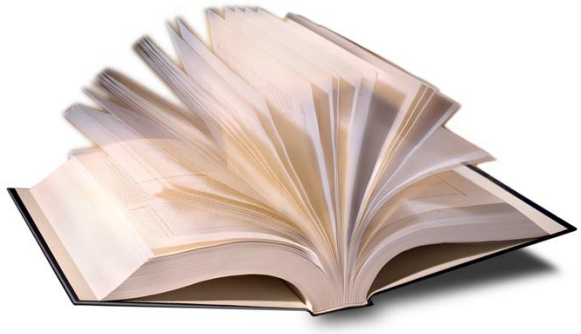
UNIVERSITY of GREENWICH

The complexity of contemporary pharmaceutical formulations demands innovative analytical approaches: are we ready?

Milan D. Antonijević

Overview of presentation

- Introduction to current problems
- Thermal Analysis by Structural Characterisation (TASC)
- Thermal Dissolution Analysis (TDA)
- Chemical Identification by Dissolution Assessment (CIDA)
- Conclusions



Acknowledgments

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Michael Morton, Cyversa
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Dave Grandy and Douglas Hourston, Loughborough University

Potential drugs

Possible solutions

- Large molecules – Biotechnology
- Revisit failed projects (drug leads) and try to improve
- Improve existing medications via better performance
  - New delivery strategies
  - Complex dosage forms

Crucial to all

- Good analytical support (demanding experimental procedures)
- Good predictions (reliable outcomes)

New methods

– Hyphenated approach has been popular and proved to be beneficial

Aim

- Development of a new hyphenated technique to provide 3D map of an object (complex dosage form)

- Existing solutions:
  - Raman mapping
  - FTIR mapping
  - AFM

New approach

- Optical Microscopy/AFM
- Thermal Analysis
- Separation Sciences

- Cheaper
- Potentially real 3D, good resolution
- Additional information gained
  - interactions between different components of the final dosage form
  - dissolution mechanism (drug release mechanism)

Part 1

- **Thermal Analysis by Structural Characterisation (TASC)**

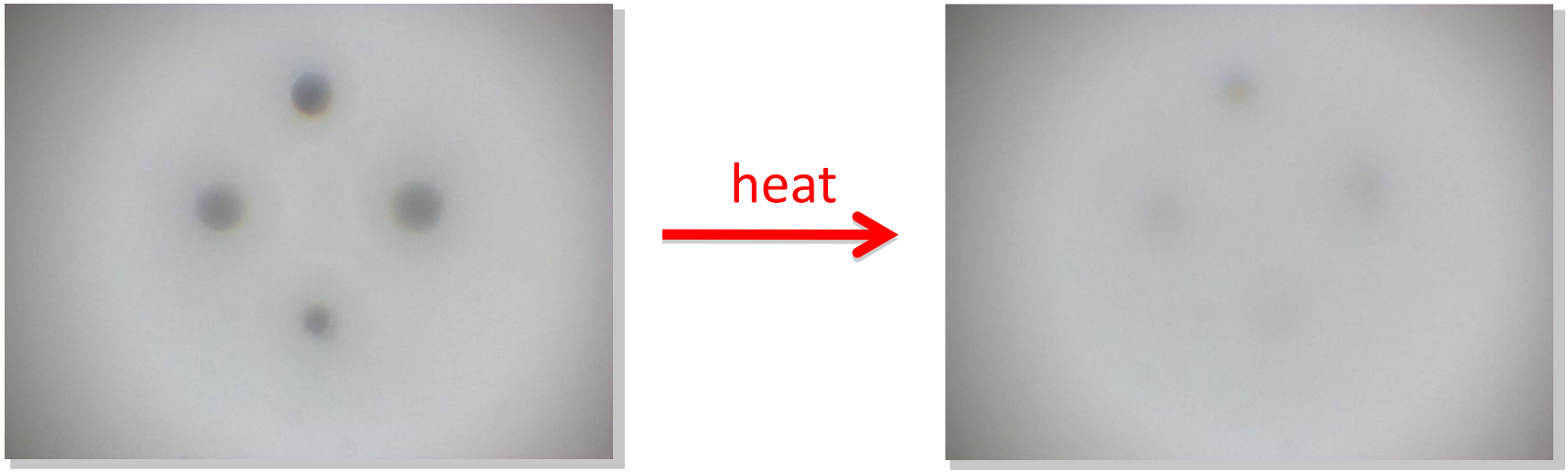
- **Thermal Dissolution Analysis (TDA)**

- **Chemical Identification by Dissolution Assessment (CIDA)**

Aim

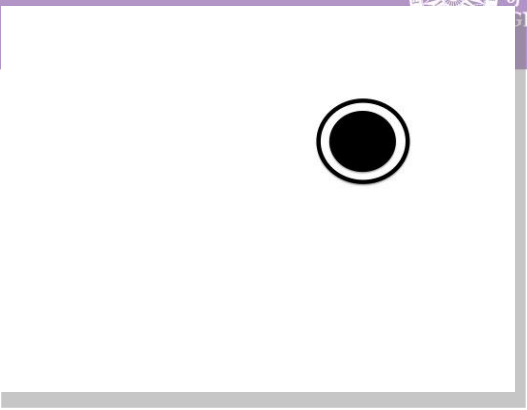
- Get important information out of microscopy
- Build software that can analyse complex images
- Get both qualitative and quantitative data (shape and size of features)

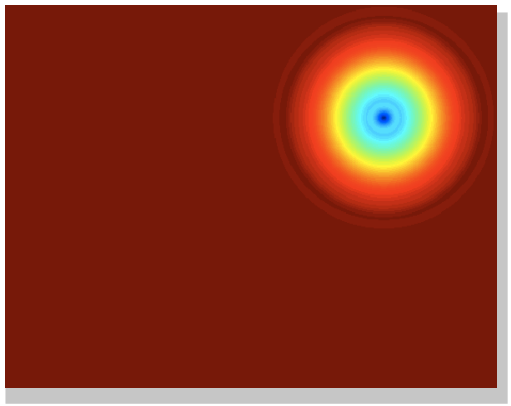
TASC consists of imposing a pattern on the surface of a sample or exploiting pre-existing structure, then characterizing how that pattern changes as the sample is heated; in this case Optical Microscopy was used but it can be applied to other forms of microscopy such as electron microscopy and Atomic Force Microscopy.

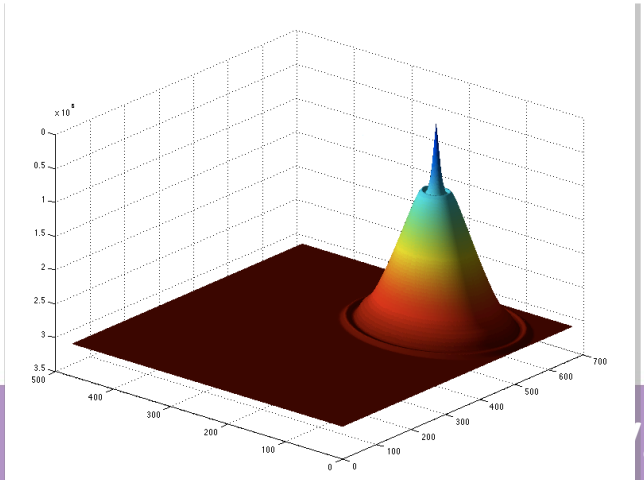


The TASC algorithm scans an area and tries to identify whether a designated structure exists and where it is located. **Top right** there is a schematic of an indentation, underneath this is the result of a TASC analysis.

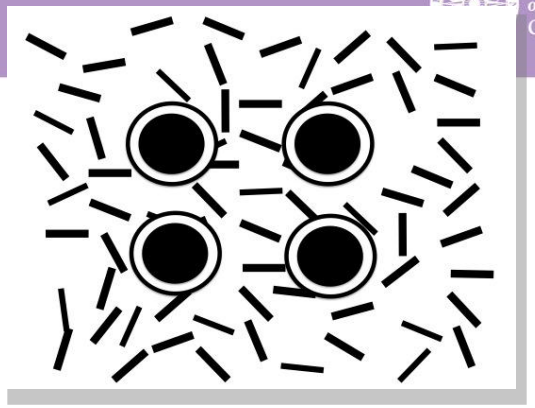
Right is a 3D representation of the output of the TASC analysis. The apex of the cone provides the location of the feature

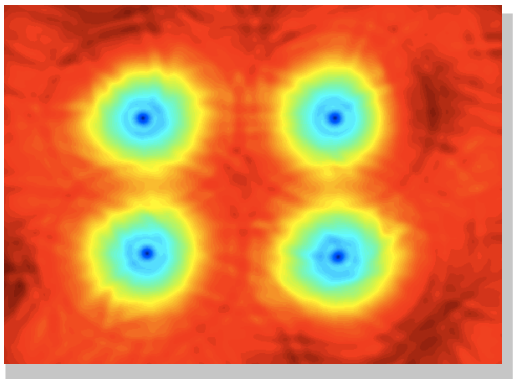




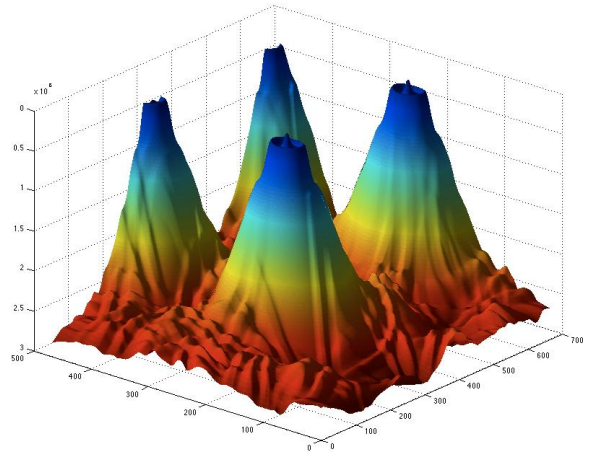


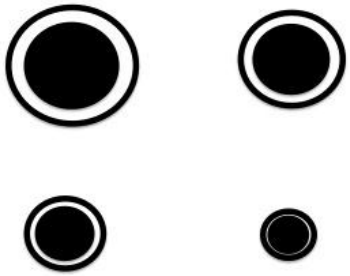
It is important that the algorithm is robust because it must deal with non-ideal samples. **Above right** there is a schematic of 4 indentations in a 'noisy' background. Below this is the result of a TASC analysis.

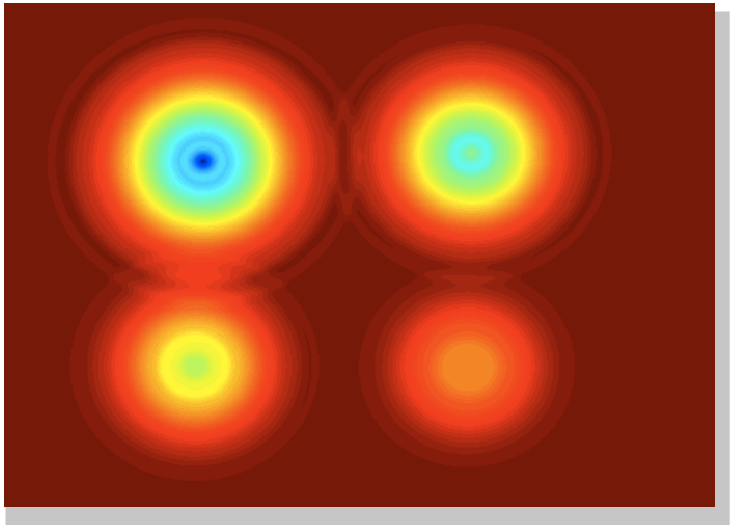




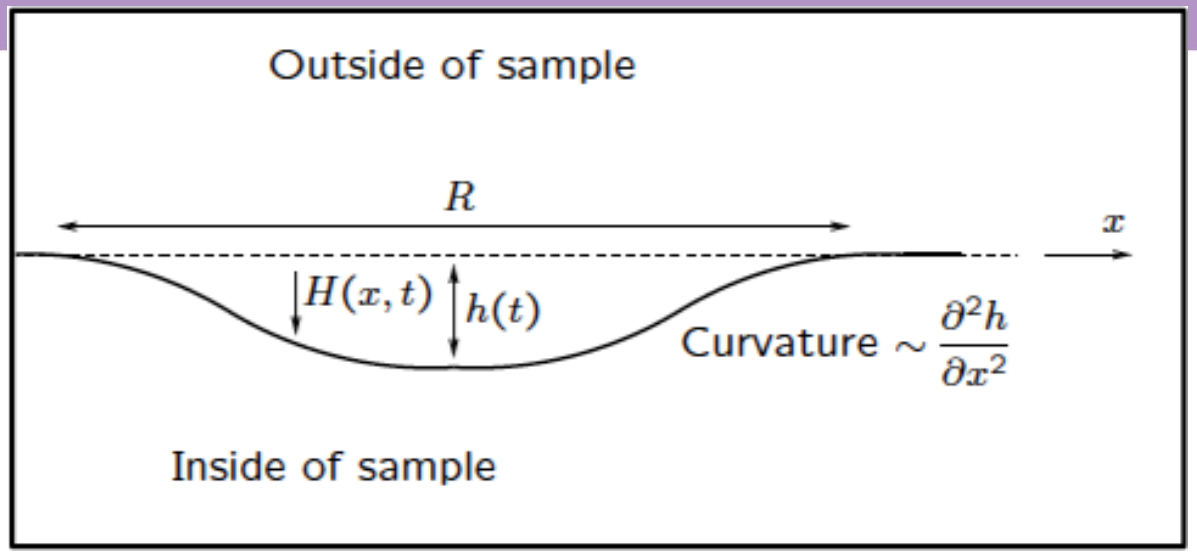
Right is a 3D representation of the output of the TASC analysis with the noisy background.







Above shows a series of schematic indentations of decreasing size. The degree of recognition by the TASC algorithm decreases as the size of the indentation decreases.



where γ is the surface tension,

$H(x,t)$ is the local depression of the surface of the sample at position x

$h(t)$ is a measure of the depth of the dimple

R gives an indication of the expanse of the depression

The pressure inside a sample due to the surface curvature is approximately $\gamma\partial^2 H/\partial x^2$

The gradient of pressure along the surface which drives flow inside the specimen is then $\gamma\partial^3 H/\partial x^3$

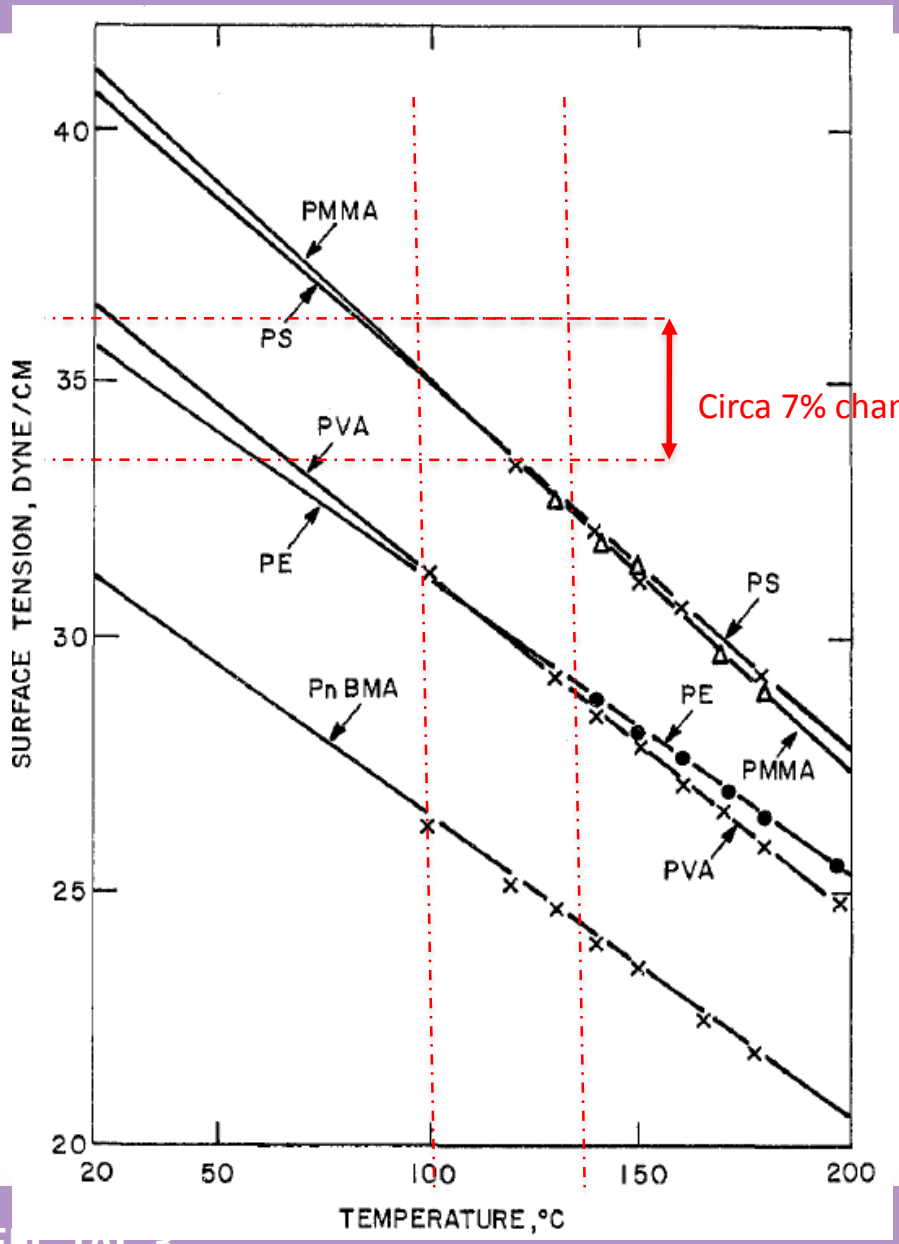
Now the indentation surface is a material boundary: it moves with the material velocity *v*.

Thus the depth of the dimple shrinks as $h \sim$ constant $\exp(- C \gamma t /(\mu R))$.

Where μ is the viscosity
C is a constant fixed by the geometry of the indentation and the sample

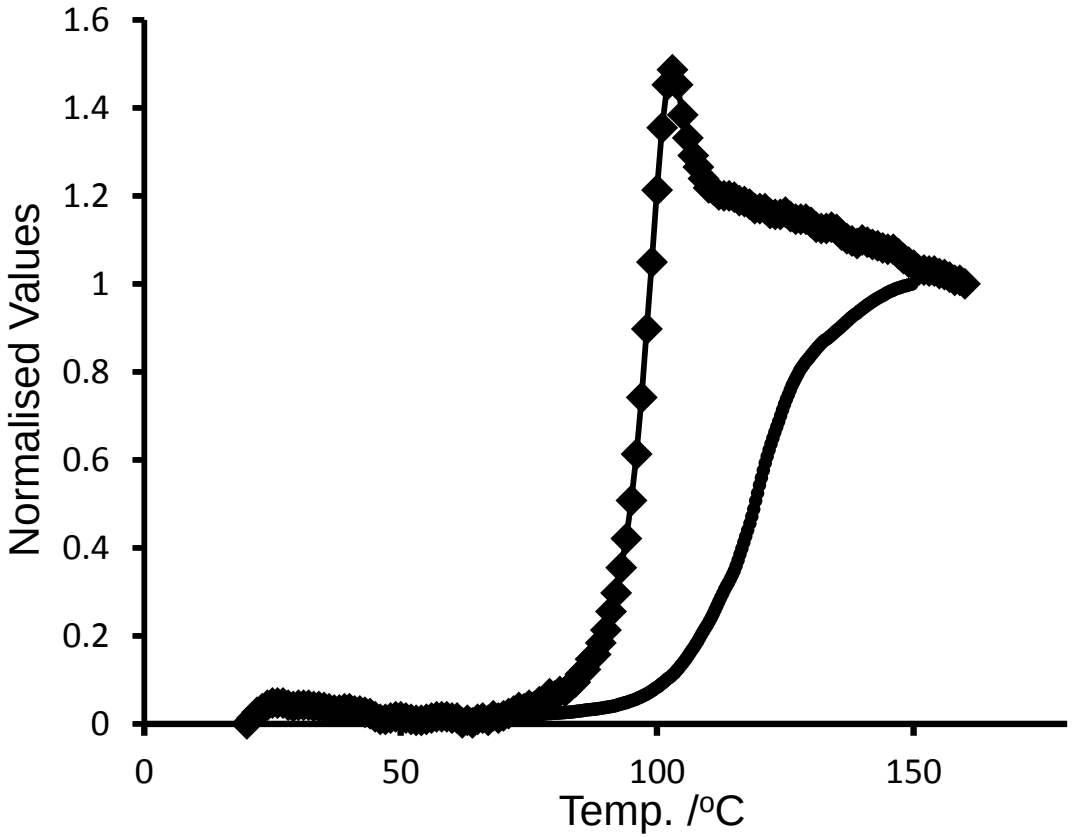
The time constant is then $\mu R/(\gamma C)$

The important conclusion is that the rate of relaxation is proportional to the surface tension, inversely proportional to the viscosity and is affected both by the size of the indentation and its geometry.

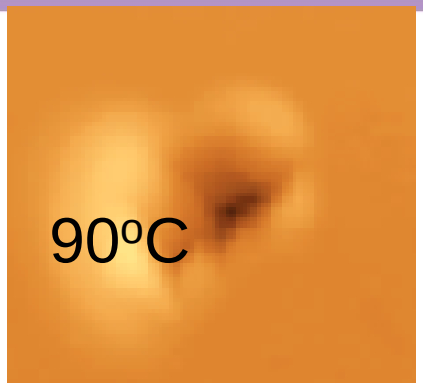


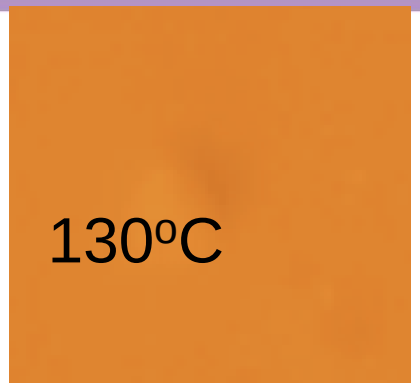
The Surface Tension is a linear function of temperature.

The PS transition glass transition takes place over about 40°C so this effect can be ignored compared to the orders of magnitude changes in viscosity with temperature

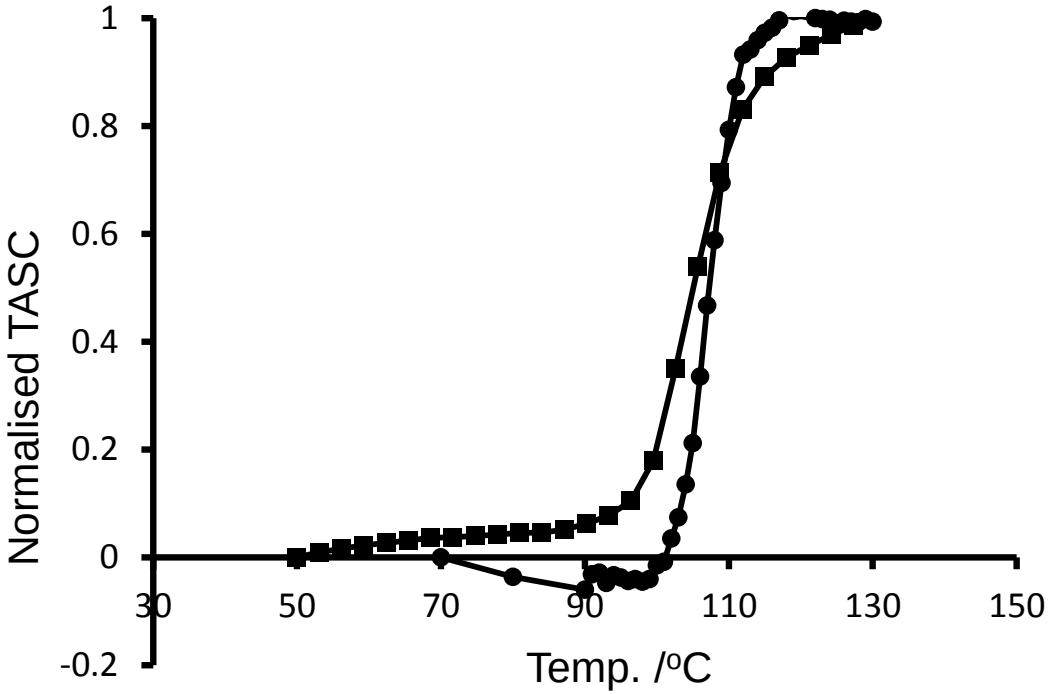


This is graph showing a co-plot of DSC and TASC data. The flow event happens after the glass transition as measured by DSC as expected.





An ideal form of microscopy is Atomic Force Microscopy. Below is a comparison of an AFM result (circles), on an indentation 500 nm in diameter with one obtained using optical microscopy on an indentation 200 µm in diameter (squares).



Part 2

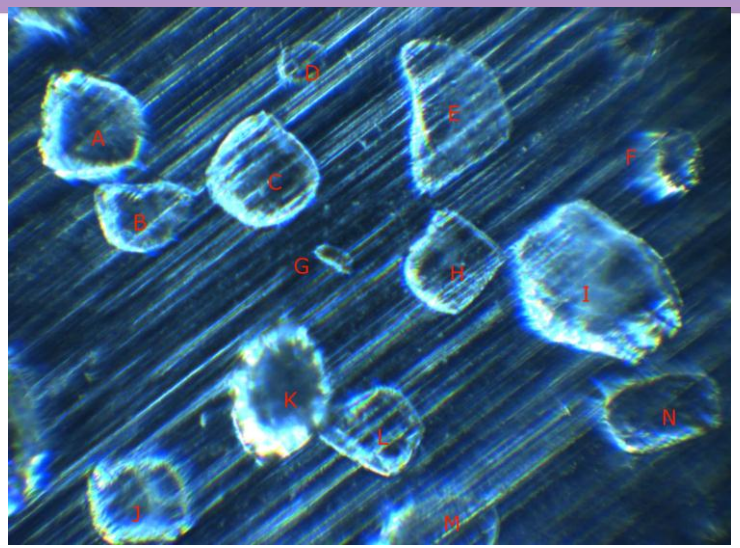
- Thermal Analysis by Structural Characterisation (TASC)
- **Thermal Dissolution Analysis (TDA)**
- Chemical Identification by Dissolution Assessment (CIDA)

Aim

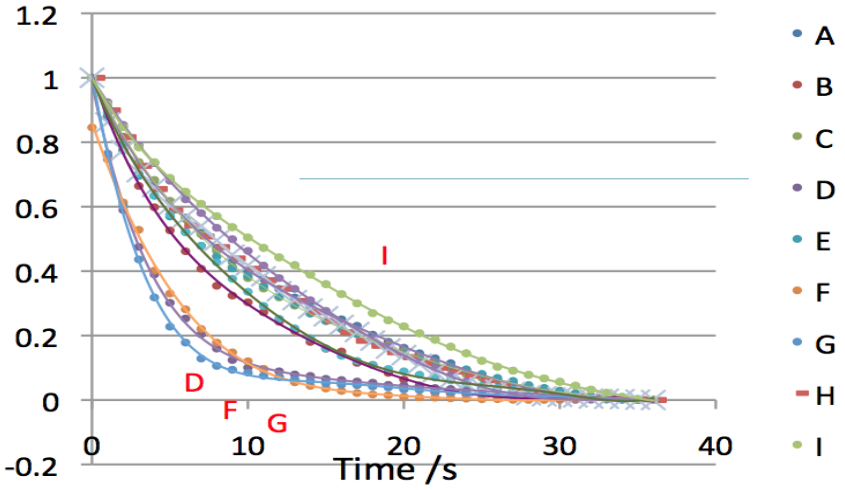
- Follow changes in surface properties while solvent interacts with it

- Understand chemical nature of material and its interaction with the solvent at different temperatures (heating/cooling rates)

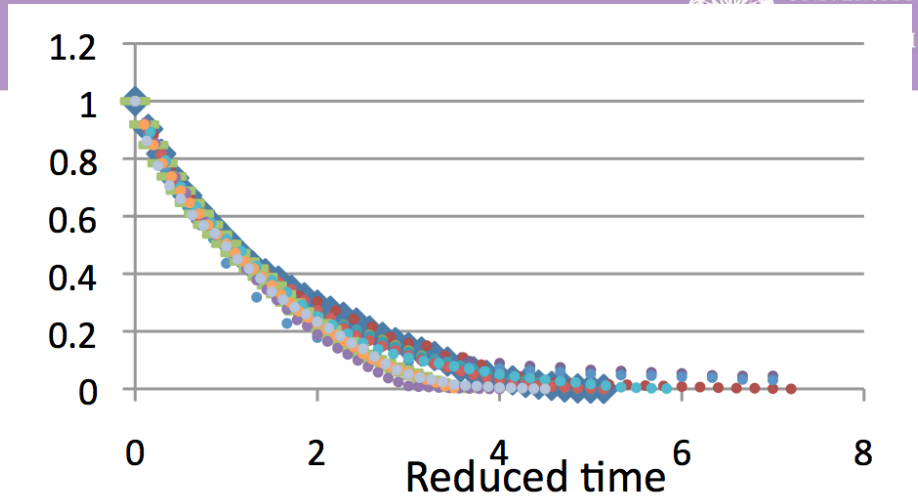
Right is an image of a collection of sugar crystals in water in a DSC crucible. The TASC algorithm can follow their disappearance.



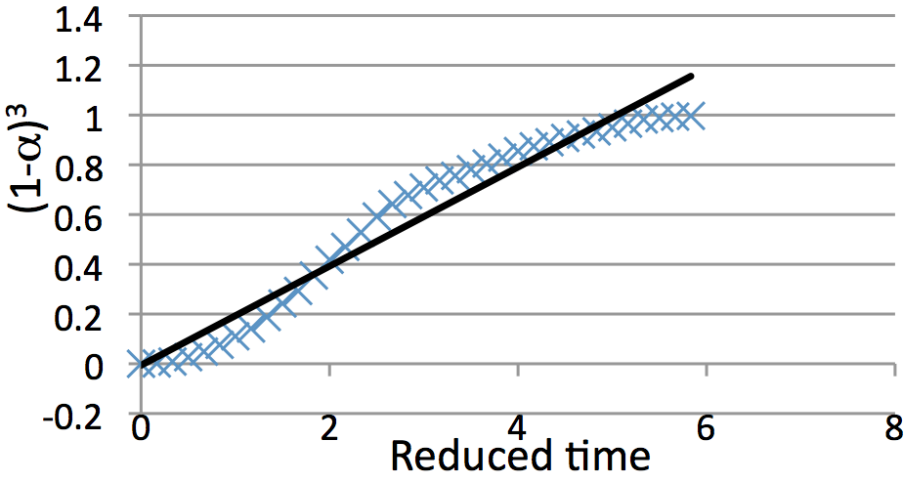
In the graph shown **right**; it can be seen that small crystals D, F and G disappear much faster than the large crystal I.



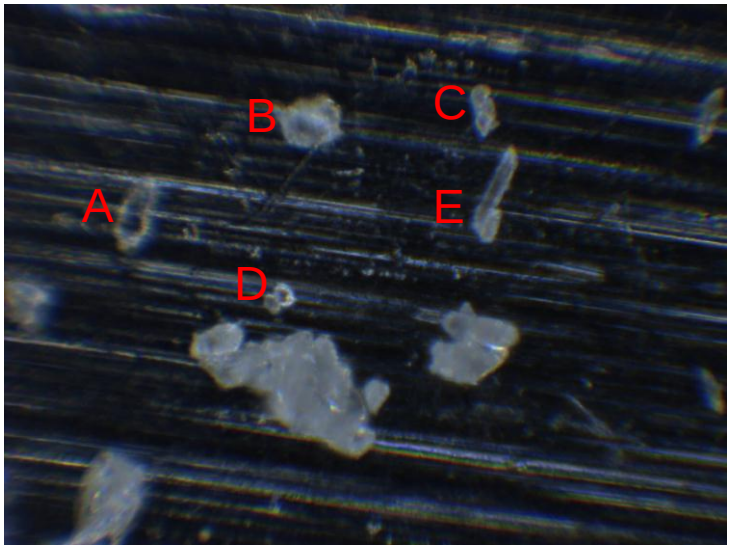
Right shows a reduced time plot of all of the crystals.

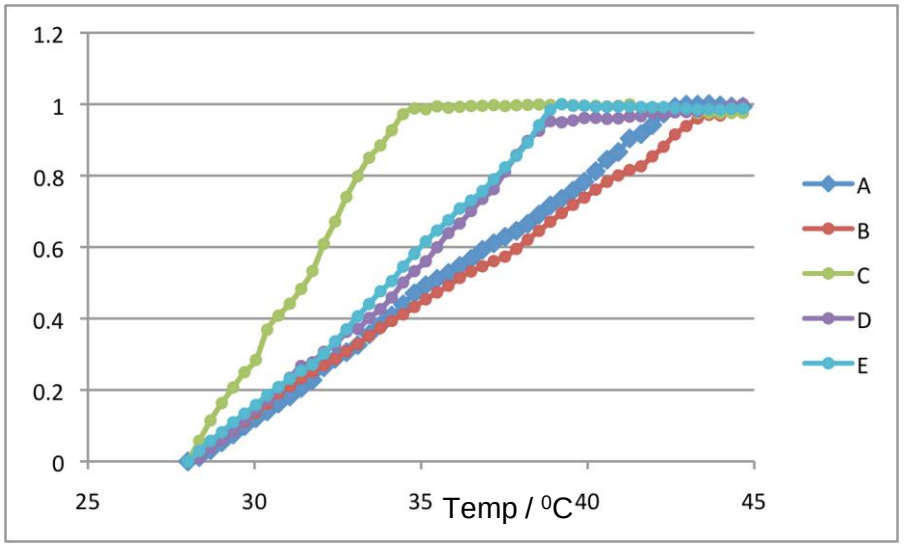


Right, averaged data are plotted against $(1-a)^3$, an approximately linear graph is obtained as would be expected for a shrinking 3D object.

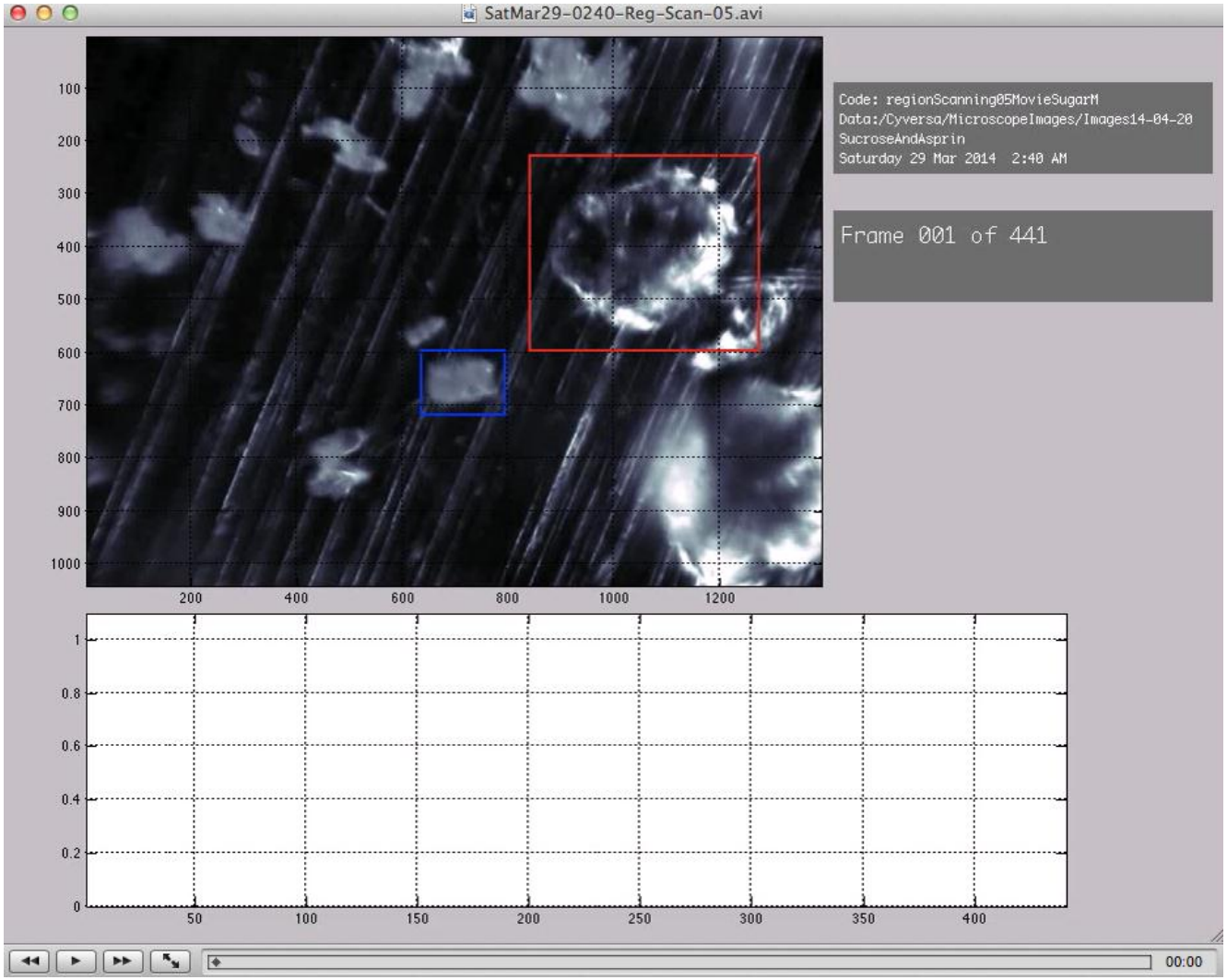


Thermal Dissolution Analysis





TASC is used to track the dissolution of the salicylic acid crystals in the field of view of the microscope. The temperature program was 5°C/min.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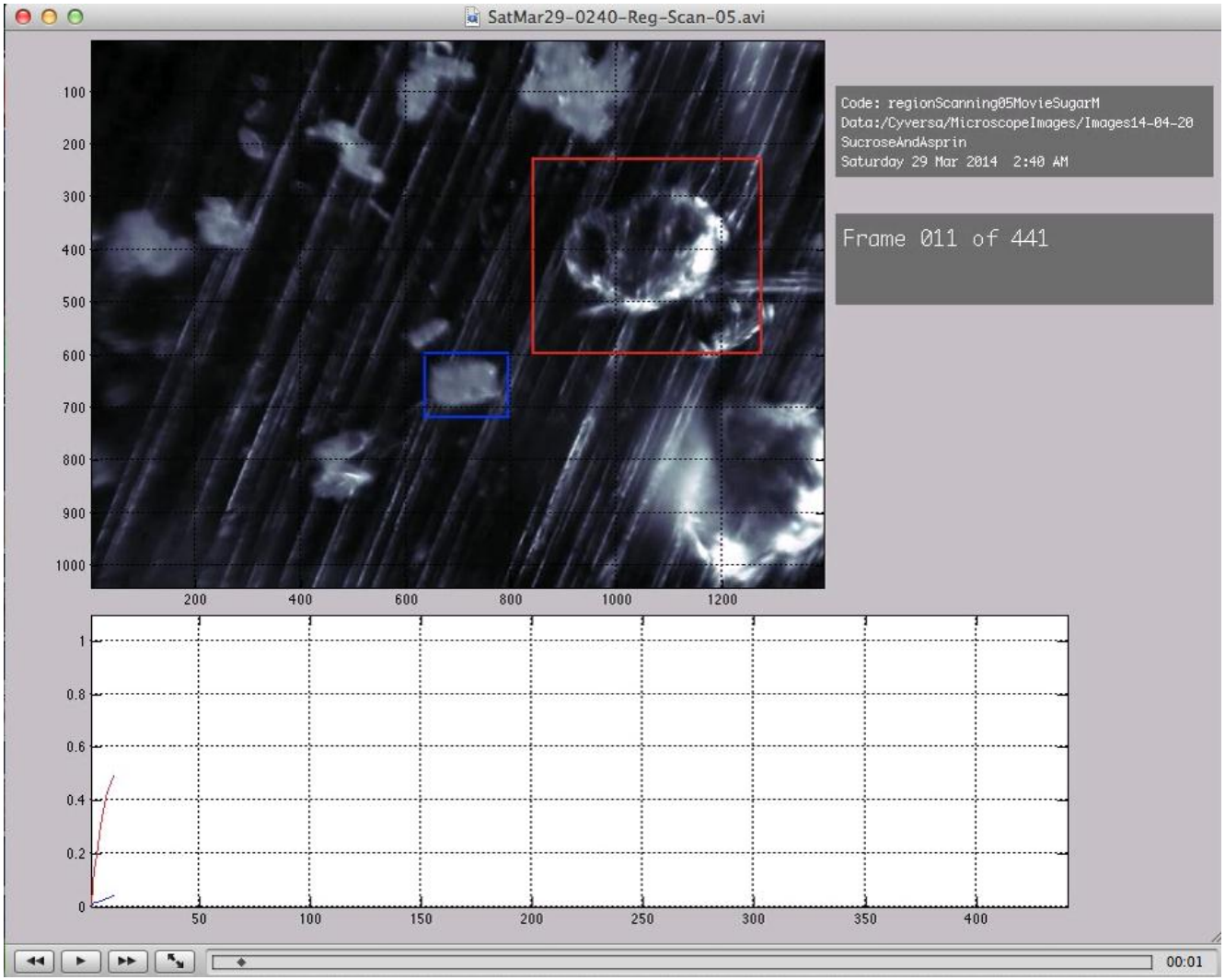
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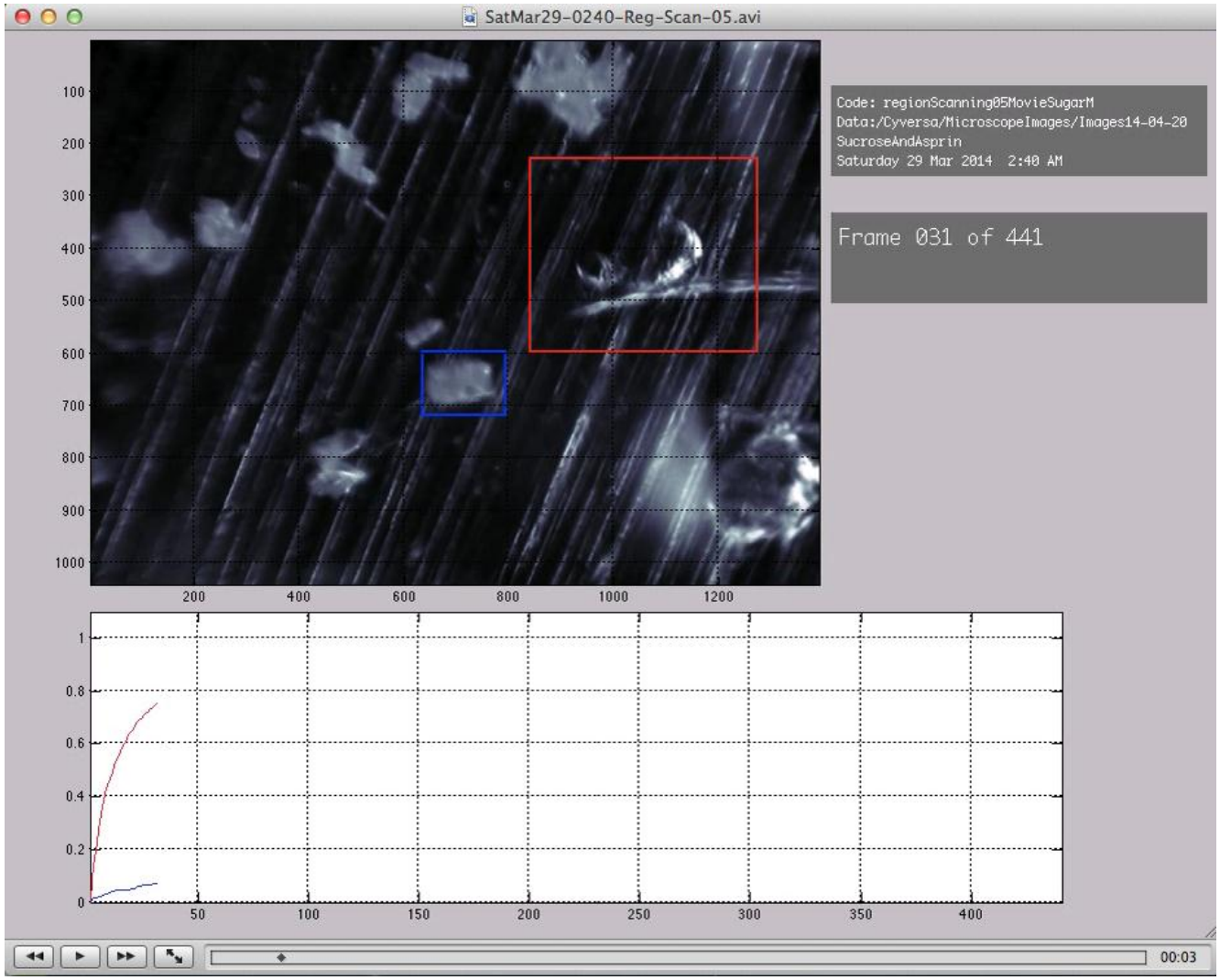
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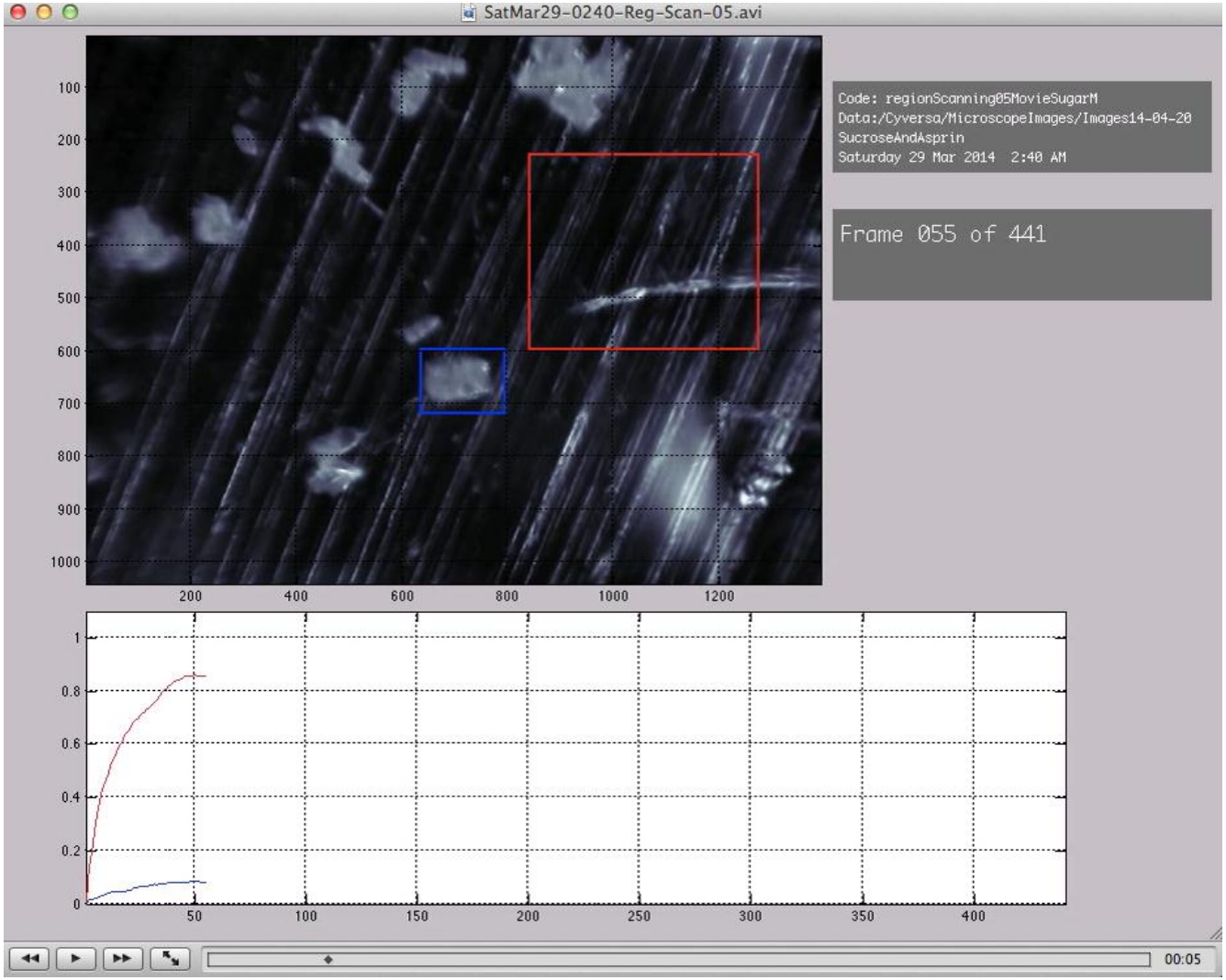
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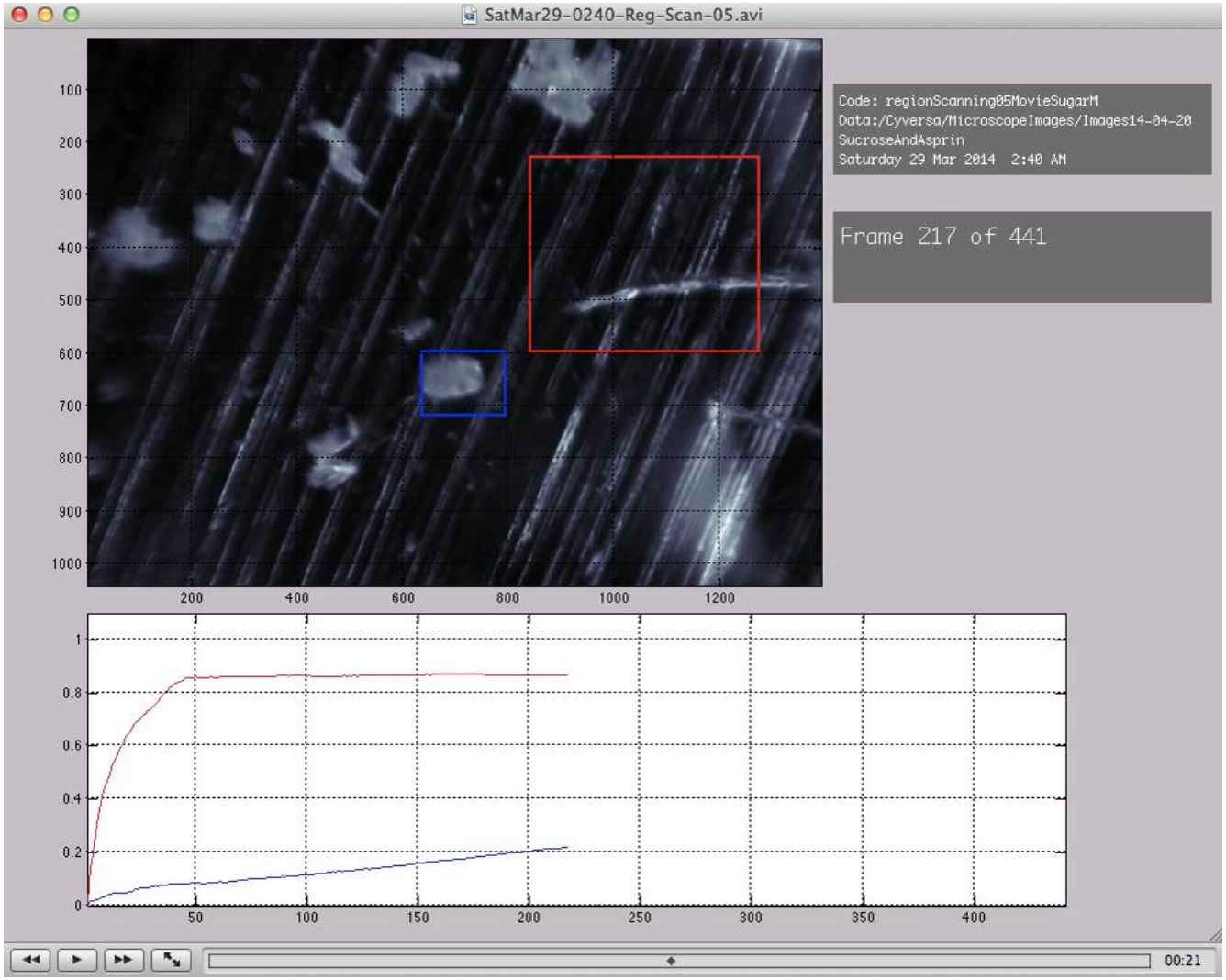
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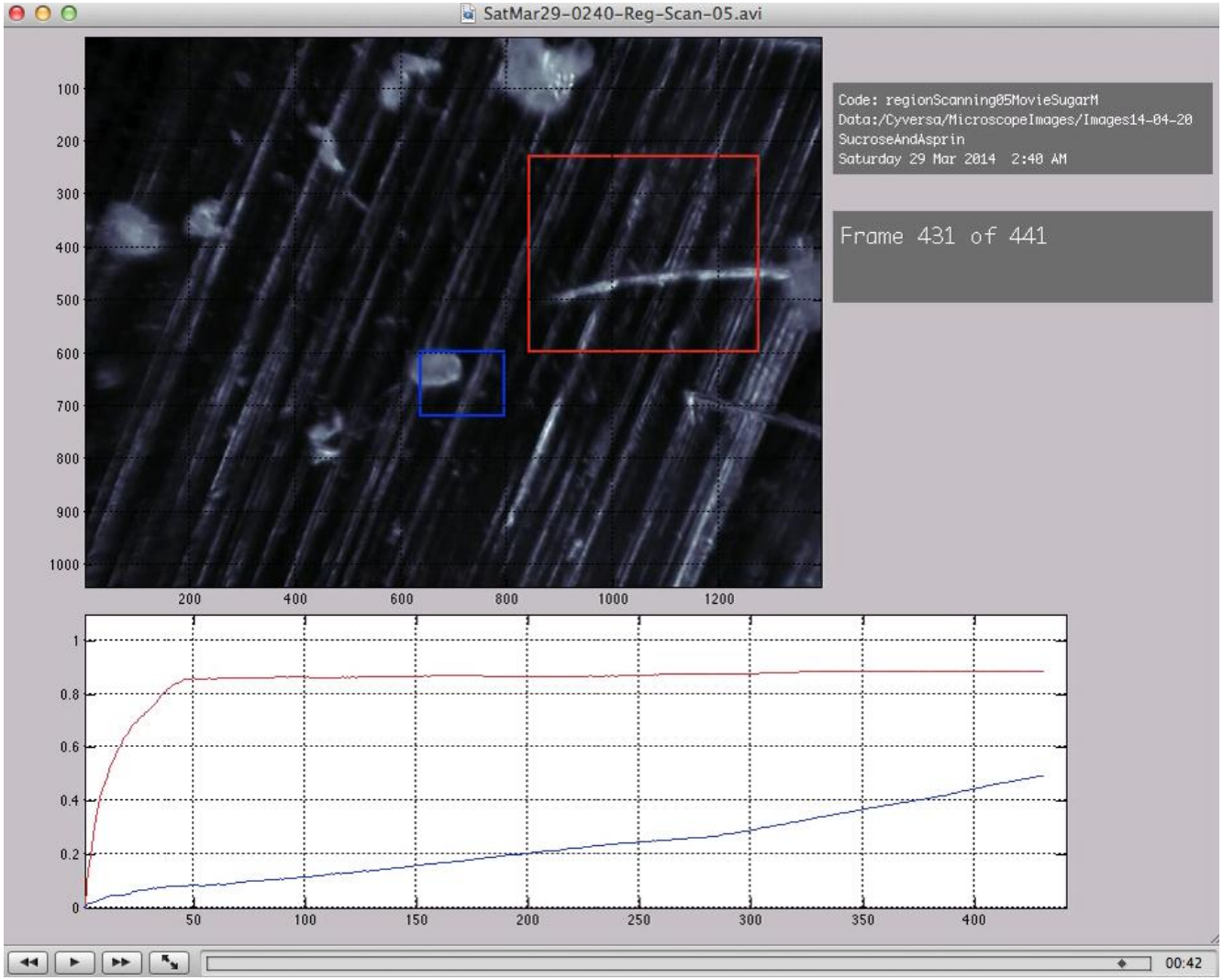
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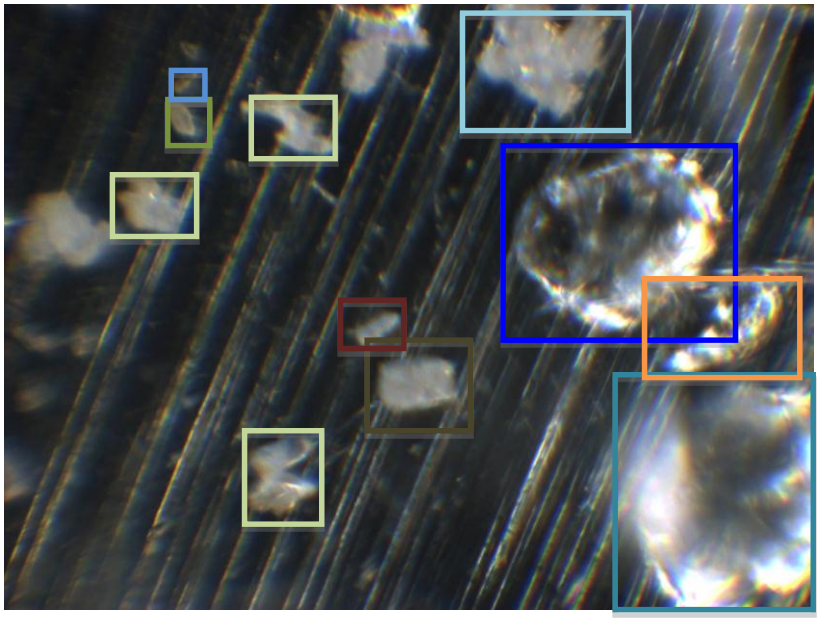
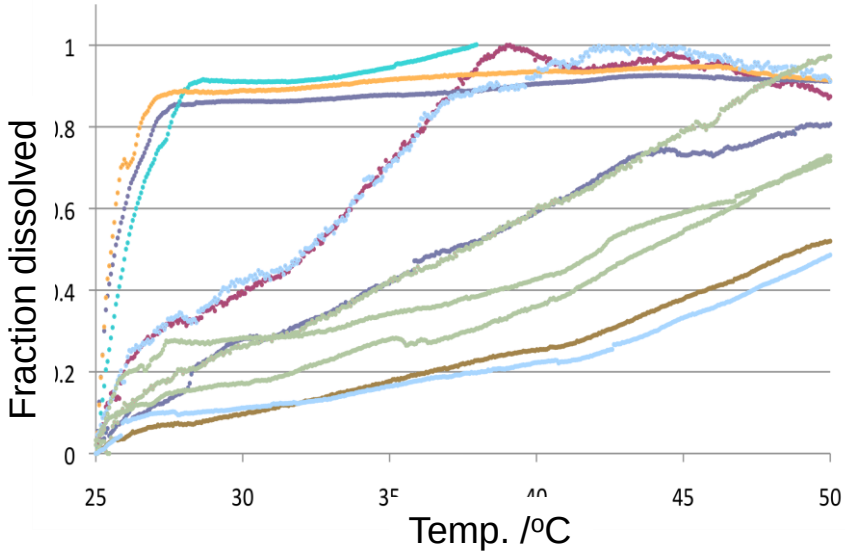
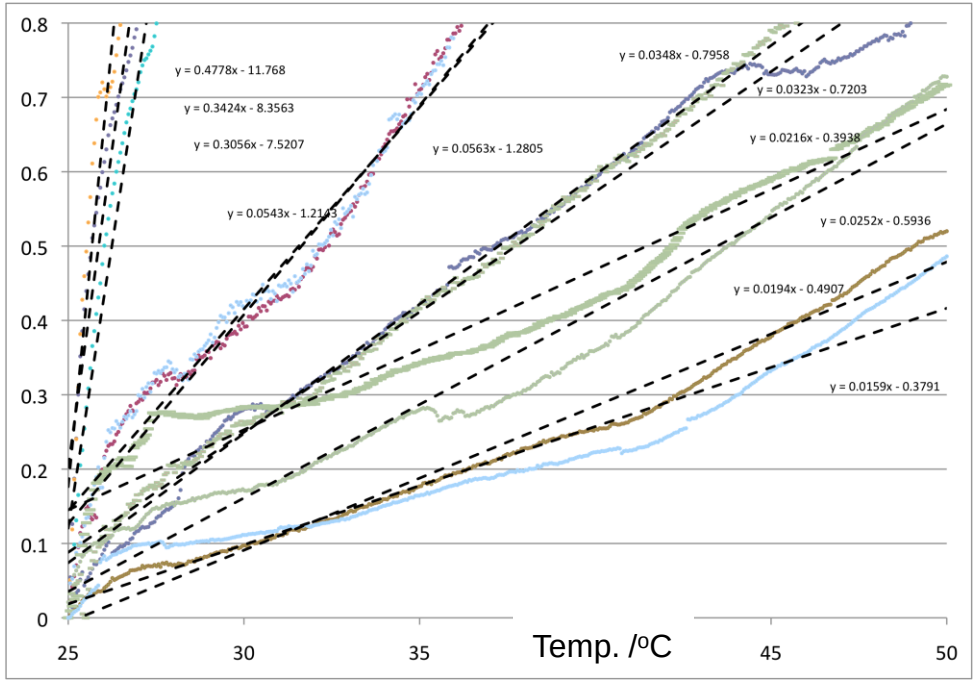
Thermal Dissolution Analysis

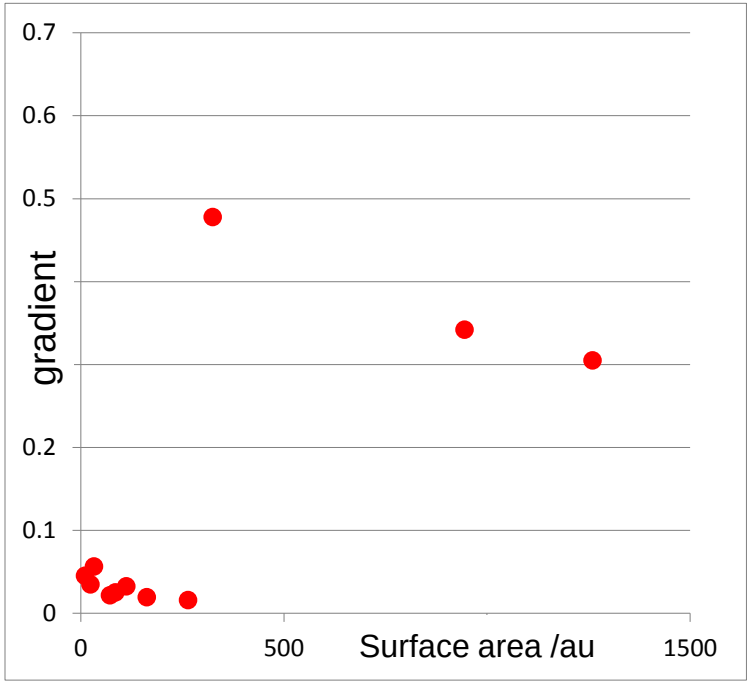




TASC is used to track the dissolution of the objects in the field of view of the microscope. The temperature program was 5°C/min.

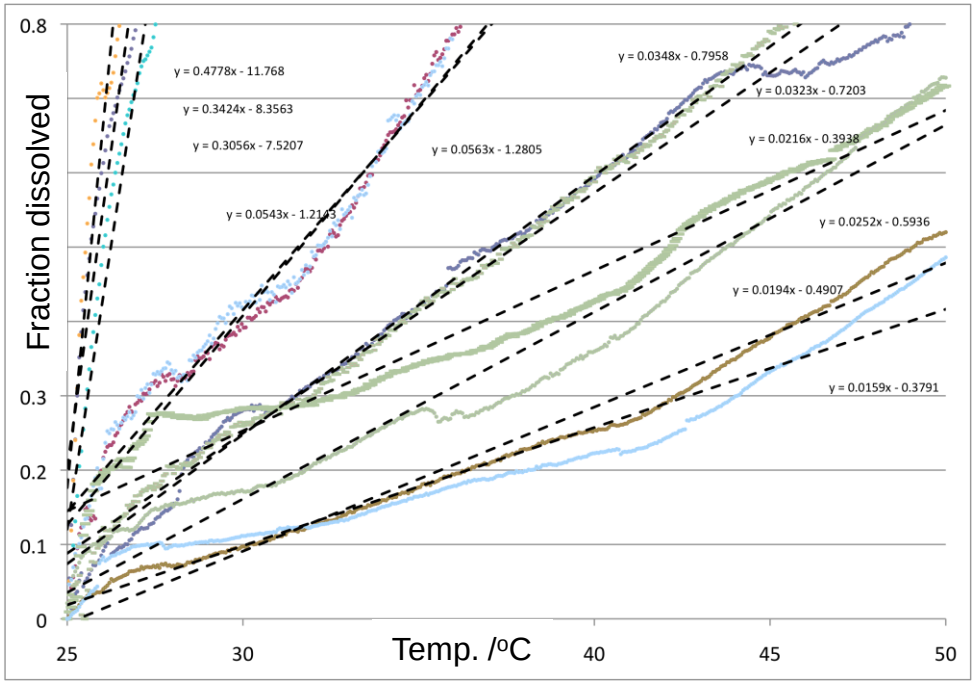
Thermal Dissolution Analysis

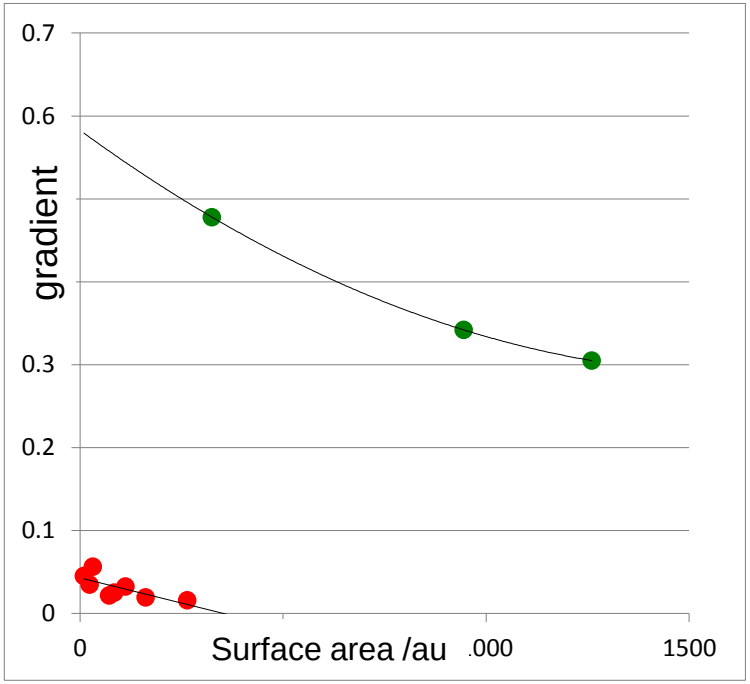




A line was fitted to the linear part of the dissolution curves and the gradients were plotted against the size of the crystals.

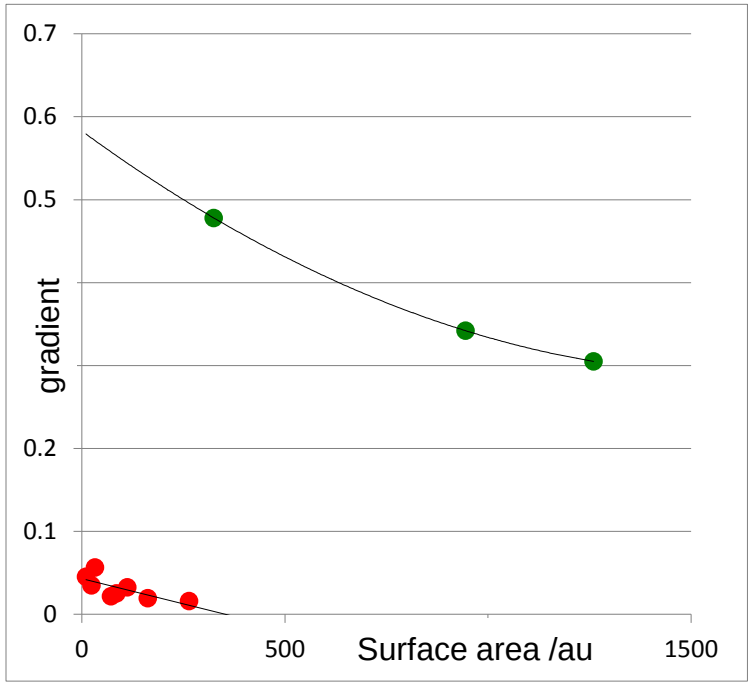
Thermal Dissolution Analysis

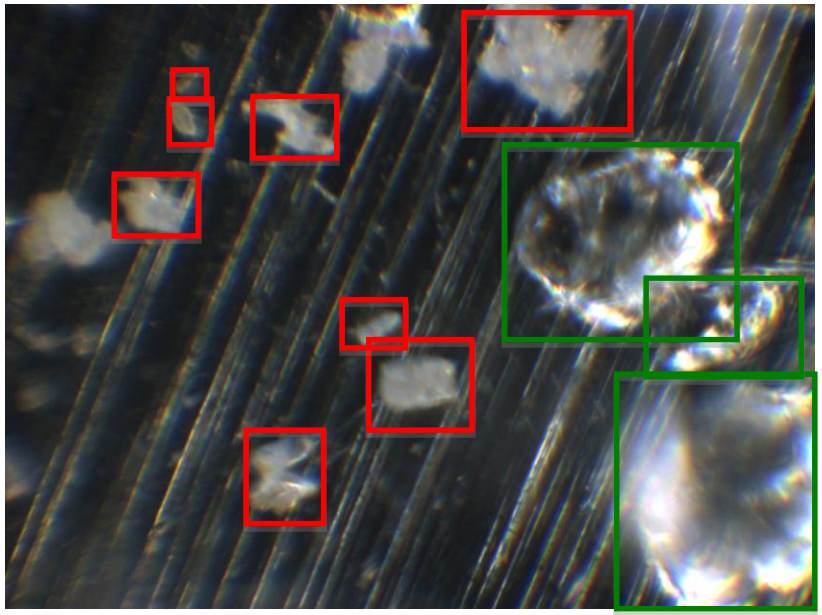




The dissolution behavior clears falls into two categories shown as red and green.

Thermal Dissolution Analysis

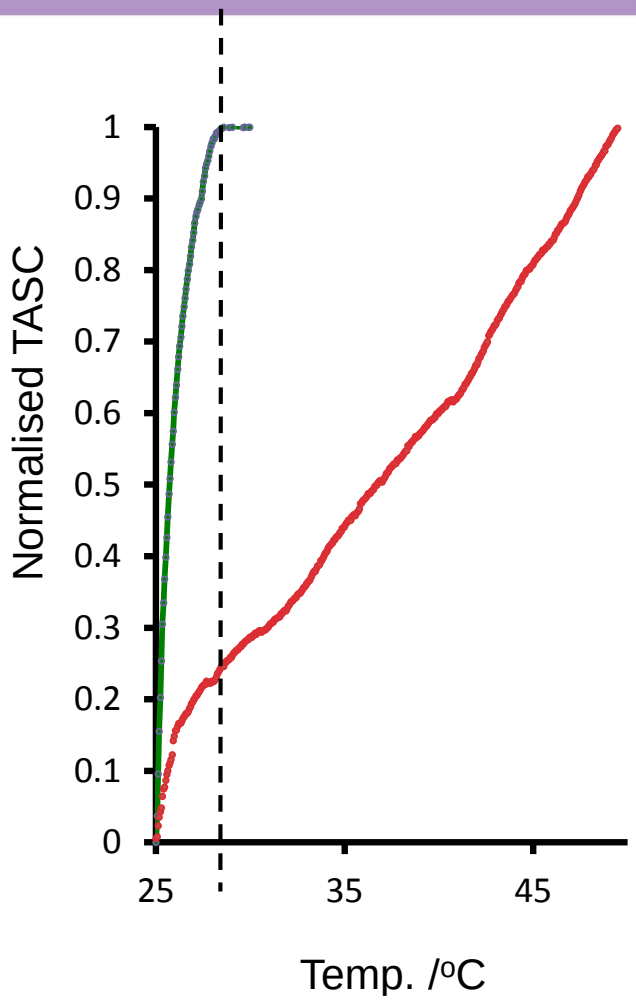


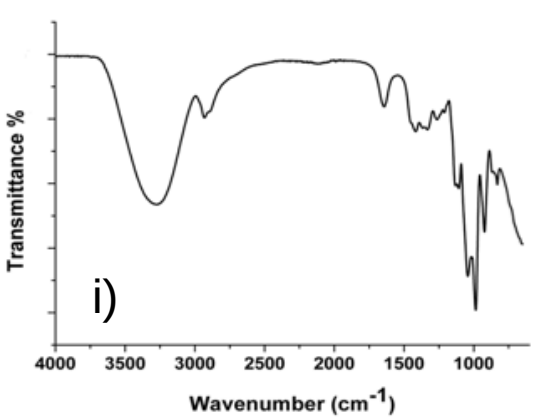


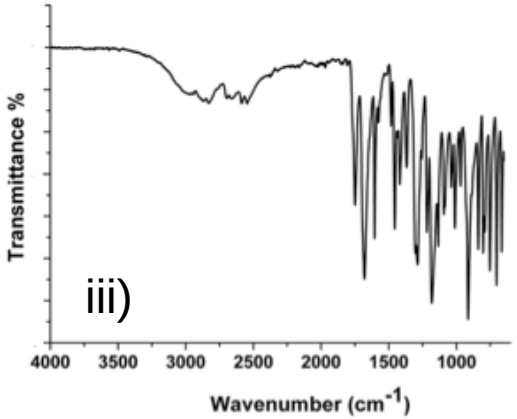
The objects in the field can be allocated to the two categories.

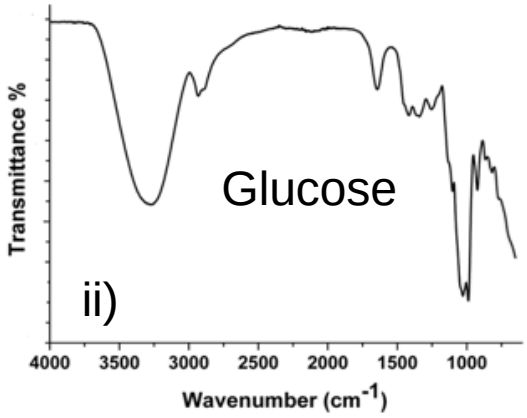
Part 3

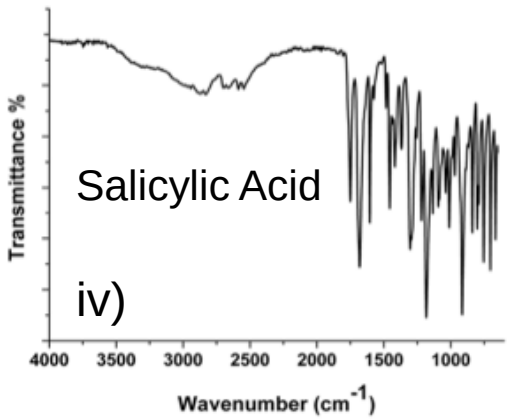
- Thermal Analysis by Structural Characterisation (TASC)
- Thermal Dissolution Analysis (TDA)
- **Chemical Identification by Dissolution Assessment (CIDA)**











Filtered i) from solvent; iii) from residue

By appropriate chemical analysis the ‘red’ and ‘green’ materials can be identified.

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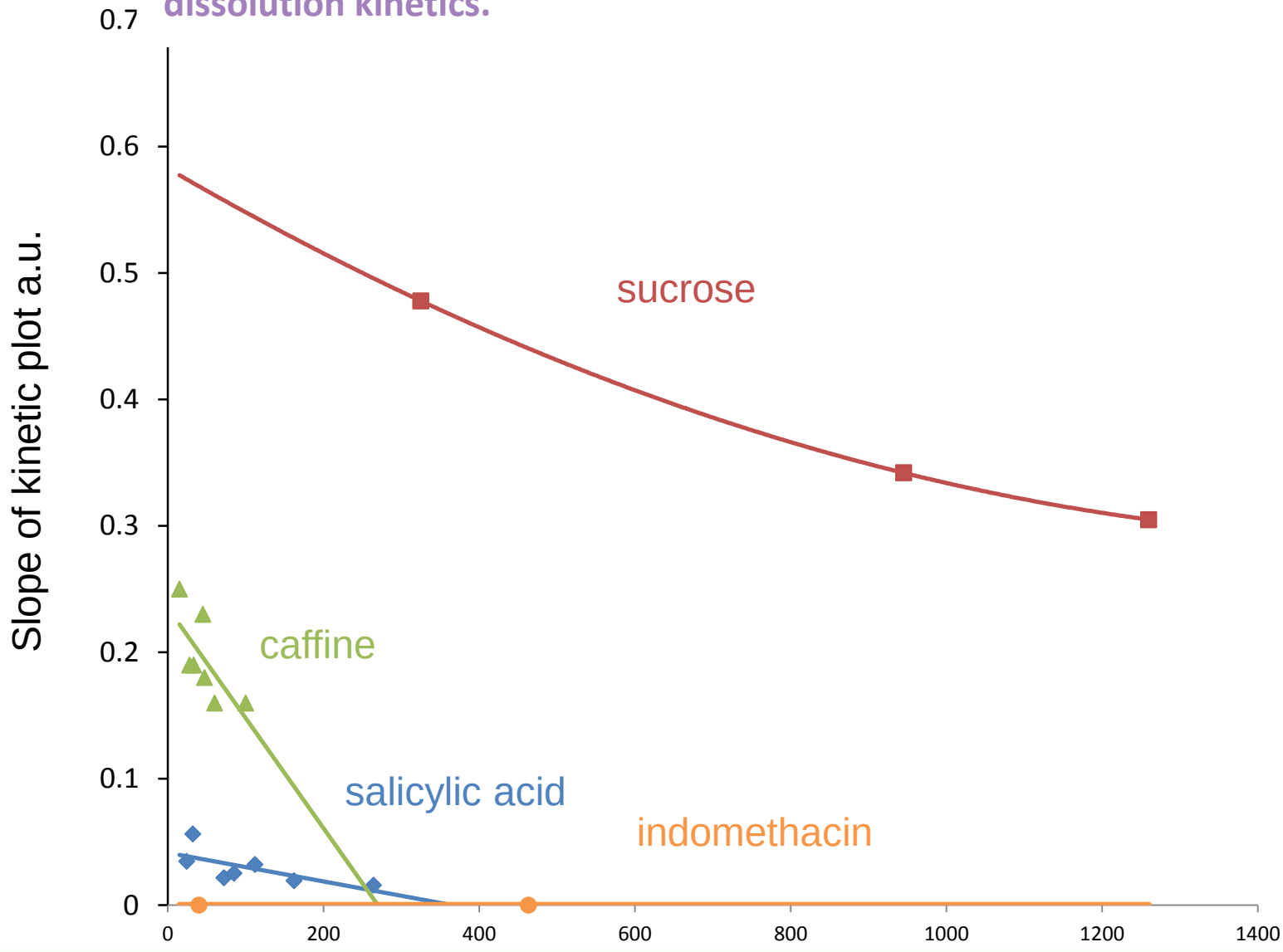
It is typically the case that different material have different dissolution kinetics.



Thermal Dissolution Analysis

TGA-GC-MS

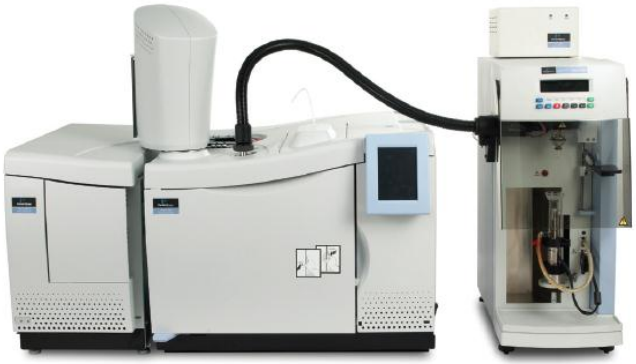


Figure 1: The Pyris 1 TGA coupled to the Clarus 600 C GC/MS gives the most sensitive method to identify evolved gases

Mass Loss

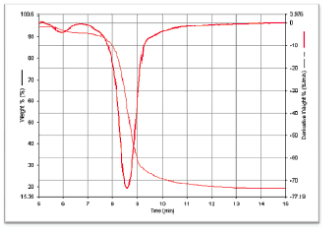


Figure 2: The TGA run of a sample of switch grass shows most weight loss occurs in one temperature range

Chromatography

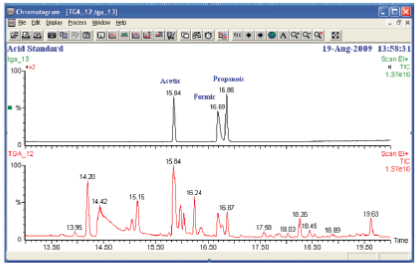
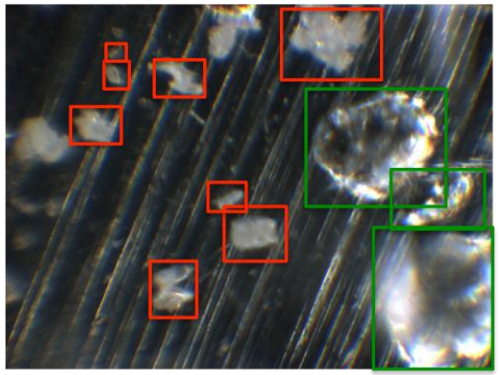
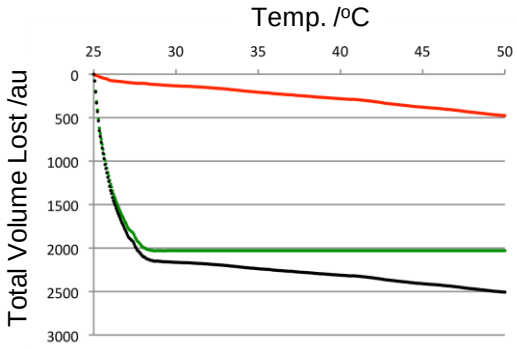


Figure 3: GC/MS on the gases evolved between 8 and 9 minutes and collected on the head of a GC column gave the chromatography seen on the bottom of the graph. MS analysis suggest that 15.8 is the acetic acid, which is confirmed above by running a standard of acetic, formic and propanoic acids

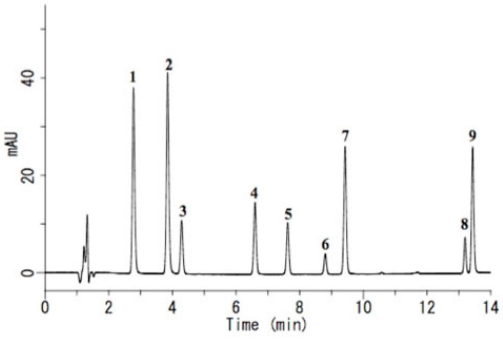
TDA-HPLC



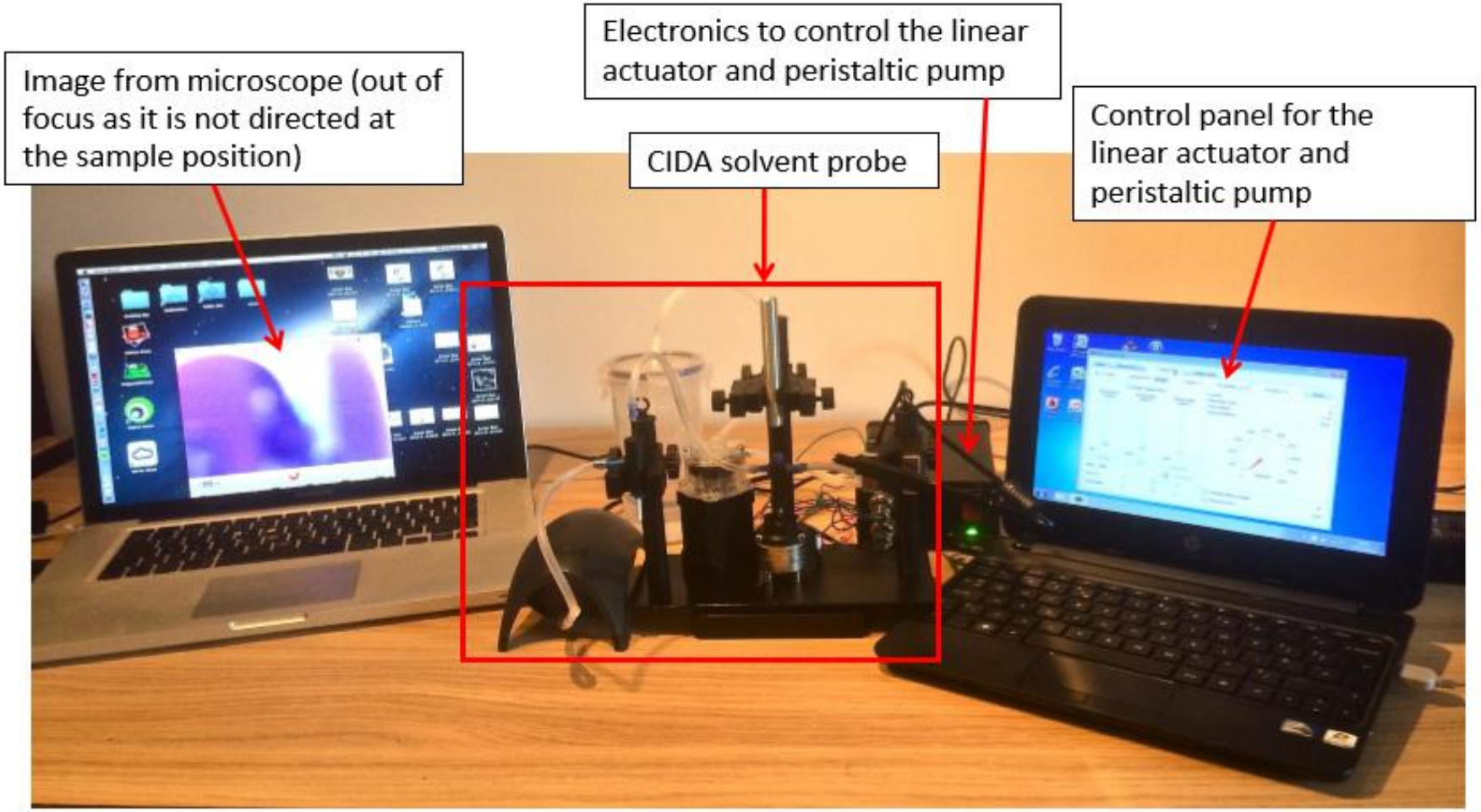
'Volume' Loss



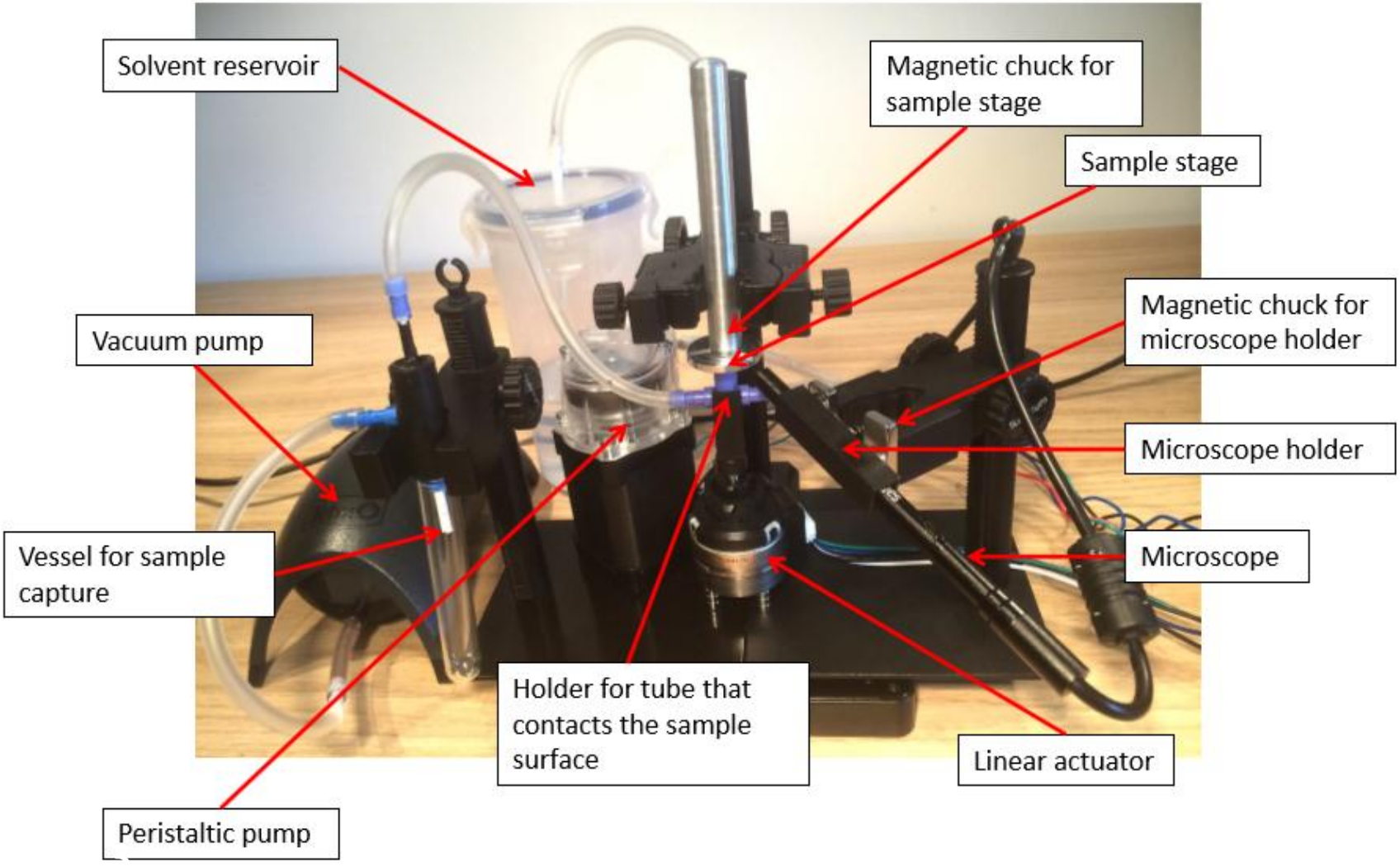
Chromatography



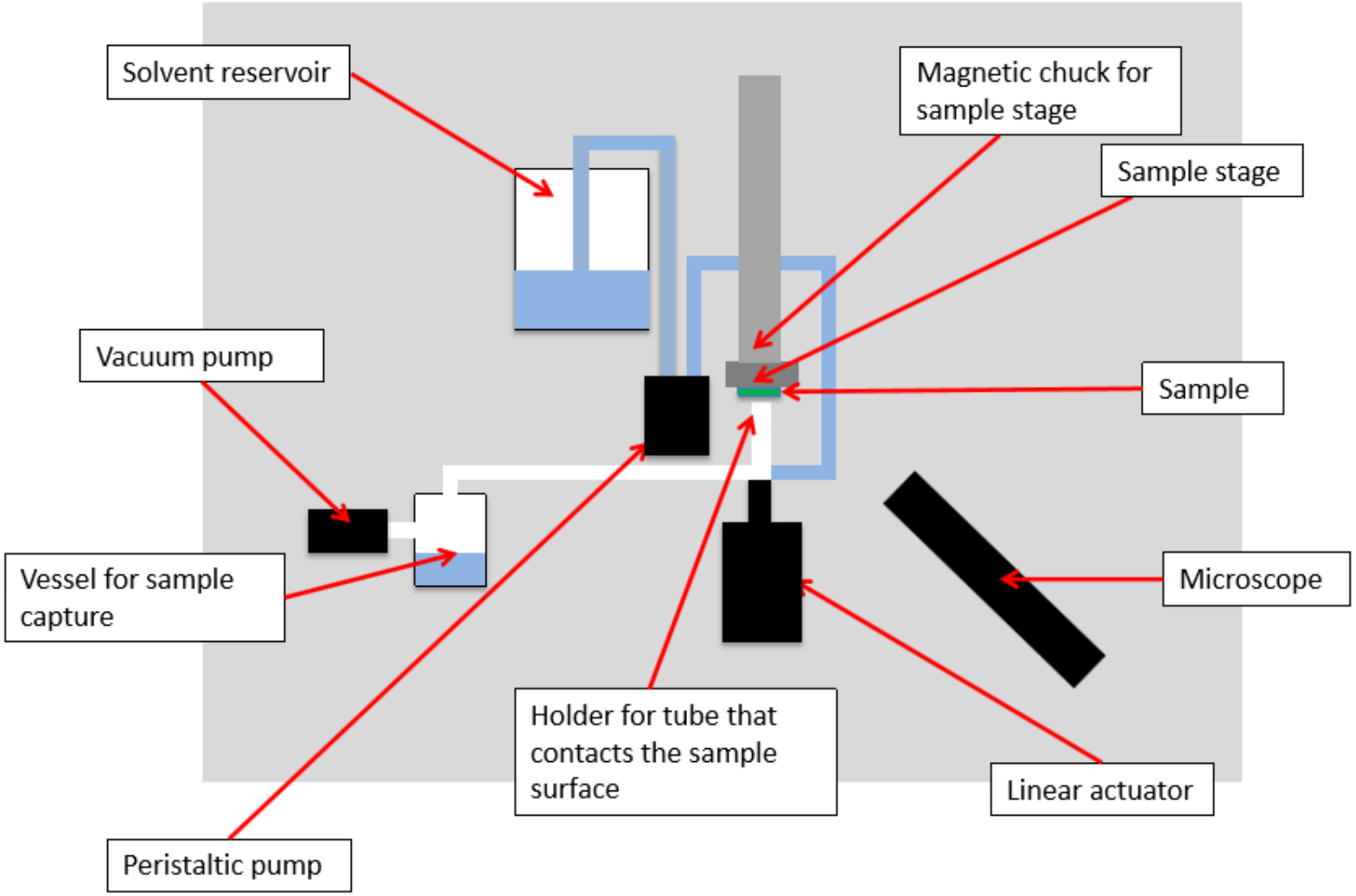
The CIDA solvent probe comprises a pump to deliver the solvent to the surface of the sample, a means of placing a delivery tube onto the surface of the sample in a controlled way and a means of rapidly removing the solvent and capturing it so the solvated material can be analysed. The introduction of the solvent to the sample is done under scrutiny using a microscope. The current system uses one computer to control a pump and an actuator while the images from the microscope are displayed on a second computer.



The system uses an inverted configuration i.e. the surface of the sample is facing downward as the solvent is applied (this point will be discussed further below). The tube that carries the solvent is moved toward the sample using a computer controlled linear actuator. The solvent is pumped by a computer controlled peristaltic pump.



The vacuum pump is then used to remove the solvent from the surface and capture it in a test tube. There is also the option of using a coaxial tube, as illustrated below, with a continuous or intermitted flow.



Upgrades for future CIDA solvent probes

- Multiple Solvents
- Syringe option
- Heated tip
- X-Y translation
- Microscope to observe the sample and select area to be solvated under computer control
- Automatic control of approach to sample using the images from the microscope
- Force transducer to control the force with which the probe is pressed against the surface
- On-line analysis
- Nano pipette for very high resolution solvation

Conclusions

The real power of the CIDA approach is that analysis can be reliably applied to a single sample, a wide variety of solvents can be used, physico-chemical changes in surface properties and detection of removed chemicals are simultaneously monitored at the micro/nano scale; the use of chemicals is minimized. Unique information about surface properties and changes therein is obtained and the methodology used can be easily automated

Further info

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M. Reading, M. Morton, M. Antonijevic, D. Grandy, D. Hourston and A. Lacey. “New Methods of Thermal Analysis and Chemical Mapping on a Micro and Nano Scale by Combining Microscopy with Image Analysis”. In A. Méndez-Vilas (Ed.) Microscopy: advances in scientific research and education – Volume 2, Formatex Research Center (2014), 1083-1089


Thank you for listening