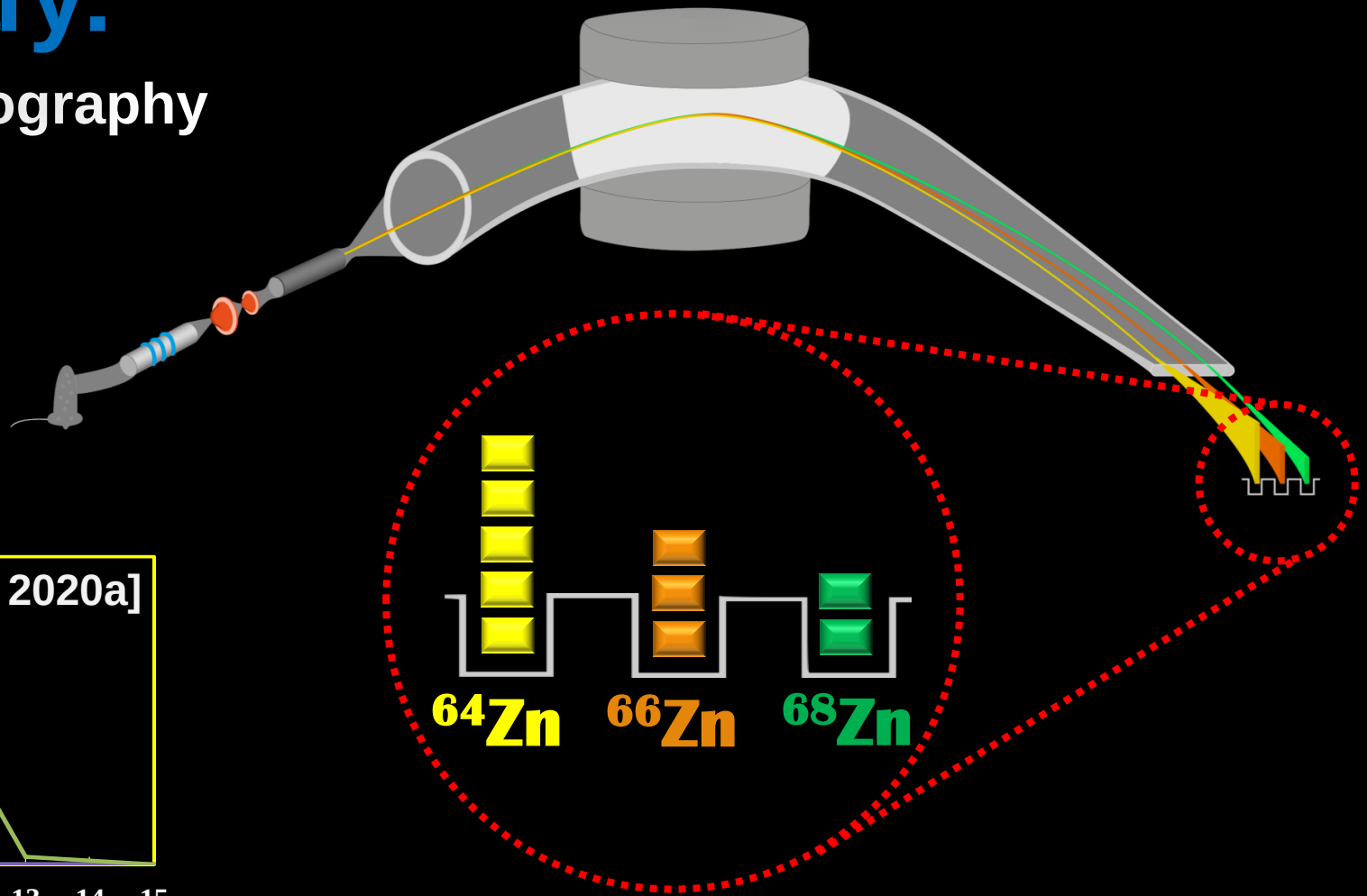


The rate-limiting step of conventional isotope geochemistry:

Manual Ion Exchange Chromatography (IEC)





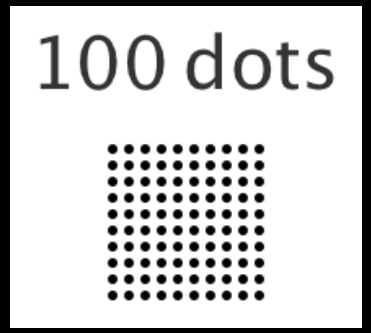


Act 2:

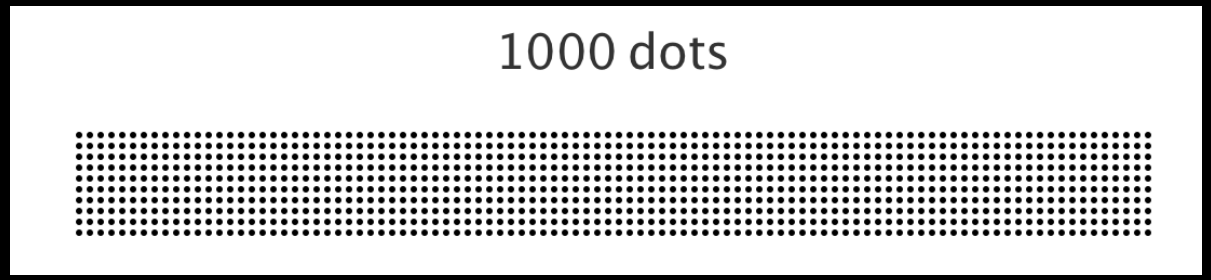
Conflict & The Monomyth…

The Achilles' heel of conventional isotope geochemistry:

[*n*] for an <u>ambitious</u> isotope geochemistry project:



[*n*] for for routine ore exploration, soil, clinical analyses:



The Achilles' heel of conventional isotope geochemistry:

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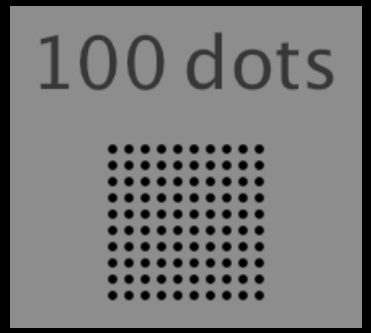
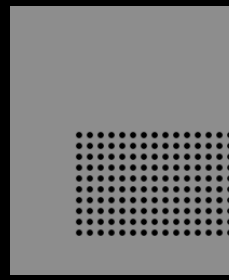
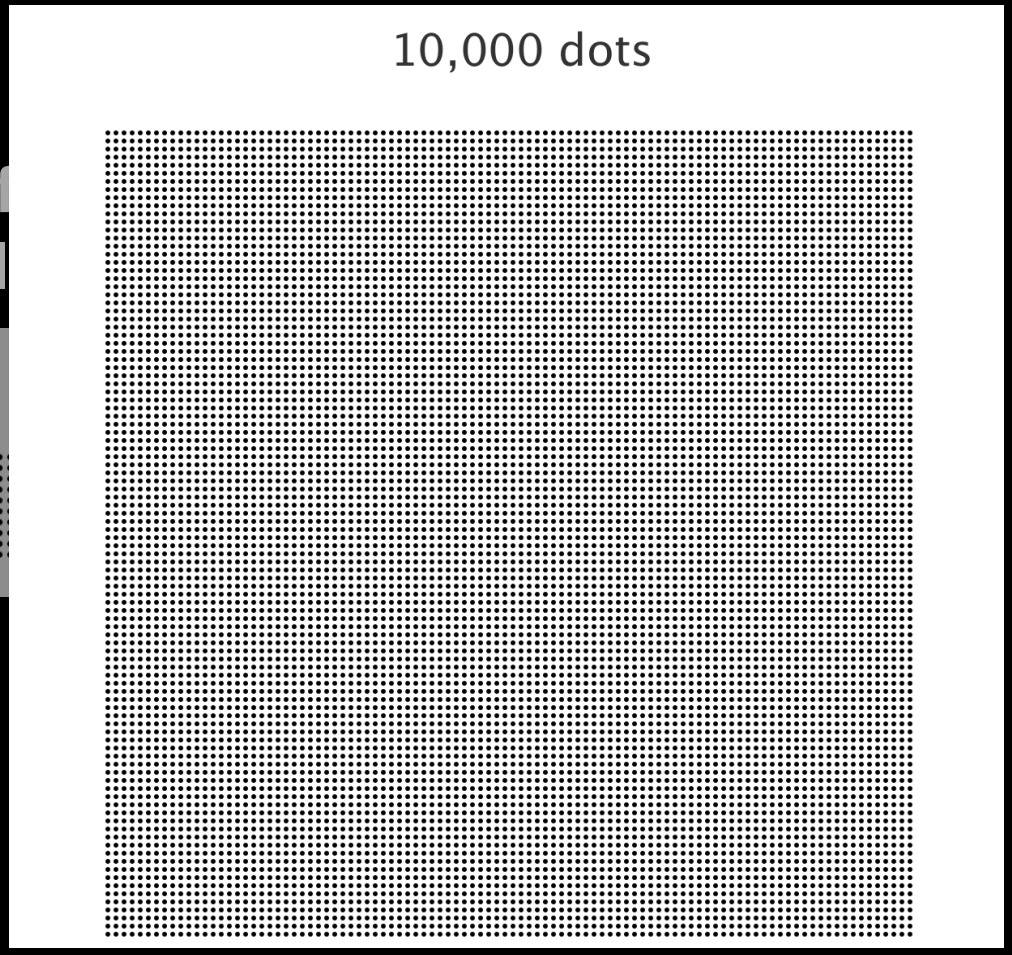


[*n*] for f
clinical



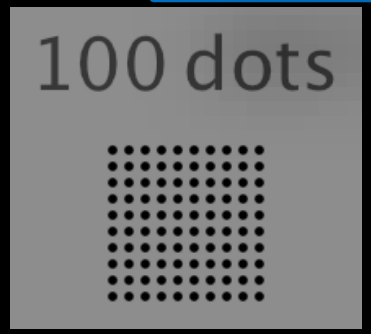
or even:



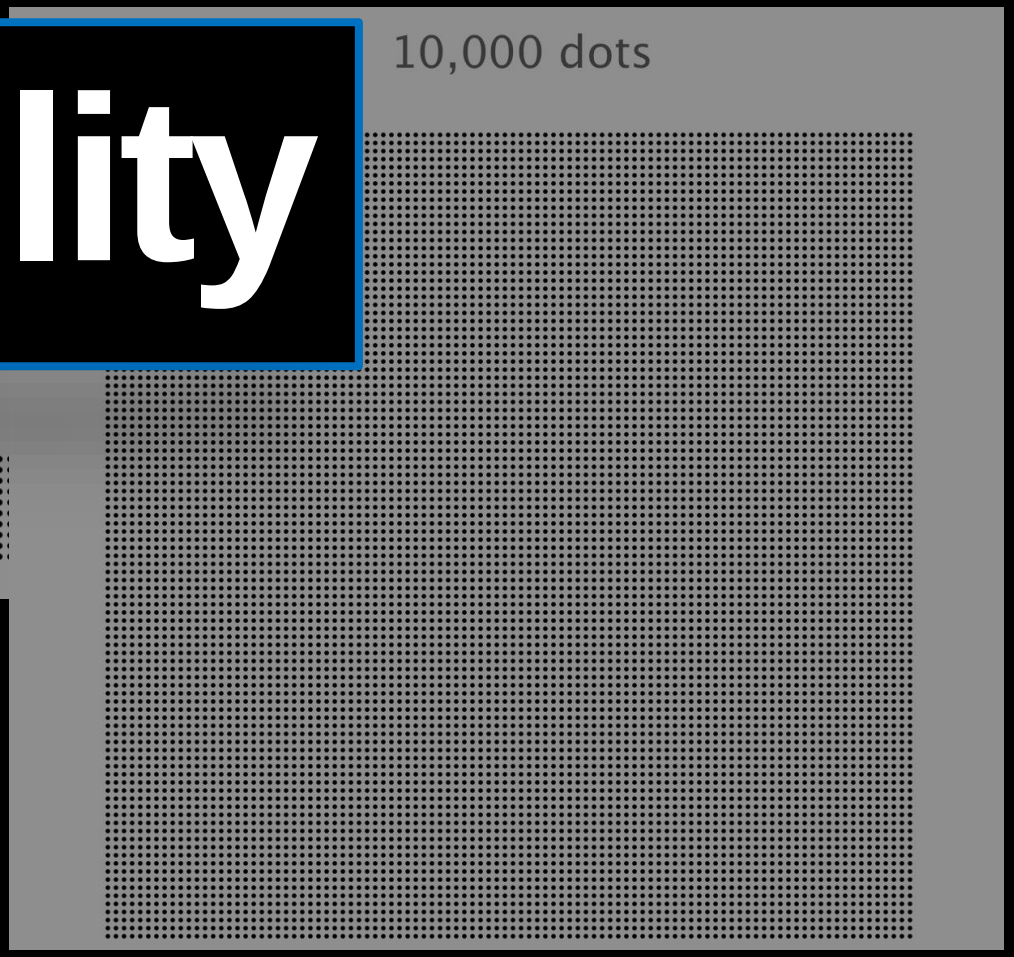
The Achilles' heel of conventional isotope geochemistry:

[*n*] for an ambit
isotope geoche
project:

Scalability



or even:



The Achilles' heel of conventional isotope geochemistry:

[*n*] for an ambit
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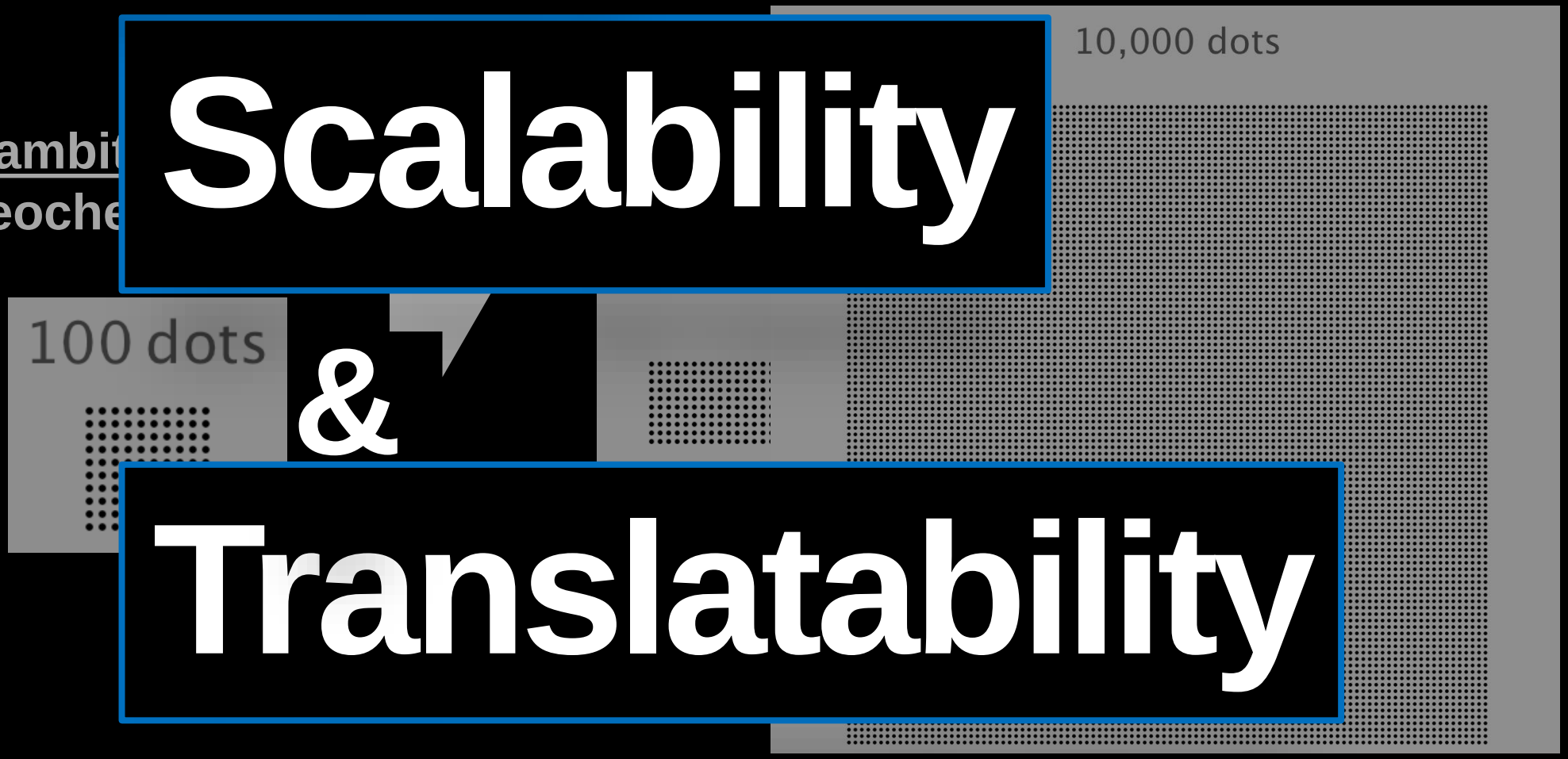
project:

Scalability

&

Translatability



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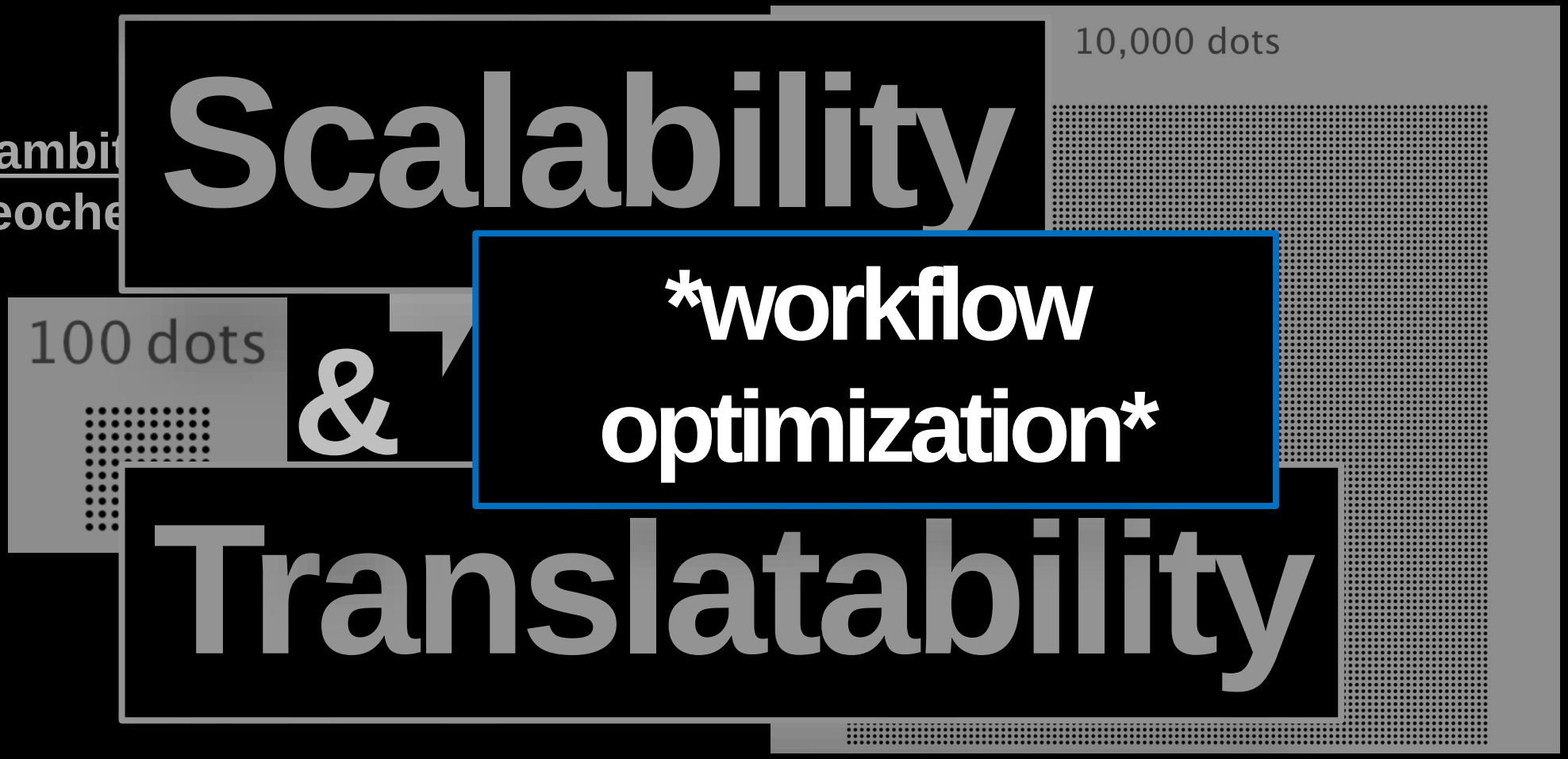
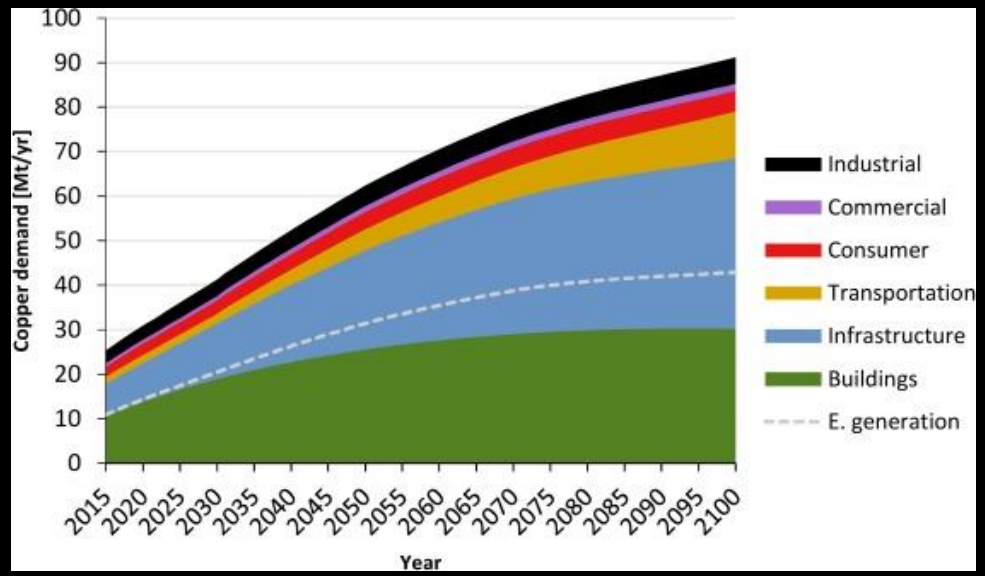


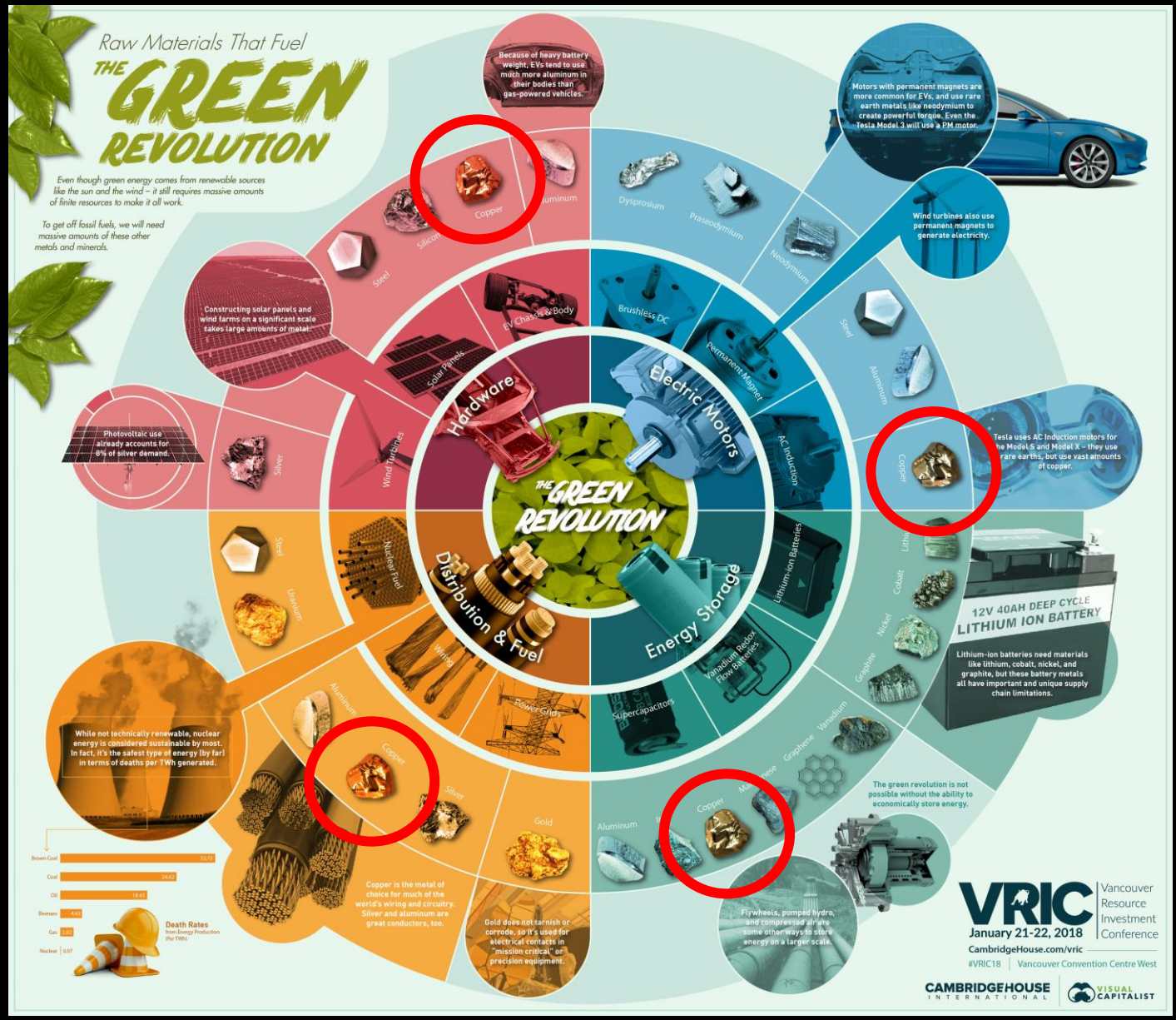
Act 2:

…The Heroics of it All

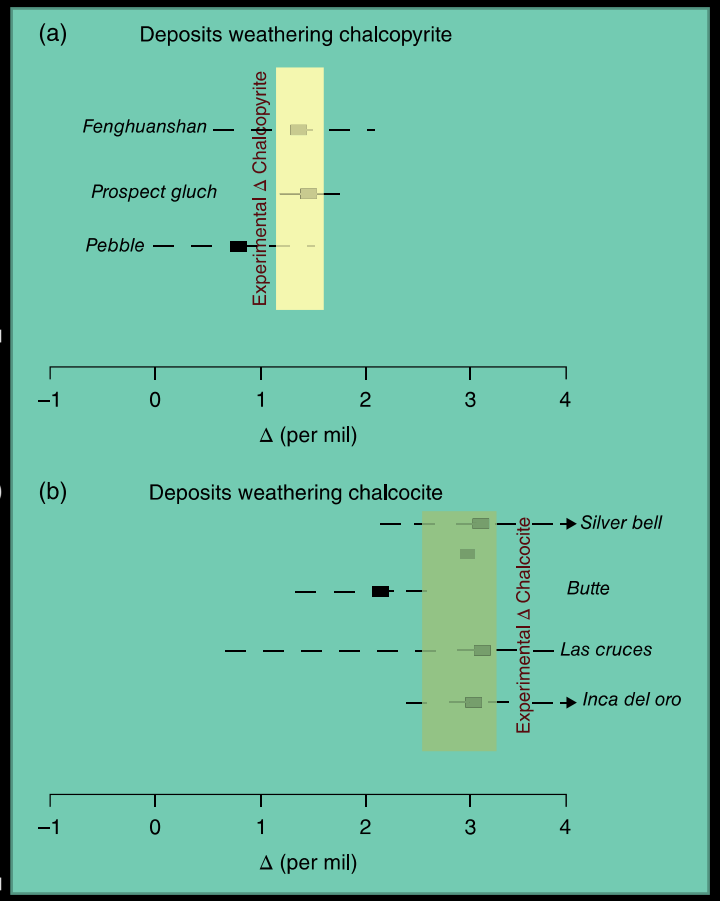
Application #2: *Ore vectoring*

Copper,
Copper,
& More Copper



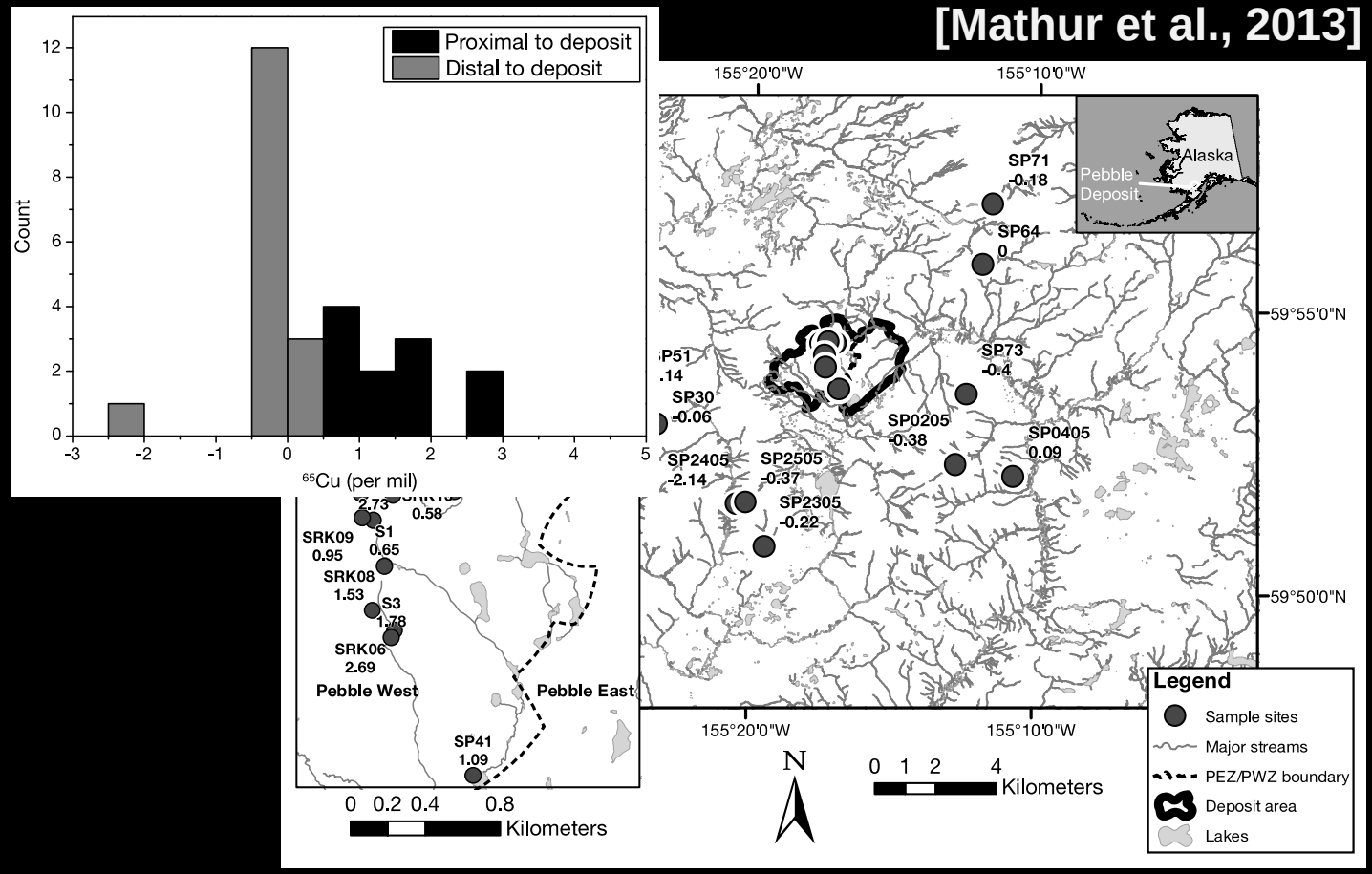


Application #2: *Ore vectoring*



[Mathur and Wang, 2019]

[Mathur et al., 2013]



Application #3:
Early disease diagnostics

Metallome [ca. 2001, Williams]

definition : chemically active and/or organically bound metal or metalloid species present in biological cells, tissues and systems

Metallomics [ca. 2002, Haraguchi]

definition : the ensemble of research activities related to metals of biological interest

Application #3:
Early disease diagnostics

Isotope Metallomics [ca. 2017, Albarède]

definition : the application of stable [metal] isotopes to biological systems

Foundational Question:

Why metal isotopes and not just concentrations?

- *Enrichment/depletion of metals in tissues/fluid is largely unpredictable and highly variable*
- *ICP-MS analytical precision is typically ~3-5%*

Application #3:
Early disease diagnostics

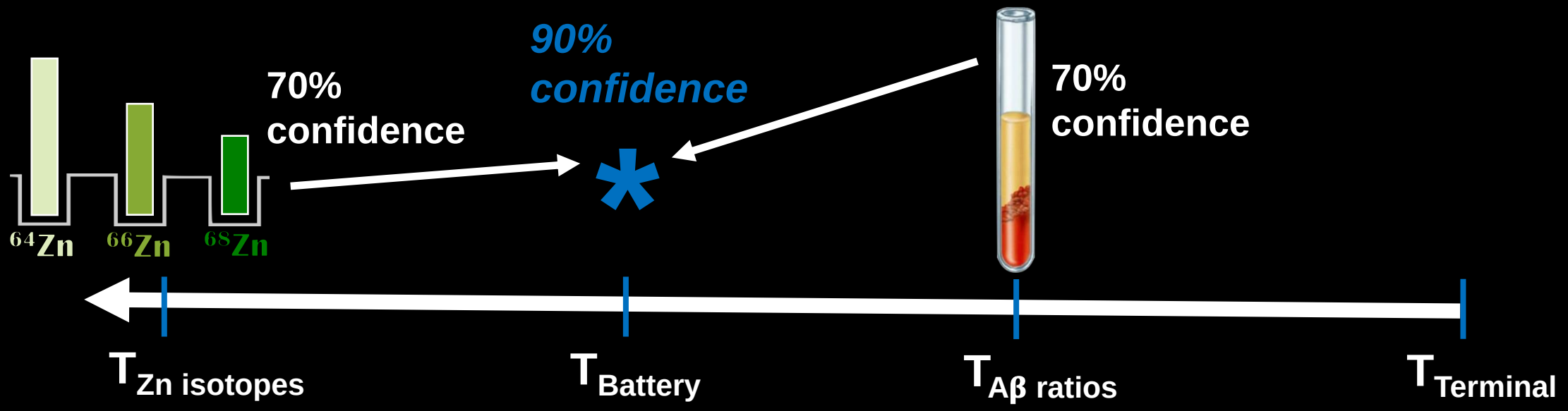
Foundational Question:

Why metal isotopes and not just concentrations?

- ***Isotope distribution is governed by physics, i.e. the strength of chemical bonds, generally decreasing in order O>N>S (respective heavy→light trending)***
- ***Isotopes fractionate independent of concentrations***
- ***MC-ICP-MS analytical precision ~0.05-0.1‰, or ~100-1000x more precise***

The Point:

- *Some isotopes may be quasi-uniquely sensitive to shifts in bonding environment associated with AD plaques and tangles*
- *Combined with other tests, early diagnostics may be developed*

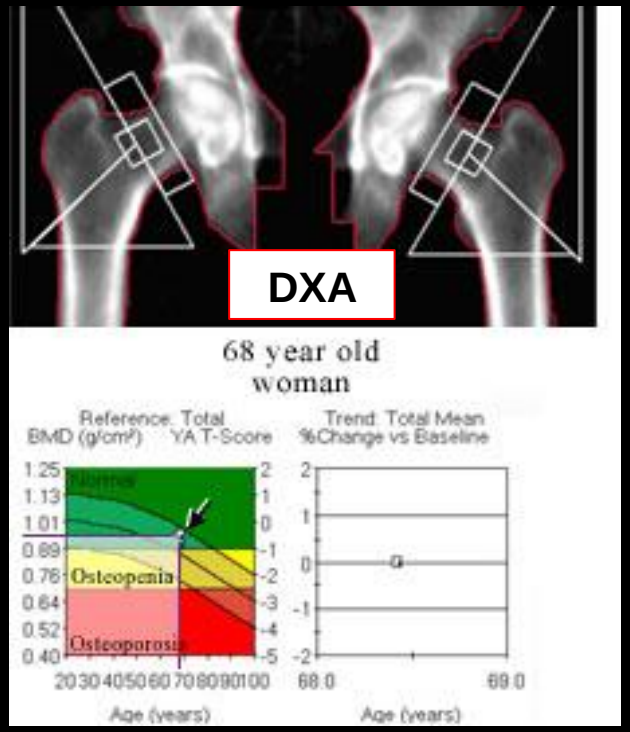


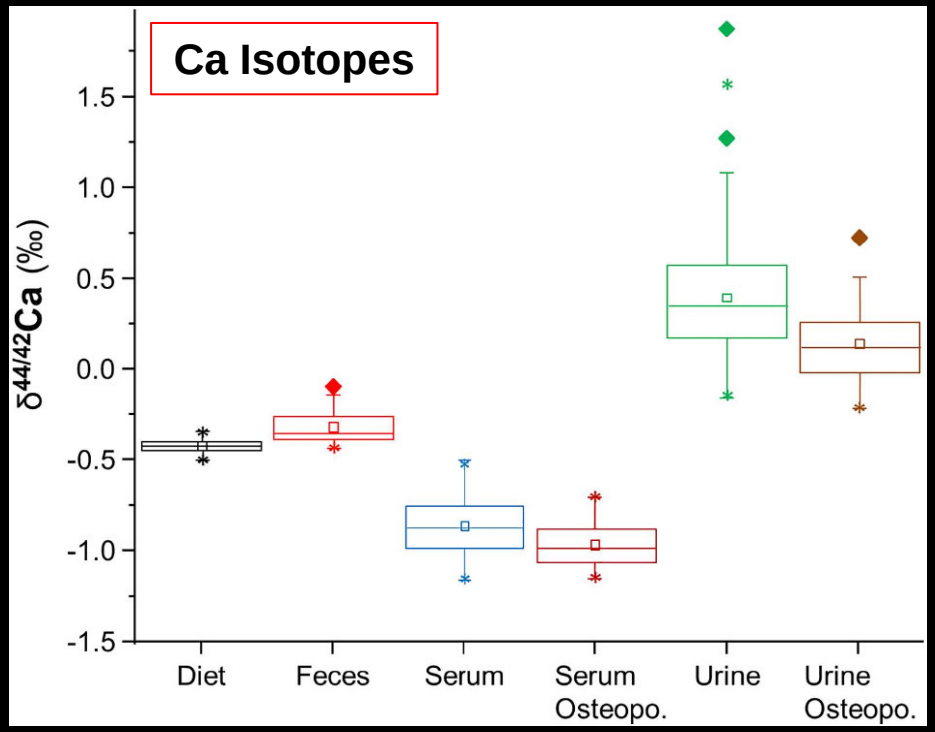
Application #3:
Early disease diagnostics

Ca isotopes as an early, quantitative osteopororis diagnostic

[Eisenhauer et al., 2019]

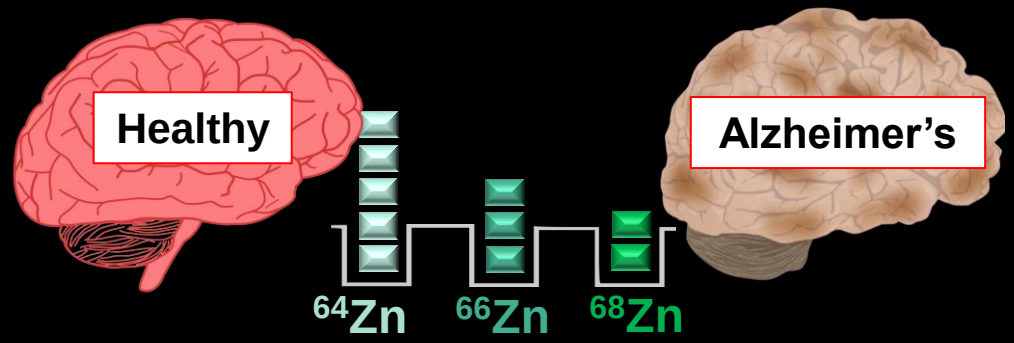
- Current DXA scans only detect disease after significant bone loss
- Bones enriched in light Ca isotopes, and therefore bone loss flushes light isotopes into bloodstream
- Signal can be detected in blood and urine, is predictive against DXA, and can estimate bone loss amount



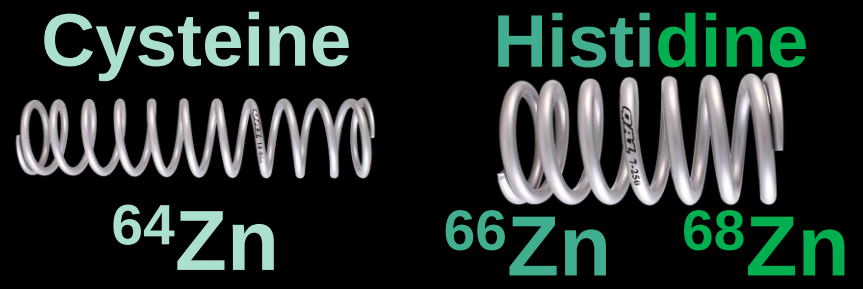


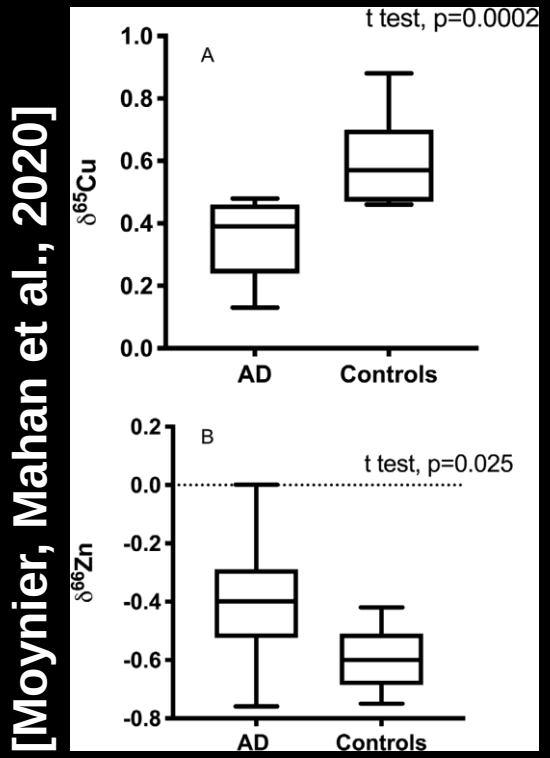
Application #3:
Early disease diagnostics

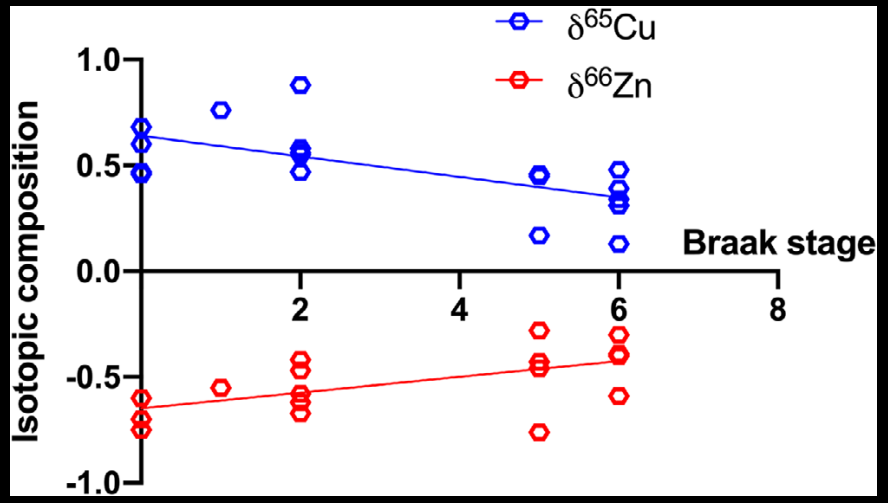
Cu and Zn isotopes as diagnostic of Alzheimer's Disease (AD)



- Cu and Zn are bound differently in the healthy vs AD brain, leading to isotope fractionation
- The isotope fractionation is statistically significant for both Cu and Zn
- Magnitude of fractionation correlates with Braak stage, a metric for pathological disease progression

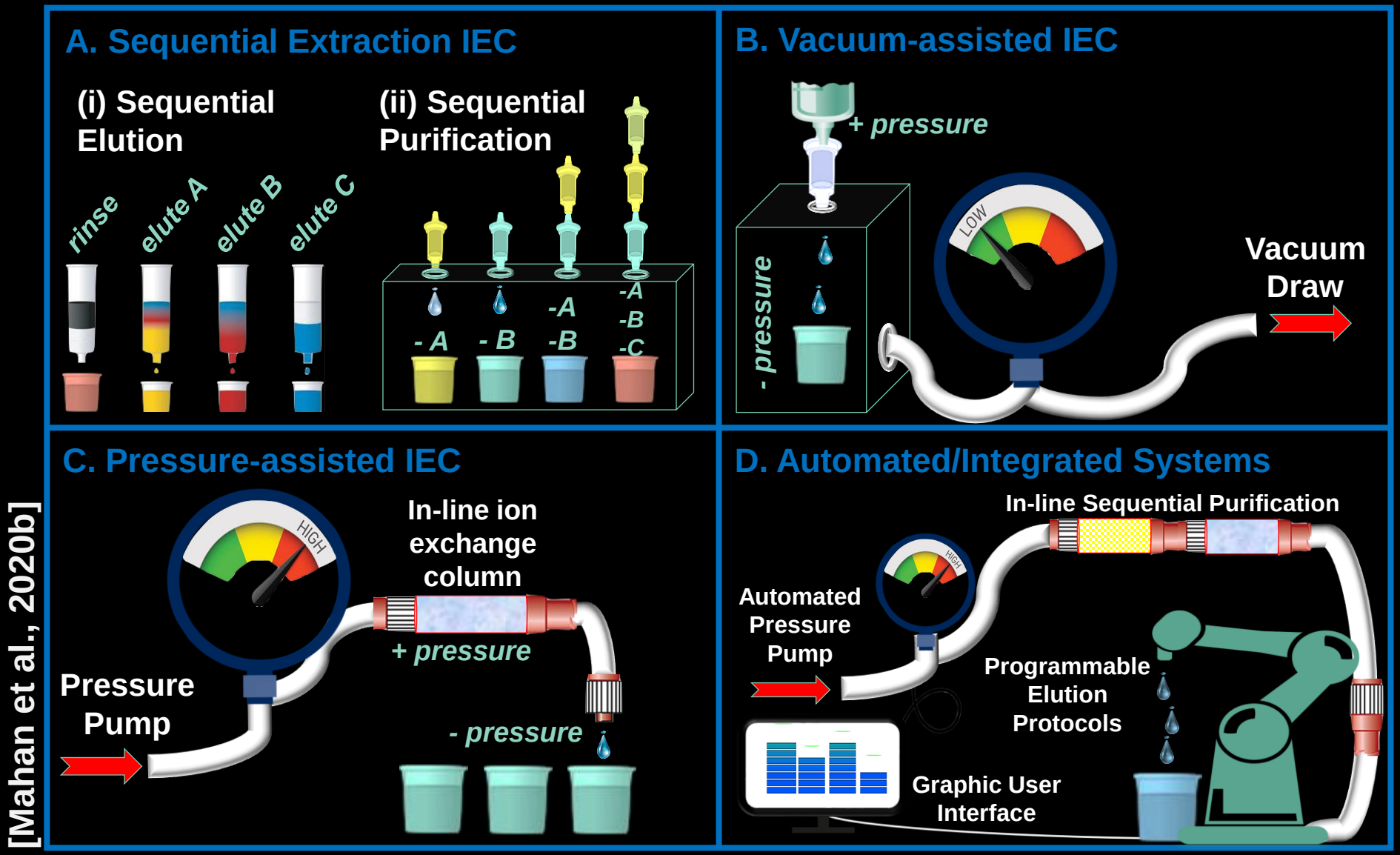






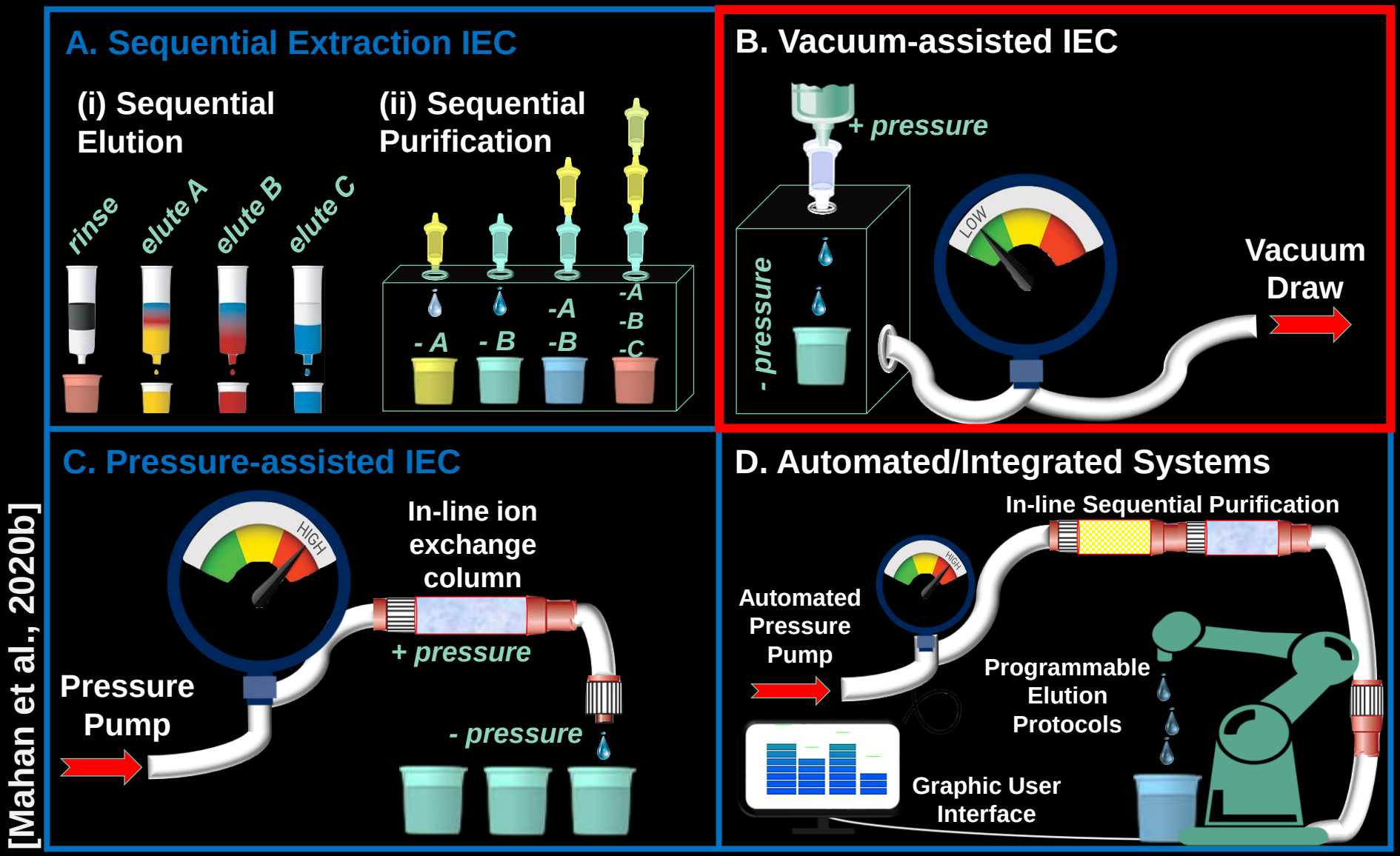
Act 3:
Breaking Through Procedural Barriers

Scalable Workflow Strategies



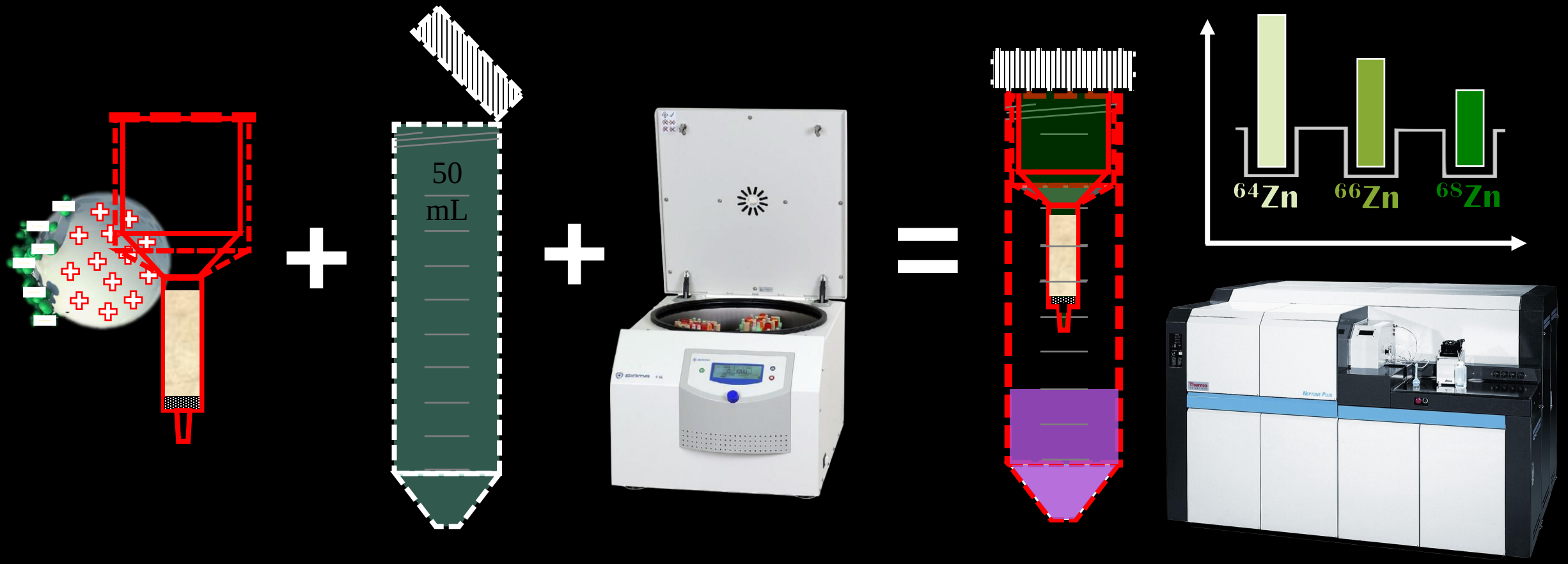
[Mahan et al., 2020b]

Scalable Workflow Strategies



[Mahan et al., 2020b]

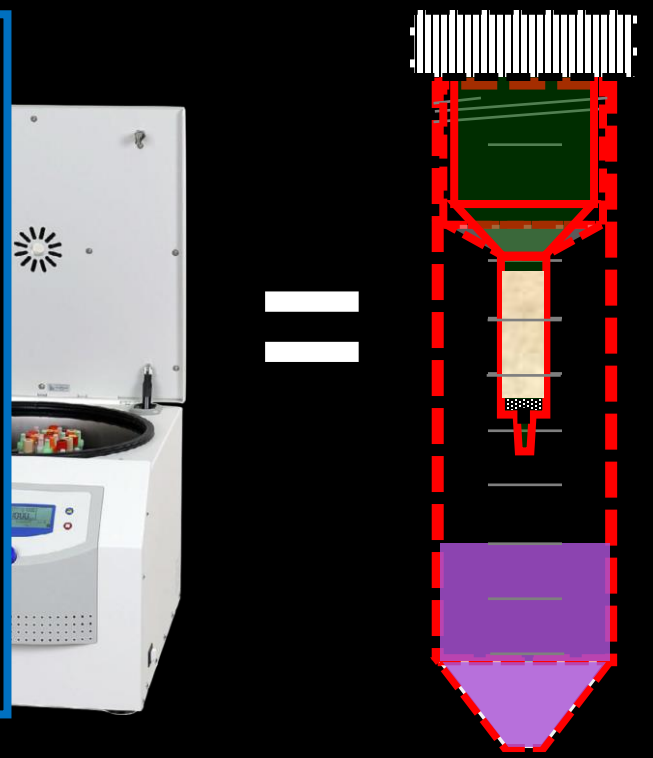
Pathway #1:
SpinChem™ IEC with centrifugation



[Mahan et al., 2020a]

Pathway #1:
SpinChem™ IEC with centrifugation

Speeds up Zn sample prep for isotope analyses 5-10× (*Mahan et al. 2020a*)



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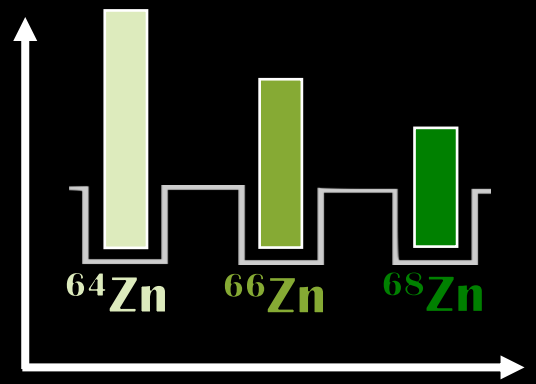
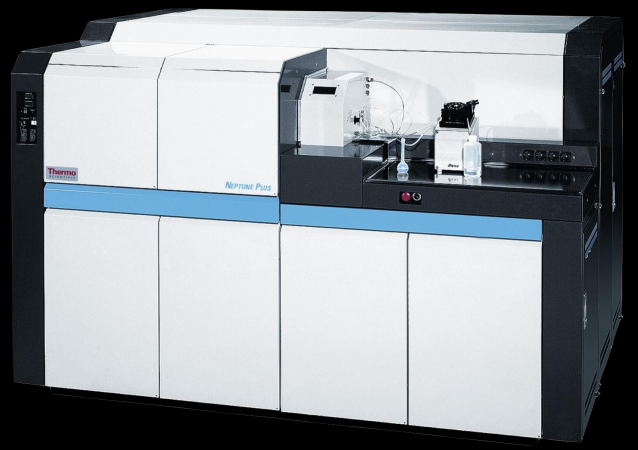


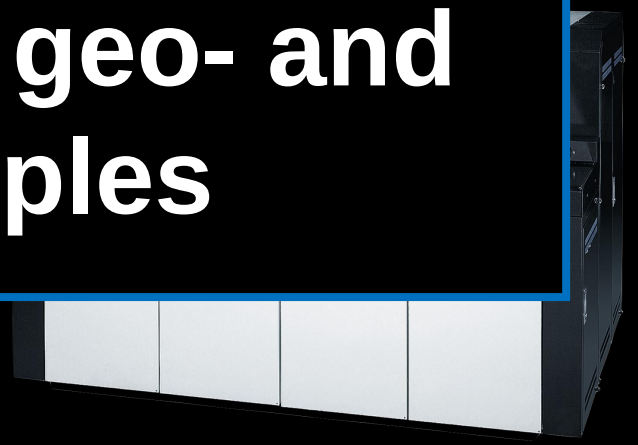


[Mahan et al., 2020a]

Pathway #1:
SpinChem™ IEC with centrifugation

Speeds up Zn sample prep for isotope analyses 5-10× (*Mahan et al. 2020a*)

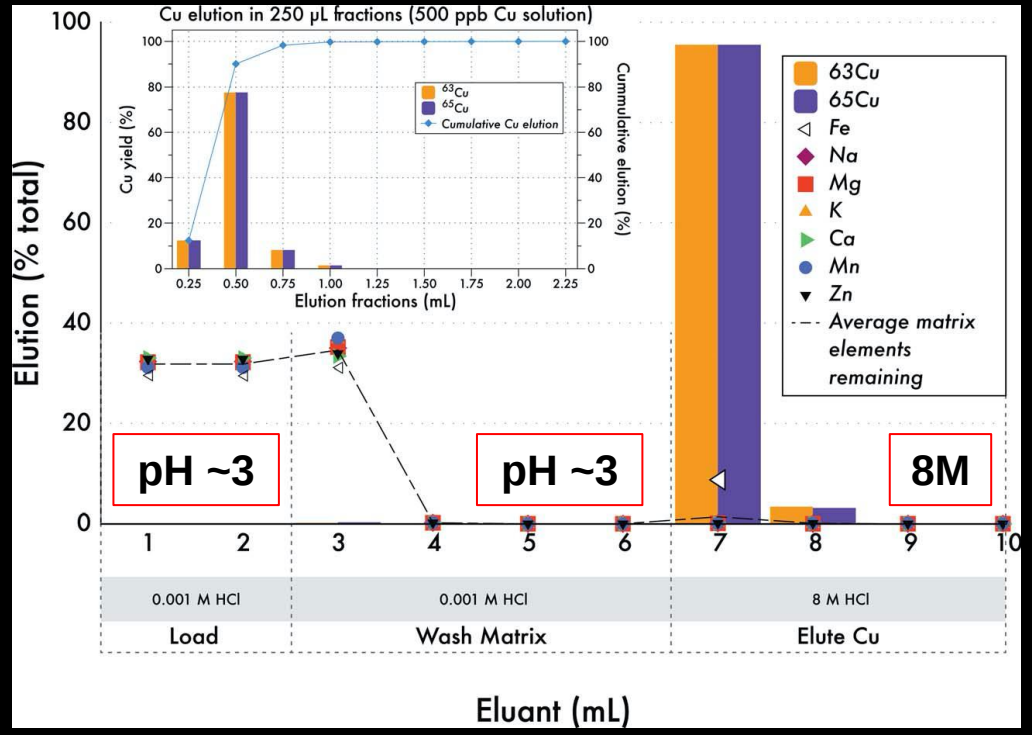
New CU Resin protocol can be used for geo- and bio- samples



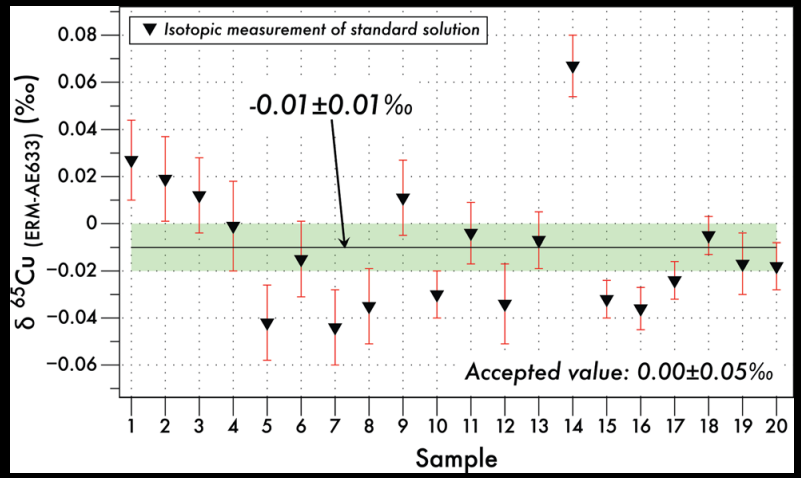
[Mahan et al., 2020a]

Pathway #2:
Cu Vacuum Box IEC

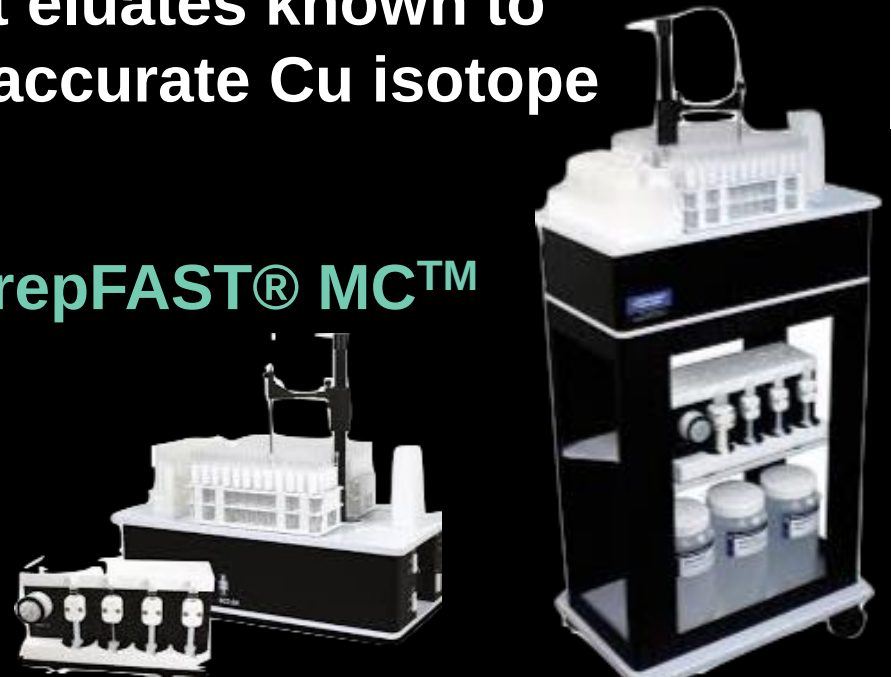
- Cu separation known to work at elevated flow rates
  - Centrifugation ✓
  - prepFAST automation ✓
- Resultant eluates known to produce accurate Cu isotope analytics



[Enge et al., 2016]

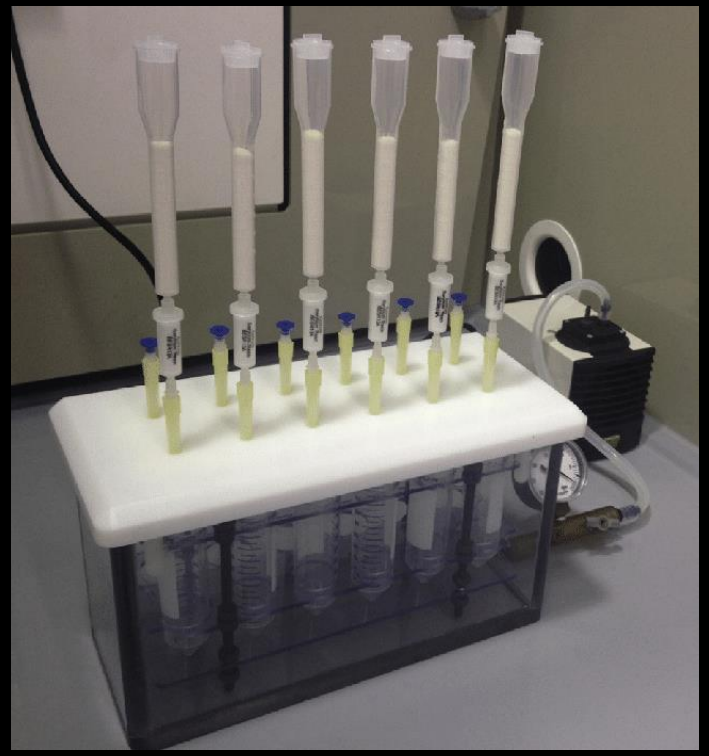


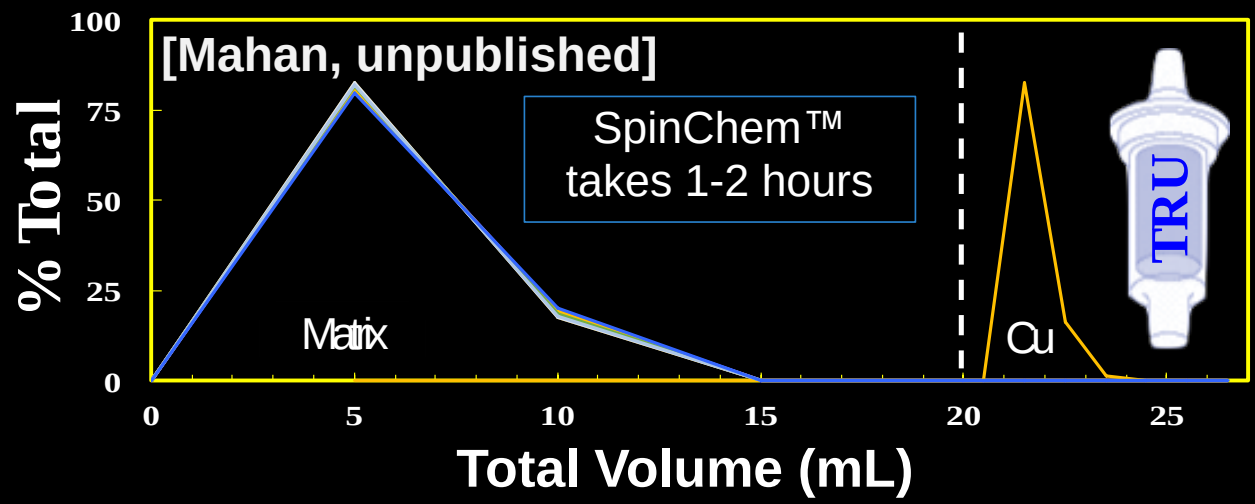
prepFAST® MC™



Pathway #2 (Geo): *Cu Vacuum Box IEC*

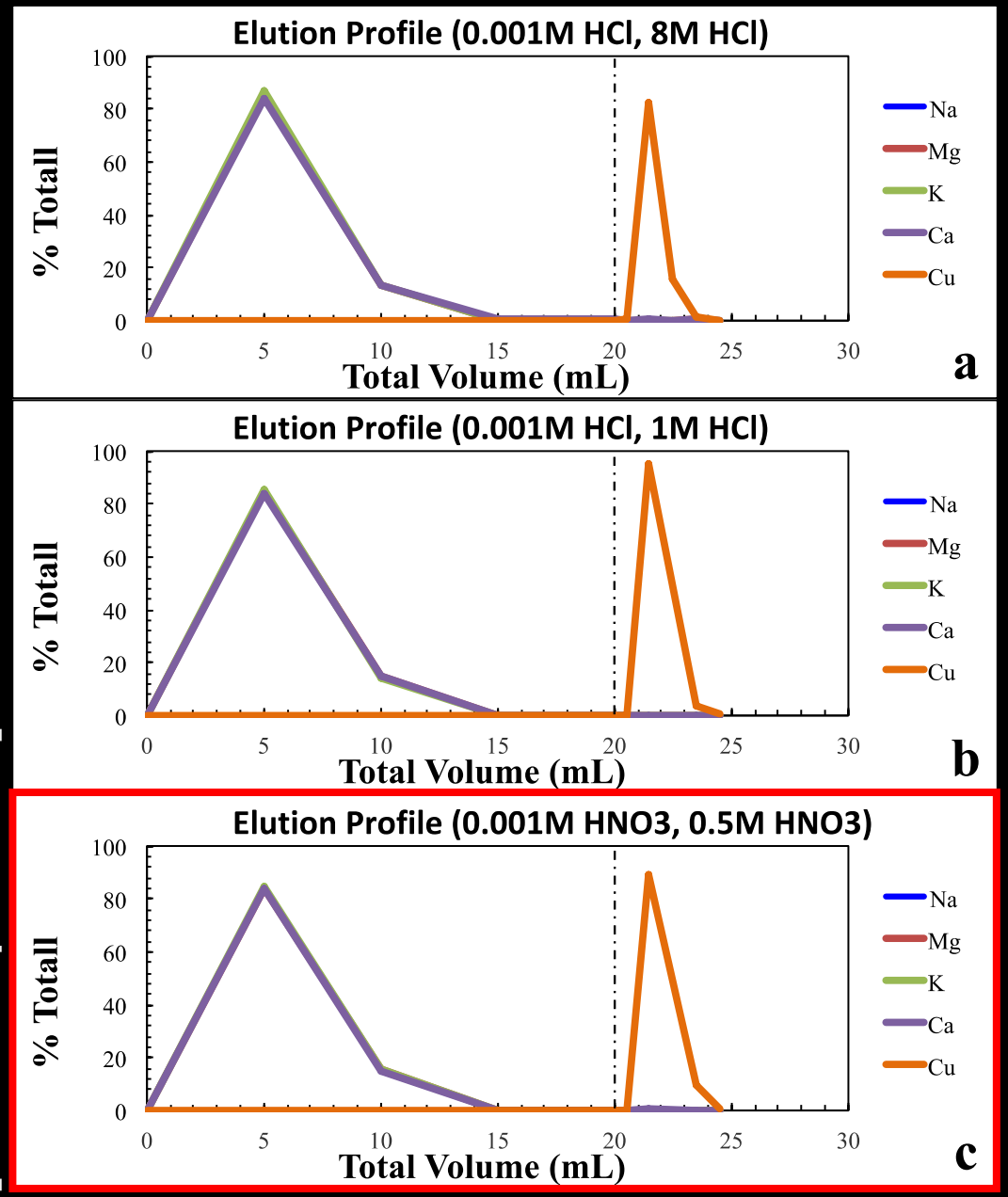
- Cu separation known to work at elevated flow rates
  - Centrifugation ✓
  - prepFAST automation ✓
- Resultant eluates known to produce accurate Cu isotope analytics
- **New Cu protocol ideally suited for vacuum box adaptation**
  - **Stack direct CU to TRU**





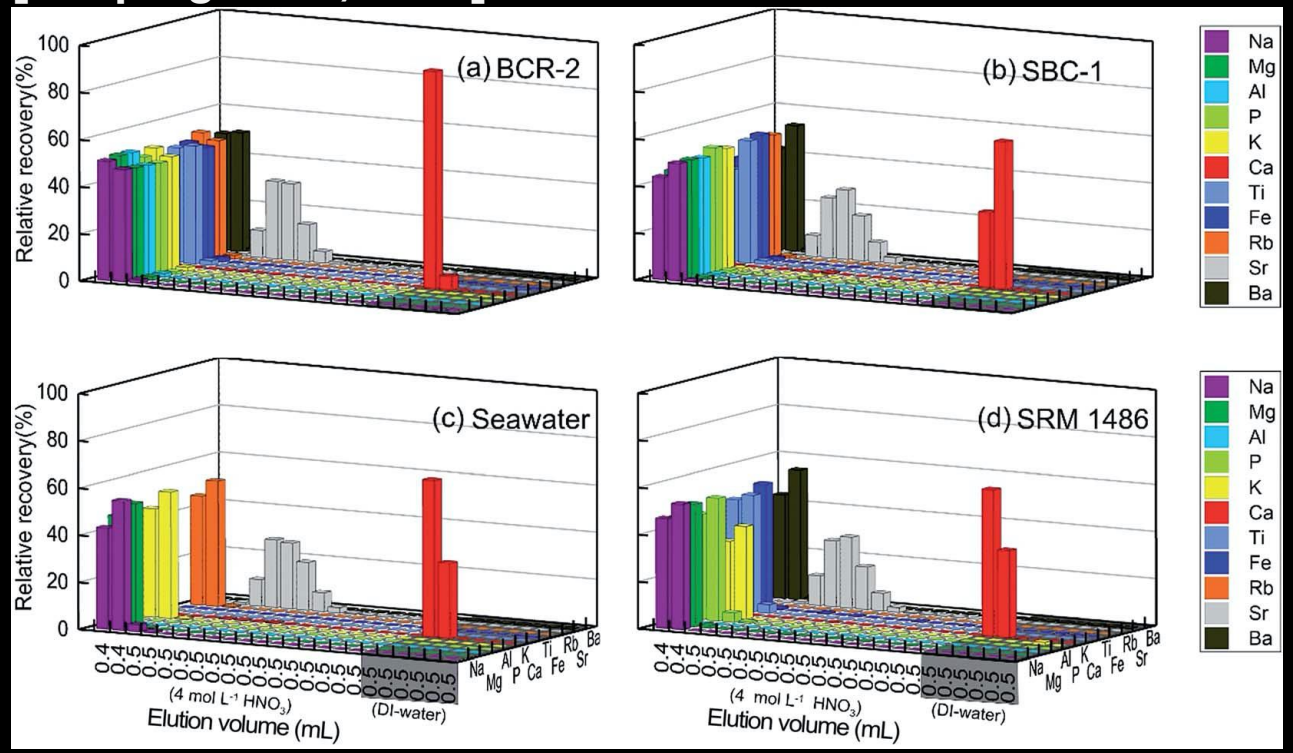
Pathway #2 (Bio): *Cu Vacuum Box IEC*

- Cu separation known to work at elevated flow rates
  - Centrifugation ✓
  - prepFAST automation ✓
- Resultant eluates known to produce accurate Cu isotope analytics
- **New Cu protocol ideally suited for vacuum box adaptation**
  - **HNO_3-based protocol**
  - ***Direct to MC-ICP-MS ???***

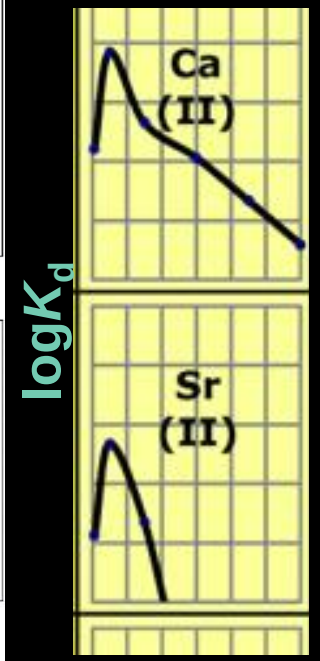


Pathway #3 (All): *Ca High-Flow IEC*

[Lanping et al., 2018]



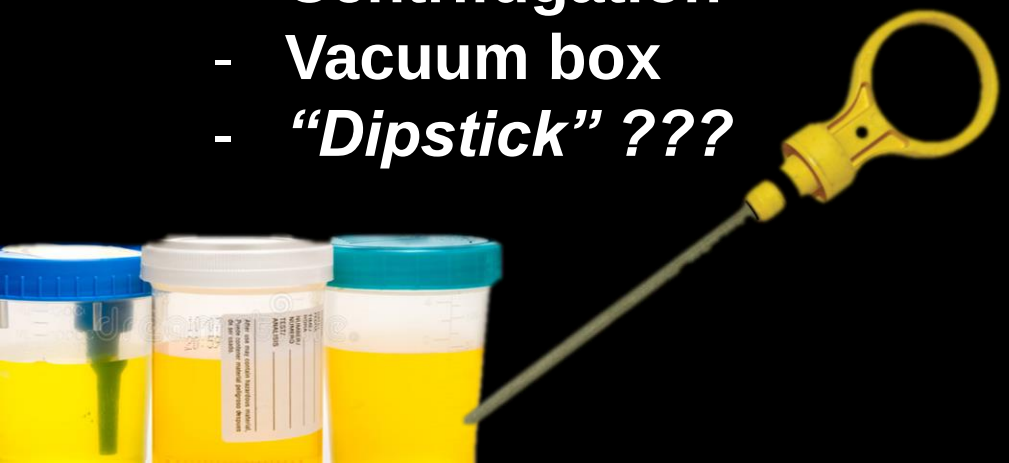
DGA Resin

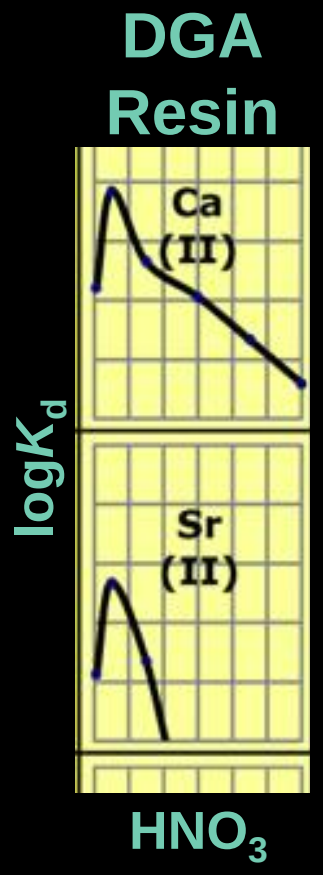


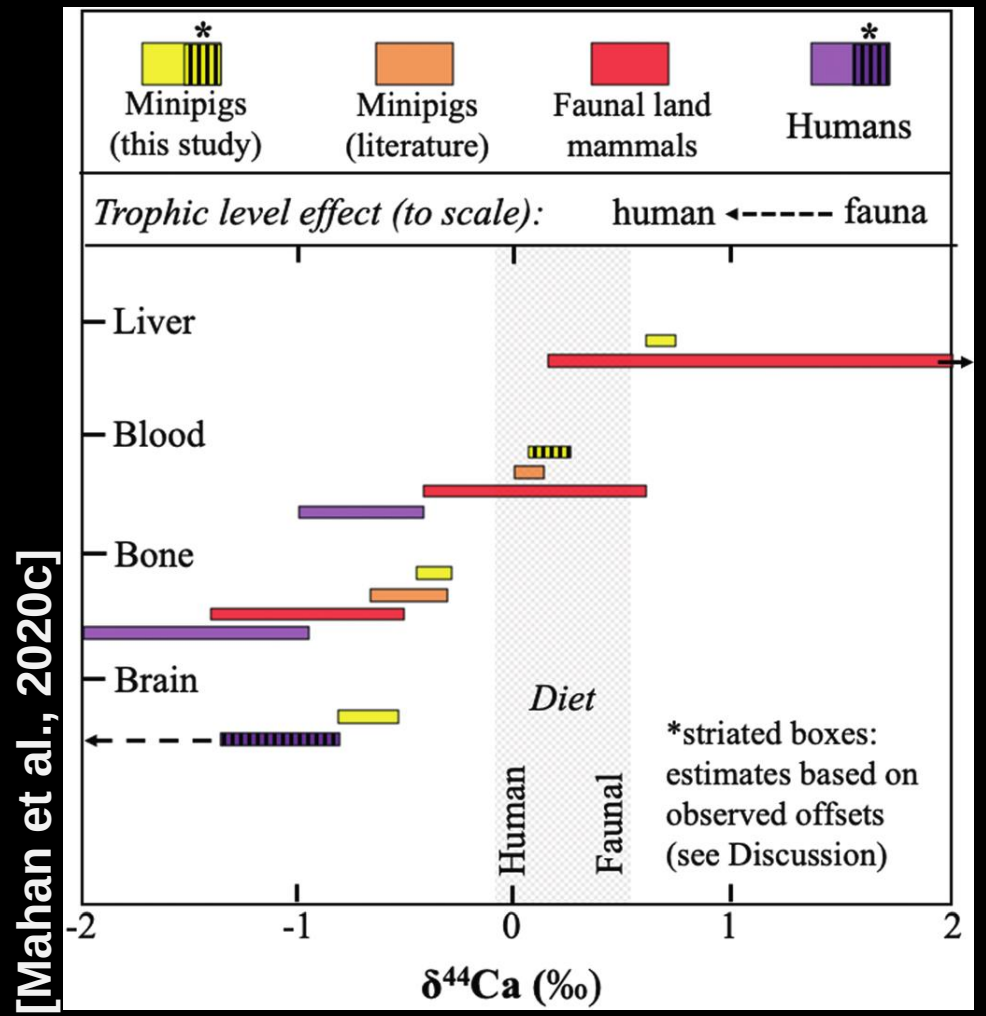
- Ca separation known to work at elevated flow rates
  - Vacuum box ✓
  - prepFAST automation ✓
- Resultant eluates known to produce accurate Ca isotope analytics
- Ca isotope variability in rocks and the body is very high

Pathway #3 (All): *Ca High-Flow IEC*

- On/off purification achievable using 4M HNO_3 load/rinse, and H_2O Ca collection
- Easily adaptable to high flow rate IEC
  - Centrifugation
  - Vacuum box
  - *"Dipstick" ???*







! Thank You !

Questions ?

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lots of others as well…