Dynamic Micro-CT: Non-destructive imaging in the fourth dimension

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INTRODUCTION

Micro-computed tomography (micro-CT) in both the laboratory and at synchrotron beam lines has evolved into a well-known, commonly used technology over the past decades. Ever since commercial micro-CT systems were first introduced in the late 1990s, the number of installed instruments has constantly been growing and the market has been expanding. Today, micro-CT has become a methodology that is available at most universities worldwide, with industrial companies catching up.

Micro-CT is the only existing microscopy method that is capable of imaging the internal structure and composition of samples – ranging in size from a couple of millimeters to tens of centimeters – without imposing any damage to the sample[1]. This, and the absence of complicated sample preparation or handling procedures, greatly explain the success of the technique. To acquire datasets of the exterior and interior of samples, a sample is placed between an X-ray source and a detector, and while the sample is rotating over 360 degrees, hundreds to thousands of X-ray shadow images or radiographs are acquired. These radiographs, or projections as they are called, are then loaded into a reconstruction package, and by the principle of back-projecting them into the virtual space, a full three-dimensional volume of the sample can be reconstructed. Although many factors influence the resolution of the acquired images, such as the spot size of the X-ray source and the pixel size of the detector used to capture the projections, the main influence is the ratio between source-to-sample and source-to-detector distance. This provides a geometric magnification of the sample and will ultimately determine the voxel (3D pixel) size of the resulting 3D dataset. As a result, small samples, which can be brought very close to the X-ray source, can be imaged at higher resolution than larger samples.

It is important to note that the 360 degrees rotation can either be obtained by rotating the sample, as in the majority of conventional micro-CT systems, or by rotating the entire source-detector assembly around the sample, similar to medical CT scanners – this is the unique capability of the TESCAN DynaTOM.

TIME-RESOLVED MICRO-CT

The non-destructive nature of micro-CT quickly opened new and unique opportunities to follow the behavior of samples over time. This is referred to as time-resolved micro-CT or 4D CT, where time is defined as the fourth dimension.

While it started with following spontaneous sample changes, specialized sample manipulation devices were developed to induce changes to samples or to expose them to different environmental conditions. Commonly used examples are the monitoring of fluid flow behavior in porous media – with applications for ground water management and environmental studies – or compression or tensile tests on engineered materials such as alloys, metal foams or concrete.

Although 4D micro-CT exposed the scientific community to a whole new method to follow processes in samples at micrometer-scale resolutions from the inside out, the method still had a few limitations. Traditionally, micro-CT in the lab is a relatively slow imaging method.

Although scan times can be as short as a few minutes, typically one or multiple hours are needed to acquire images with good enough quality to be segmented and analyzed in a later stage. As it is of paramount importance that a sample remains stable during the 360 degrees rotation of the stage or source-detector assembly, this meant that time-resolved CT in the lab could traditionally only be used for very slow processes such as corrosion of metals, creep processes or slow crystallization phenomena. In the case

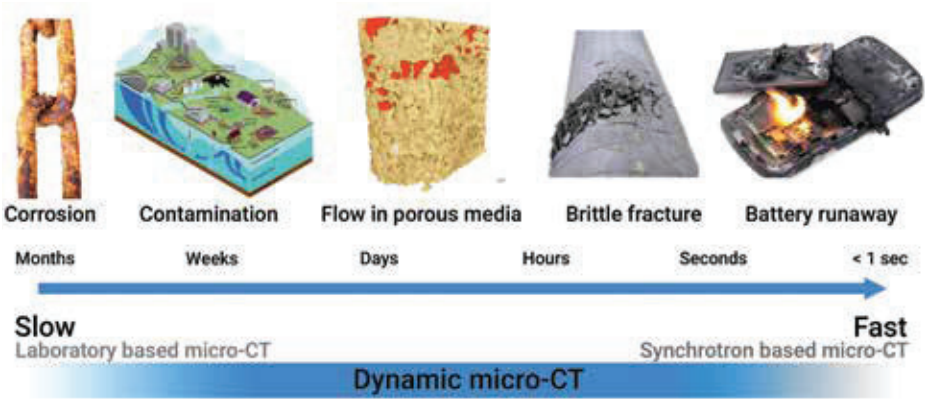

FIGURE 1 *Dynamic micro-CT as a bridge between conventional laboratory-based micro-CT and synchrotron micro-CT.*

BIOGRAPHY

Wesley De Boever is Product Marketing Manager for Micro-CT at TESCAN. He holds a Ph.D. in Geology, obtained as a researcher at the Ghent University Centre for X-Ray Tomography (UGCT). Wesley has over a decade of experience in conventional and dynamic micro-CT and its combination with other microscopy techniques such as optical and scanning electron microscopy.

ABSTRACT

Micro-computed tomography went through a dramatic evolution over the last years, from a novel and niche technique to a well-established and widely used method in materials and life sciences. The unique capability of micro-CT to provide non-destructive 3D imaging of a sample's internal structure, its flexibility and lack of sample preparation caused the method to be a game-changer for scientists and engineers in all fields of application. Furthermore, the non-destructive nature of the method has always enabled users of micro-CT to investigate the behavior of their sample over time and under changing environmental conditions. However, without the use of limited synchrotron facilities, laboratory-based micro-CT systems could only allow slow processes to be followed. Now, recent developments in both hardware and software bring a revolution in the field of micro-CT and introduce true dynamic micro-CT at high temporal resolution to the lab.

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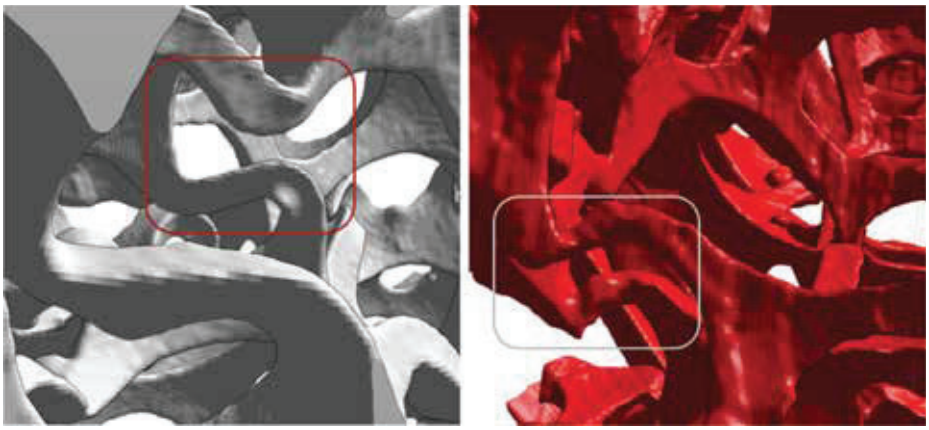

FIGURE 2 *Buckling of foam struts in experiment (left) and simulation (right).*

of damage-inducing experiments, such as compression experiments, it implied that the experiment needed to be halted at different stages, in order for the imaging to take place. This also means that samples are given the chance to relax and adapt to this new 'static' situation, which does not really correspond to real-life events that these materials will be exposed to. Such an interval-based imaging methodology is referred to as time-lapse CT, in correspondence with the well-known time-lapse imaging that is often performed in standard photography.

DYNAMIC MICRO-CT AND TEMPORAL RESOLUTION

Time-lapse based 4D imaging is revolutionary for many research fields, but has limitations. Both the sample relaxation and the inability to track fast and uninterrupted processes are a real caveat of the methodology. Since many processes happen in a seconds-to-minute timeframe, time-lapse 4D imaging cannot be used in these cases.

Temporal resolution, which is the time needed to acquire one complete 3D dataset, is a limiting factor for laboratory-based 4D imaging, so fast dynamic processes were traditionally imaged at synchrotron beam lines. The extremely high X-ray flux and specialized detectors with very fast read-out speeds enabled time-resolved experiments at temporal resolutions well below one second per rotation.

Real-time imaging of flow in rock cores, imaging of very discrete events such as brittle fracture of materials or thermal runaway of batteries are examples of processes where synchrotron facilities play a vital role to deepen the understanding of important processes (figure 1). Although synchrotron imaging is and will remain the gold standard for ultra-fast 4D imaging, their limited availability, expensive running costs and proposal-based access means they are not work-horse or standard solutions for researchers and engineers.

Therefore, there was a need to push the limits of temporal resolutions for laboratory-based micro-CT experiments. Over the last years, this led to the development of TESCAN's laboratory-based dynamic micro-CT solutions. By optimizing every component of the micro-CT scanner – including the X-ray source, detector, and rotation stage – temporal resolution in the lab could be brought back from hours to just a few seconds, bridging the gap between conventional laboratory- and synchrotron-based imaging.

The keys to this true dynamic micro-CT imaging are of course fast acquisition speeds, including high-power X-ray sources and detectors with a high read-out speed, enabling to acquire a full 3D tomogram in just a matter of seconds. Furthermore, it is important that a continuous and endless rotation of the sample or source-detector assembly is possible, as temporal resolution is defined as the resolving power of events separated by time. Therefore, tens or even hundreds of tomograms need to be acquired in an uninterrupted manner. Finally, software solutions need to be able to handle these huge data volumes, from acquisition, over reconstruction, to visualization.

DYNAMIC CT AS A TOOL TO VALIDATE COMPUTATIONAL MODELS

In this example, dynamic CT was used as a validation tool of numerical models, predicting and simulating the mechanical properties of metal foams. These metal foams are a key material for many objects and materials that are present in our daily lives. They are used in lightweight vehicles without compromising on strength (aerospace, automotive), have applications in vibration-dampening and are used as crumple zones in cars.

However, characterizing these metal foams is not an easy task, as they are non-transparent, complex 3D structures. Traditional mechanical testing only provides a macro-view of properties and is therefore not capable to fully understand processes on a local level. Therefore, numerical modelling came up as a new tool to simulate experiments and predict the stress-strain behavior of metal foams. Up until now, there was no real way to validate the results of these numerical models, hence dynamic micro-CT was brought in to evaluate the effectiveness of metal foam compression simulation.

In this study, 20 x 20 x 20 cm cubic samples of an aluminum alloy foam were compressed in a Deben CT5000 compression stage. By connecting this stage through a slip-ring connection on the TESCAN CoreTOM's rotation stage, 280 uninterrupted tomograms at a temporal resolution of 20 seconds per rotation could be obtained while the foam was compressed over a range of 7 mm. The voxel size of 32 micrometer was tuned to the compression speed of 100 µm per minute (33 µm per rotation) to ensure no movement artefacts were present in the tomograms. In the dynamic micro-CT experiments, different deformation modes, such as buckling or bending of struts or collapsing of cells could be observed and analyzed in the software (figure 2).

The compression experiments were then compared to numerical modelling of the compression, using the initial dataset of the dynamic experiment as input. A compression of no less than 35% was possible thanks to a voxel based FFT solver in the GeoDict software package by Math2Market. Two ways were used to verify the model: the stress/strain curves of simulation and experiment were compared and a visual comparison between the experiment and the model could be performed.

To be able to validate the model, two samples of the same foam were tested, analyzed, and simulated. The experimental data from the first sample was used to determine the material characteristics, which are in many cases unknown to the manufacturers. Subsequently, those material properties were used as an input for a simulation of the second sample. On that second sample, the full compression experiment was repeated to ensure that the model was robust enough to be used on different samples of a similar material (figure 3).

Results show great correspondence between the data obtained by experiment and simulation. This was shown both by comparing stress-strain-curves and discrete events like buckling happening on the local scale. The study proves that numerical simulation can play a very big role in the development of new materials and can greatly reduce development time of these materials since different varieties can be tested before being produced.

DYNAMIC CT AS A TOOL TO QUANTIFY FAST STRUCTURAL CHANGES IN PHARMACEUTICAL TABLETS

Dynamic CT was used to get a better mechanistic understanding of the disintegration process of pharmaceutical solid dosage forms (tablets or capsules). Dosage forms are the predominant form to control active pharmaceutical ingredients

FIGURE 3 *Left + middle: segmented datasets from the dynamic micro-CT experiment at 0 and 35% compression. Right: Simulated sample at 35% compression.*

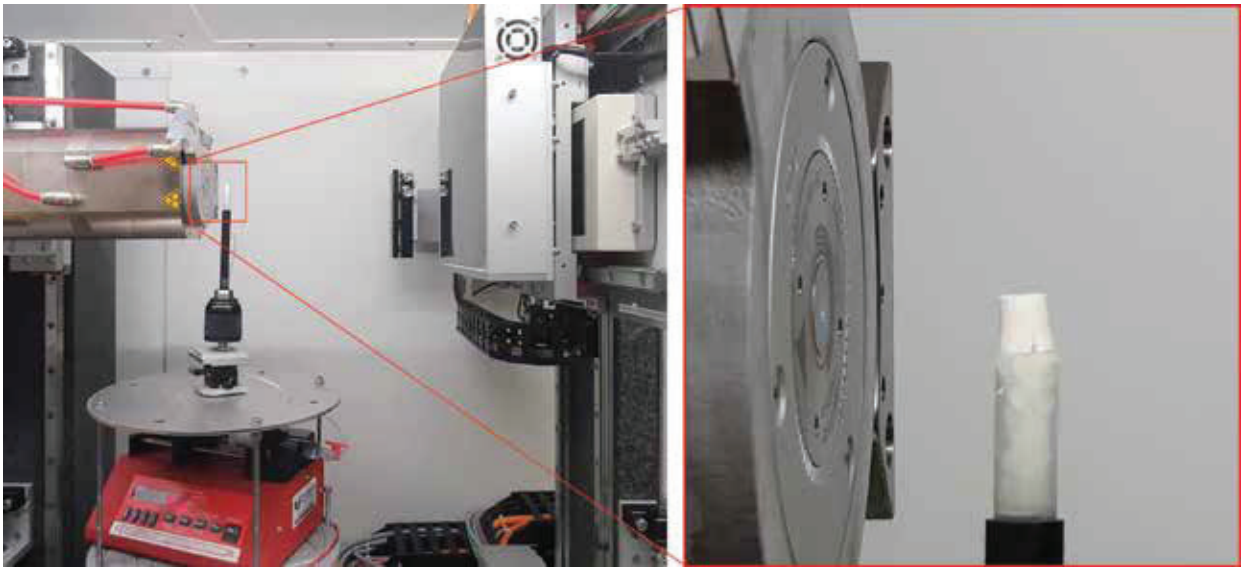

FIGURE 4 *Experimental setup of the experiment inside the cabinet of the TESCAN UniTOM HR. Left: syringe pump mounted on the rotation stage with connections to the sample. Right: close-up of the sample undergoing cracking and swelling due to water absorption.*

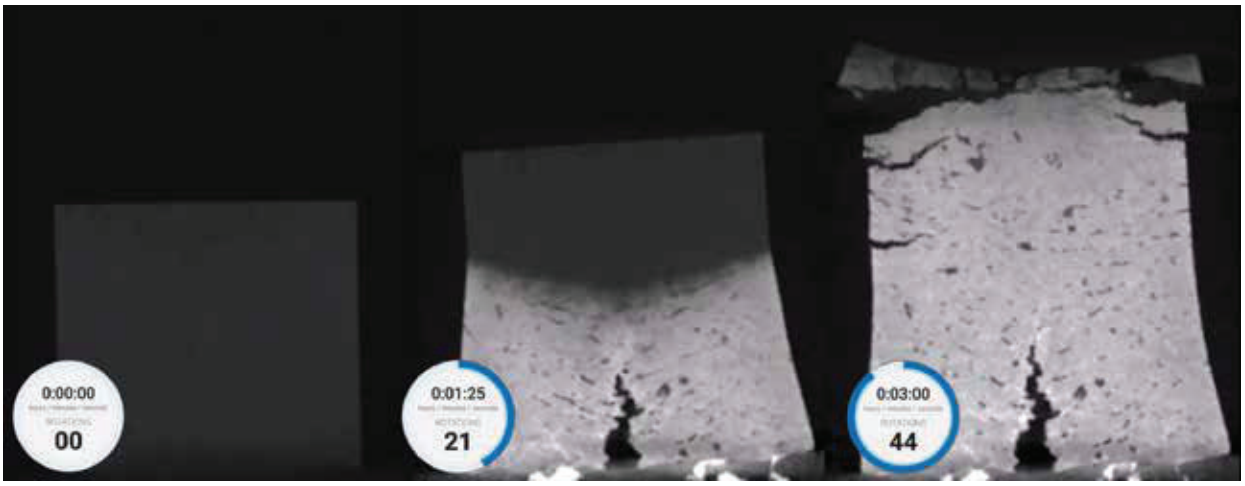

FIGURE 5 *Three different time steps of the dynamic experiment. The water front moves very quickly up the tablet. After water absorption large cracks and voids are present in the sample, and a large volume increase is observed.*

to a patient and typically consist out of compacted powder with added excipients. In order to deliver the active pharmaceutical ingredients to the patients, the compacted tablet needs to mechanically break up into smaller particles. Therefore, the admixture of excipients is essential as it controls the process of the drug release in the body and assures a high product quality. As a result, solid dosage forms are complex structures with high heterogeneities on different length scales.

Most quantitative studies to understand the disintegration behavior of tablets are based on measuring the volume increase of the complete tablet or individual grains[2]. Typically, the volume increase is due to swelling mechanisms when the product comes in contact with water. The water can be added by a droplet method or directly by capillary uptake and the changes in volume are usually visually recorded[3]. However, in order to simultaneously study the penetration of the water inside of the tablet, the disintegration and swelling, one needs to visualize the process non-destructively and in full 3D.

In this study, dynamic micro-CT with high temporal resolution was used to visualize the penetration of water inside the tablet and the disintegration of immediate-release tablets. The tablets fully disintegrate and dissolve upon exposure to water in a short period of time (a couple of minutes)[4]. The rapid disintegration poses challenges for slower, time lapse (or interrupted) micro-CT procedures and the disintegration process cannot be stopped during the actual experiment.

The tablet was compacted in a 6 mm die at a predetermined thickness to control the maximum in-die relative density (0.8) at Purdue University (Prof. Gonzalez Research Group). The formulation used was: MMC (89%) + APAP (9%) + MgSt (1%) + Cab-O-Sil (1%). MMC or MicroCrystalline Cellulose is widely used in pharmaceuticals, primarily as binder in oral tablets. It also has disintegration properties that makes it useful in tableting. Acetaminophen (APAP) is a pain reliever and fever reducer. Magnesium Stearate (MgSt) is primarily used as a lubricant. Colloidal Silica Dioxide (Cab-O-Sil) can have multiple uses, some include anti-caking agent, adsorbent, disintegrant or glidant to allow powder to flow when tablets are processed. Cab-O-Sil and MgSt can coat the particles and modify the wettability and thus the drug release rate of the compact. Cesium chloride was added to the water in order to increase the attenuation contrast inside of the tablet.

The tablet was placed in the TESCAN UniTOM HR on a styrofoam sample holder with a syringe pump attached. The pump added water at an injection rate of 2ml/min to the styrofoam. The water was absorbed by the tablet through capillary uptake at the bottom. This complete *in situ* set up was mounted on the rotation stage of the TESCAN UniTOM HR and powered through the slipring of the system. By doing so, an endless, uninterrupted rotation of the complete *in situ* set up was possible as fluid cable tangling was bypassed (Figure 4).

In order to capture the fast, mechanical dynamics of the disintegration process, a high temporal resolution was needed. The total time for complete disintegration of the tablet was seven minutes. In the experiment, 100 uninterrupted tomograms at a temporal resolution of four seconds (200 projections/360°, 20 ms exposure time) per rotation could be obtained while water was absorbed inside the tablet. The voxel size of the scan was 13 µm, small enough to visualize the deformation mechanics inside of the sample.

The resulted reconstructed volumes clearly demonstrate the disintegration pattern of the samples (figure 5). A crack forms at the bottom of the sample, opening upwards during the water absorption. The water front itself is not uniform throughout the complete sample and shows a faster absorption on the boundaries of the sample. Micro-cracks developed throughout the sample, some of them filled with liquid while others remain dry. A more thorough investigation, including image analysis, is required to fully understand the behavior of the sample, but the principal disintegration mechanisms are captured throughout the process.

The realization of fast, complex *in situ*, dynamic micro-CT, in the context of complex pharmaceutical solid dosage forms, may open doors to new experiments with different formulations. Besides optically or indirect measurements of disintegration processes, it now becomes possible to investigate underlying mechanisms of swelling directly.

CONCLUSIONS

Dynamic micro-CT in the lab is a new frontier in time-resolved, non-destructive imaging. The ability to image very fast, uninterrupted processes on a laboratory micro-CT system opens new evaluation methods for advanced materials and enables engineers to validate or correct material behavior through *in situ* experiments. Combined with numerical models using specialized solvers, this new analysis method will dramatically increase the development speed of new materials and devices, whilst simultaneously reduce their development cost.

Article, and references available online at: analyticalscience.wiley.com/publication/microscopy-and-analysis