



## **Industrial needs and available techniques for geometry assurance for metal AM parts with small scale features and rough surfaces**

Downloaded from: <https://research.chalmers.se>, 2026-04-04 23:07 UTC

Citation for the original published paper (version of record):

Berglund, J., Söderberg, R., Wärmeffjord, K. (2018). Industrial needs and available techniques for geometry assurance for metal AM parts with small scale features and rough surfaces. *Procedia CIRP*, 75: 131-136.  
<http://dx.doi.org/10.1016/j.procir.2018.04.075>

N.B. When citing this work, cite the original published paper.

15th CIRP Conference on Computer Aided Tolerancing – CIRP CAT 2018

# Industrial needs and available techniques for geometry assurance for metal AM parts with small scale features and rough surfaces

Johan Berglund<sup>a,b,\*</sup>, Rikard Söderberg<sup>a</sup>, Kristina Wärmefjord<sup>a</sup>

<sup>a</sup>Chalmers University of Technology, 41296 Göteborg, Sweden

<sup>b</sup>Swerea IVF, PO Box 104, 43153 Mölndal, Sweden

\* Corresponding author. Tel.: +46-31-7066050; E-mail address: [johan.berglund@swerea.se](mailto:johan.berglund@swerea.se)

## Abstract

From an industrial perspective this paper aims to explore the state of the art regarding GD&T for metal additive manufacturing, specifically regarding product definition and inspection. The available techniques for geometry assurance for parts with small scale features and rough surfaces are evaluated in terms of suitability for the task and readiness for industrial implementation. It is found that many of the remaining challenges seem to be related to processing of data rather than obtaining data. Current difficulties are related to issues such as calibration, surface determination and defining the most relevant parameters to tolerance and inspect.

© 2018 The Authors. Published by Elsevier B.V.

Peer-review under responsibility of the Scientific Committee of the 15th CIRP Conference on Computer Aided Tolerancing - CIRP CAT 2018.

*Keywords:* Product definition, Inspection; Additive Manufacturing

## 1. Introduction

In order to design and efficiently produce products that meet functional needs, those needs have to be specified through material and geometry with tolerances, e.g. Geometrical Dimensioning and Tolerancing (GD&T).

In recent years there have been a number of reviews and research papers published on various topics related to geometrical tolerancing and inspection of AM parts.

The comprehensive CIRP STC Dn keynote of 2016 covers many aspects of additive manufacturing including the need for process-specific design rules as well as challenges for metrology and quality control after production [1].

Ameta et al. reviews tolerancing of AM parts and related issues in two publications 2015 [2,3], studies that are followed up by Witherell et al. in 2016 [4].

In the above mentioned publications the need for additional AM-driven specification standards and additions to current tolerancing standards are discussed [1–4]. It is pointed out that AM processes bring together the specification issues of material and geometry. The standards in material and geometry specifications will have to work together in order to

address the standards related challenges posed by AM processes [2,3]. In the newer review it is noted that these challenges still have not been handled [4]. Alternative approaches such as the Enriched voxel-based volumetric representation presented by Moroni et al. [5] have recently been suggested for how to deal with some of the challenges.

Challenges also are present regarding inspection, relating to evaluation of dimensions as well as surface topography, regarding obtaining, processing and evaluation of measurement data.

The objective of this paper is to explore the state of the art regarding GD&T for metal additive manufacturing specifically regarding product definition and inspection from an industrial perspective.

The paper is structured accordingly: First, two industrial examples are given which serve as examples for identification of needs. Then, with the basis in those examples some general research questions are formulated. After that, the paper will review and discuss available methods and technologies from the perspective of helping to solve these research questions in the industrial contexts that they originate from. In this way,

the given industrial examples also serve as delimitations for the review. Lastly, there is a discussion on remaining needs.

## 2. Identification of industrial needs

Two industrial examples are given below in which specific needs can be identified.

### 2.1. Industrial examples

**Example 1:** Hyproline was an EU funded research project with various industrial partners (High performance Production line for Small Series Metal Parts, FoF.NMP.2012-4). The studied geometry contains features with dimensions and tolerances which were representative of the requirements of the industrial partners in the project. The specific example that will be used here is the width of some rectangular pockets which was specified to  $3 \text{ mm} \pm 10 \text{ }\mu\text{m}$  after post processing using laser finishing. The AM process was Digital Metal from Höganäs using various metallic materials. Directly after printing the parts typically had a surface finish of  $Rz \approx 60\text{-}80 \text{ }\mu\text{m}$ . In this example, adequate detecting, referencing and positioning of the part would have been critical to be able to successfully perform the post processing.

**Example 2:** AMtoFlex is, at the time of writing this paper, an ongoing Swedish research project (Additive Manufacturing of Tooling for Flexible Production and Optimized Product Properties, Vinnova d-nr: 2016-03305). One of the case studies in the project is a tooling insert for hot stamping with free form forming surfaces and conforming cooling channels at a certain distance below the forming surface. In hot stamping the cooling efficiency of the tooling is critical because it sets the required cycle time in the process, directly influencing the economical efficiency, as well as influencing the quality of the produced parts. FE simulations are used to optimize the tooling design to produce formed components with the correct geometry and material properties as efficiently as possible. Therefore, the diameter, internal surface roughness and positions of the cooling channels in relation to the forming surface are of great interest.

### 2.2. Research questions

The research questions below are generalized and based on the needs from the industrial examples above. In both examples some critical features have to be post processed in order to fulfill the required tolerances.

1. How to ensure adequate referencing and positioning to accommodate successful post processing?
2. How to evaluate geometry (dimensions) when surface roughness is relatively large?
3. How to measure external and internal geometries?
4. How to measure surface topography on external and internal surfaces?

## 3. Product definition

In their 2016 paper Witherell et al. presented a model for different stages of an AM product definition [4], see Figure 1. In the model there are four stages, of which some possibly could be further subdivided into more stages. Different types of information need to be associated with the product depending on which stage that is considered. In the first stage, *as designed*, there are specifications on the finished product itself such as geometry and material properties, that are needed to ensure the product's function. The next stage, *as manufactured*, includes specifications that are related to the AM process such as support structures, build direction and placement in the build chamber. The third stage, *as finished*, are specifications for any post-processes, such as removal of support structures and surface finishing e.g. blasting. The fourth stage, *as inspected* includes specifications needed for the inspection of the finalized part [4].

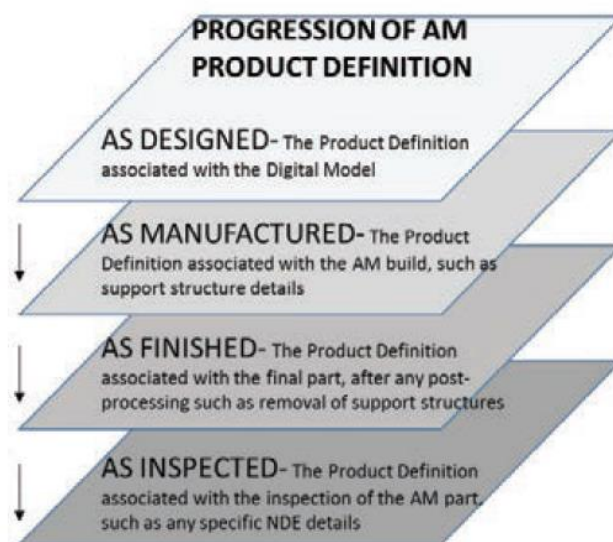


Figure 1: Intermediate stages of AM product definition [4], reproduced with permission.

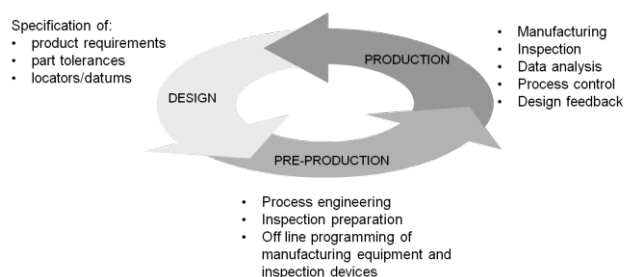


Figure 2: Product realization loop, adapted from [6].

The four stages in Figure 1 can be related to different phases of the Product realization loop [6–8], see Figure 2, which is general and not connected to any specific manufacturing method:

1. The first stage in Figure 1, *as designed*, is related to the *design phase* in the Product realization loop. Focus is on

functional requirements for the finalized product and specifications needed to fulfill the intended function.

2. The second stage, *as manufactured*, is related to the *pre-production phase*. Here process engineering takes place, hence, specifications made here need to be adapted to the manufacturing processes that are to be used.
3. The third stage, *as finished*, also is related to the *pre-production phase*. Again, here process engineering takes place and specifications made here need to be adapted to the finishing processes that are to be used.
4. The last stage, *as inspected*, is related to the *production phase* and specifications here are for process control.

As mentioned in the introduction, a need for additional AM-driven specification standards and additions to current tolerancing standards has been expressed. Similarly, there are other processes which have process-driven specification standards for parts such as composite processes and parts made using casting, forging, and molding processes [3]. In these processes, specific process related things occur, e.g. parting lines in injection moulding. Some features of a metal AM part can be regarded similarly, e.g. visual texture or anisotropic material properties related to build direction.

Either these properties caused by process specific conditions are desired in the final product or they are not. If they are not desired then they should not have to be considered in the *design phase*. However, they have to be considered during the process engineering in the *pre-production phase* so that they can be handled by a post process if needed. Reversely, if the manufacturing process related properties are desired in the final product then they should be included in the product specifications in the *design phase* so that they are considered in the *pre-production phase* during the process engineering.

#### 4. Referencing and positioning

The, for metal AM parts most relevant, issue of non nominal datum features was explored by Armillotta in 2016 [9]. This issue is especially relevant for the first research question in the present paper, referencing and positioning of parts before post processing. In the paper, an approach for simulating the effect of rough mating surfaces on geometric errors of the assembly is presented [9]. This could be applied e.g. in the case of simulating positioning of a rough AM part in a fixture or vice for post processing.

As previously noted, metal AM surfaces are typically relatively rough after manufacturing. For referencing and optimization of post processing it is necessary to construct datum features. In a 2017 research paper Shakarji and Srinivasan address the problem of establishing datums using constrained least-squares fitting to input points sampled on non-linear elements such as circles, cylinders, and spheres. [10]. The methods have to be extended to include continuous sets of points to be fully applicable to free form geometries. They also have to be implemented in commercially available software to be industrially easily accessible.

## 5. Inspection

### 5.1. Measurement of dimensions

Contacting (CMMs) and non-contacting (e.g. structured light) methods both rely on a line of sight between the measurement system (e.g. tip or sensor) and the point that is to be measured. X-ray computed tomography (CT) is an alternative method to be able to measure internal features or parts of outer surfaces that are not accessible, e.g. undercuts.

In the 2016 review on form metrology for metal AM parts Stavroulakis and Leach concludes that the optical techniques laser triangulation and structured light are currently the most suitable options for form measurement of metal AM parts [11] which obviously only can be the case for optically accessible surfaces. Typical metal AM surfaces are not optically smooth which means that these methods works quite well since they rely on diffuse reflectance rather than specular reflectance. They are also relatively quick methods. Structured light is suggested as the method for as printed AM parts and laser triangulation for finished parts if two methods can be used [11].

With X-ray computed tomography (CT) it is possible to perform geometry measurements of otherwise hidden features such as internal cavities or deeply recessed points on an external surface [12], see

Figure 3. Even surface topography of internal surfaces can be measured [13]. Another advantage of CT technology, very relevant for metal AM, is that it allows performing dimensional quality control and material quality control simultaneously [12]. In the CIRP STC P keynotes from 2011 [12] and 2014 [14] as well as in the review by Thompson et al. from 2016 [15] thorough reviews of the technology and example applications are given, e.g. an AM part with cooling channels [14].

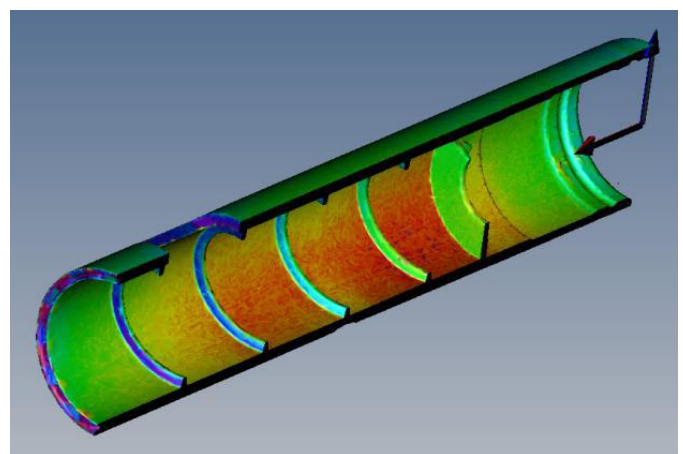


Figure 3: Representation of results using the Actual/Nominal comparison using a CAD model of a cut-out to identify variations inside the part, cropped from [16], reproduced with permission.

There are many factors that influence the capability of a specific dimensional CT setup, e.g. target, source power (voltage and current), workpiece orientation and scanning strategy [12]. A summary of typical spatial resolutions and object sizes for dimensional CT is presented in Figure 4. Typical material thicknesses that can be penetrated by the X-ray beam are 70 mm for steel, 250 mm for aluminum and 450 mm for plastics [14]. However, dimensional CT is a field with rapid development which means these numbers may be outdated quickly.

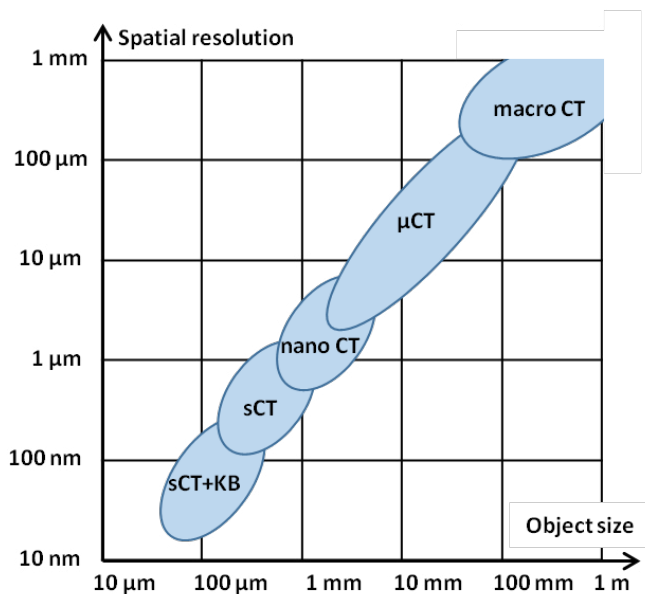


Figure 4: Typical spatial resolutions and object sizes (diameter) for macro CT, micro CT, nano CT, synchrotron CT (sCT) and synchrotron CT with KB mirrors (sCT + KB), adapted from [14].

The surface determination of CT scanning data is influenced by surface roughness. This was investigated by Carmignato et al. in their 2017 research paper [17]. In the paper, systematic dimensional errors are evaluated on samples with different characteristic textures, a polymer AM part (FDM), a turned part and a part with a triangular surface profile. Measurements by a contact CMM were used as reference. It was found that the CT scanning with least squares fitted evaluation elements were systematically smaller than the reference CMM measurements that were measuring on the peaks of the surface, which is not unexpected. More interestingly, it was found that the combined effect of profile shape and voxel size in the CT scanning had a strong influence on the evaluated geometry and that the deviations were larger for surfaces with steeper peaks/valleys [17].

The thorough review papers mentioned above includes discussions on measurement uncertainty in dimensional CT scanning [12,14,15]. Additionally, several other research papers have been dedicated to this subject [16,18–23]. In these papers different approaches for estimating the measurement uncertainties are evaluated. Nevertheless, robust and industrially useful methods for estimating measurement uncertainties and performing calibrations still seem to be lacking [24].

## 5.2. Measurement of surface topography

In addition to evaluation of geometry (dimensions) also evaluation of surface topography is of interest. Firstly, the surface roughness can be a specification that has to be fulfilled for functional reasons. Secondly, it can be useful information to be able to perform process engineering for post processing as discussed previously. Thirdly, it can be useful information for AM process development.

In contrast to optical dimensional measurements, many of the commonly used optical techniques for surface topography measurement depend on specular reflectance which means that metallic AM surfaces can be technically challenging to measure because of steep angles, high aspect ratios and varying optical properties [25], see Figure 5 for an example.

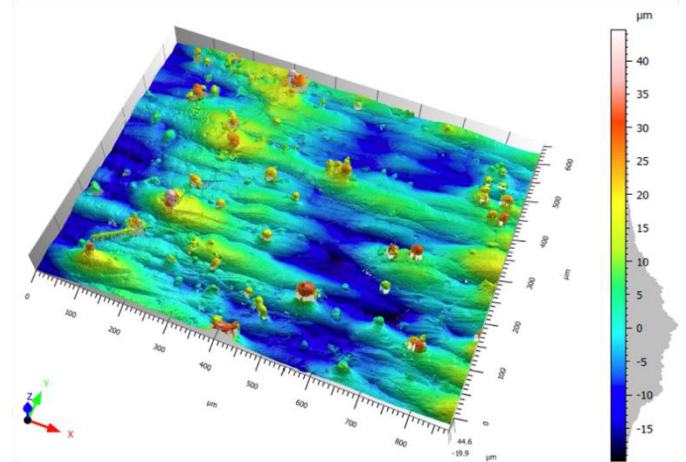


Figure 5: Example of surface topography on metal AM part.

A comprehensive review by Townsend et al. was published in 2016 [26]. In this paper the development of surface metrology for metal AM is covered. It is concluded that although surface texture is three-dimensional it has been evaluated mostly by stylus based profile measurements. This is also the case in the manufacturing industry in general [27]. It was also found that in the analyzed literature, texture characterization was mostly performed to gain a better understanding of the AM technology being studied and its capabilities. This was considered to be typical of early-stage development of manufacturing technologies.

Other research papers have focused on comparing different measurement techniques for measurement of metal AM surfaces [25,28]. Optical techniques, tactile and image processing techniques as well as CT have been tested. From these investigations it is evident that different measurement technologies can give very different results and it is not obvious which one gives the most accurate results.

Surface topography can be of interest also on internal surfaces or on surfaces with limited accessibility. In these cases, as with dimensional metrology, CT scanning is a possible technology to use. Obviously, CT scanning equipment with enough resolution is needed to measure surface texture. In most practical cases this will be a  $\mu$ CT, see Figure 4. However, data from CT scanning is not in a form that is directly useable for regular surface topography

evaluation, such as computation of roughness parameters in accordance with ISO 25178-2 [29]. In a study by Townsend et al. a method for processing the data and computing roughness parameters was demonstrated and compared to results obtained through traditional means, in this case focus variation. The results showed reasonable agreement between the methods [13]. In another study by Thompson et al. a comparison between measurements made with CT, confocal microscopy, coherence scanning interferometry and focus variation was performed. Also in this study the CT measurements produced reasonable results [25].

In another study by Townsend et al. specific methodological issues when processing CT data for surface roughness evaluation were investigated [30]. It was shown that the method for surface determination influences the accuracy of the reconstructed surface. Also, a change of filament in the CT scanning equipment had a significant effect on the evaluated results. Finally, it was shown that measuring the same surface as an external or internal surface did not give significantly different results [30].

The areal characterization parameters in the current standard for calculating surface roughness parameters, ISO 25178-2 [29], are formulated to accommodate characterization of surfaces manufactured by other methods than the comparably novel method of metal AM. Most of them describe the surface in a summarizing statistical way. There are feature parameters but these features are limited to hills and dales. On a metal AM surface typically other types of features can be found such as weld ripples, spatter and partially melted powder particles, see Figure 5. The issue of characterizing such features is dealt with in a paper by Senin et al. [31]. Here, an algorithmic approach for characterizing such typical features on metal AM surfaces is presented. These types of characterizations can prove to be more useful for AM process development than the traditional areal parameters in the ISO standard.

Another non-traditional type of characterization that can be useful for evaluation of AM surface topography is Specific Surface Area, SSA, which can be calculated as a function of scale of observation [32]. In a paper by Quinsat et al. this technique is used to characterize the total surface area of a part of a component, both external and internal surface area as well as surface area in pores. This multi scale characterization parameter could also prove to be useful for tolerancing if it can be related to the functionality of a product as well as it could be useful for process development if it can be related to different processing conditions.

## 6. Discussion on remaining needs

There are many technologies and methods available to help answer the research questions formulated in section 2.2. In many parts they are mature and some parts they need further development to be industrially useful in the contexts of the examples in section 2.1. A complete chain of methods and accompanying technologies needs to be demonstrated and verified before industrial implementation is feasible. The methods and technologies also need to be easily accessible,

e.g. included in commercially available software packages, to be accepted.

Specific identified remaining needs are:

- A complete methodology for robust use of CT scanning equipment including means for calibration to achieve traceability. This is necessary both for dimensional and surface metrology.
- Standardized ways for surface determination when processing CT data to ensure accuracy.
- A method for constructing datum features on rough free form surfaces needs to be developed and implemented to enable efficient referencing and positioning of AM parts for post processing.
- Relevant characterization parameters for metal AM parts need to be identified and standardized that preferably are related to both functional performance and the manufacturing process.

## 7. Conclusions

In the present paper the ambition has been to present a complete chain of methods and technologies that could be used for inspection of metal AM parts. Two industrial examples were given where specific needs could be identified. It is clear that there are still challenges remaining to be able to fully satisfy those needs.

Many of the remaining challenges seem to be related to processing of data rather than obtaining data. Of course, future measurement equipments with more power and higher accuracy will lead to better possibilities for inspection but the current difficulties are related to issues such as calibration, surface determination and defining the most relevant parameters to tolerance and inspect.

As with any manufacturing process also metal AM processes have limitations and process specific features. However, this should not necessarily have to be considered in the *design phase* but rather in the *pre-production phase* in the Product realization loop.

## Acknowledgements

The authors are grateful for the permission to reproduce figures in accordance with Creative Commons license CC BY-NC-ND 4.0 (Figure 1 and Figure 3).

## References

- [1] Thompson MK, Moroni G, Vaneker T, Fadel G, Campbell RI, Gibson I, et al. Design for Additive Manufacturing: Trends, opportunities, considerations, and constraints. *CIRP Ann - Manuf Technol* 2016;65:737–60. doi:10.1016/j.cirp.2016.05.004.
- [2] Ameta G, Lipman RR, Witherell PW, Moylan SP. Tolerance Specification and Related Issues for Additively Manufactured Products. NIST 2015.
- [3] Ameta G, Witherell PW, Lipman RR, Moylan SP. Investigating the Role of Geometric Dimensioning and Tolerancing in Additive Manufacturing. *J Mech Des-Trans ASME* 2015.
- [4] Witherell P, Herron J, Ameta G. Towards Annotations and Product Definitions for Additive Manufacturing. *Procedia CIRP* 2016;43:339–44. doi:10.1016/j.procir.2016.01.198.
- [5] Moroni G, Petró S, Polini W. Geometrical product specification and

- verification in additive manufacturing. *CIRP Ann - Manuf Technol* 2017;66:157–60. doi:10.1016/j.cirp.2017.04.043.
- [6] Söderberg R, Wärnefjord K, Carlson JS, Lindkvist L. Toward a Digital Twin for real-time geometry assurance in individualized production. *CIRP Ann* 2017;66:137–40. doi:10.1016/j.cirp.2017.04.038.
- [7] Wärnefjord K. Variation Control in Virtual Product Realization - A Statistical Approach. Doctoral thesis. Chalmers University of Technology, 2011.
- [8] Söderberg R, Lindkvist L, Wärnefjord K, Carlson JS. Virtual Geometry Assurance Process and Toolbox. *Procedia CIRP* 2016;43:3–12. doi:10.1016/j.procir.2016.02.043.
- [9] Armillotta A. Tolerance Analysis Considering form Errors in Planar Datum Features. 14th CIRP CAT 2016 - CIRP Conf Comput Aided Toler 2016;43:64–9. doi:10.1016/j.procir.2016.02.101.
- [10] Shakarji CM, Srinivasan V. Optimality Conditions for Constrained Least-Squares Fitting of Circles, Cylinders, and Spheres to Establish Datums. NIST, 2017. doi:924369.
- [11] Stavroulakis PI, Leach RK. Invited Review Article: Review of post-process optical form metrology for industrial-grade metal additive manufactured parts. *Rev Sci Instrum* 2016;87:041101. doi:10.1063/1.4944983.
- [12] Kruth JP, Bartscher M, Carmignato S, Schmitt R, De Chiffre L, Weckenmann A. Computed tomography for dimensional metrology. *CIRP Ann* 2011;60:821–42. doi:10.1016/j.cirp.2011.05.006.
- [13] Townsend A, Pagani L, Scott P, Blunt L. Areal surface texture data extraction from X-ray computed tomography reconstructions of metal additively manufactured parts. *Precis Eng* 2017;48:254–64. doi:10.1016/j.precisioneng.2016.12.008.
- [14] De Chiffre L, Carmignato S, Kruth J-P, Schmitt R, Weckenmann A. Industrial applications of computed tomography. *CIRP Ann* 2014;63:655–77. doi:10.1016/j.cirp.2014.05.011.
- [15] Thompson A, Maskery I, Leach RK. X-ray computed tomography for additive manufacturing: a review. *Meas Sci Technol* 2016;27:072001. doi:10.1088/0957-0233/27/7/072001.
- [16] Müller P, Cantatore A, Andreasen JL, Hiller J, De Chiffre L. Computed Tomography as a Tool for Tolerance Verification of Industrial Parts. *Procedia CIRP* 2013;10:125–32. doi:10.1016/j.procir.2013.08.022.
- [17] Carmignato S, Aloisi V, Medeossi F, Zanini F, Savio E. Influence of surface roughness on computed tomography dimensional measurements. *CIRP Ann - Manuf Technol* 2017;66:499–502. doi:10.1016/j.cirp.2017.04.067.
- [18] Schmitt R, Niggemann C. Uncertainty in measurement for x-ray-computed tomography using calibrated work pieces. *Meas Sci Technol* 2010;21:054008. doi:10.1088/0957-0233/21/5/054008.
- [19] Müller P, Hiller J, Cantatore A, Chiffre LD. A study on evaluation strategies in dimensional X-ray computed tomography by estimation of measurement uncertainties. *Int J Metrol Qual Eng* 2012;3:107–15. doi:10.1051/ijmqe/2012011.
- [20] Hiller J, Genta G, Barbato G, Chiffre LD, Levi R. Measurement uncertainty evaluation in dimensional X-ray computed tomography using the bootstrap method. *Int J Precis Eng Manuf* 2014;15:617–22. doi:10.1007/s12541-014-0379-9.
- [21] Müller P, Hiller J, Dai Y, Andreasen JL, Hansen HN, De Chiffre L. Estimation of measurement uncertainties in X-ray computed tomography metrology using the substitution method. *CIRP J Manuf Sci Technol* 2014;7:222–32. doi:10.1016/j.cirpj.2014.04.002.
- [22] Lifton JJ, Malcolm AA, McBride JW. On the uncertainty of surface determination in x-ray computed tomography for dimensional metrology. *Meas Sci Technol* 2015;26:035003. doi:10.1088/0957-0233/26/3/035003.
- [23] Kraemer A, Lanza G. Assessment of the Measurement Procedure for Dimensional Metrology with X-ray Computed Tomography. *Procedia CIRP* 2016;43:362–7. doi:10.1016/j.procir.2016.02.018.
- [24] Ferrucci M, Leach RK, Giusca C, Carmignato S, Dewulf W. Towards geometrical calibration of x-ray computed tomography systems—a review. *Meas Sci Technol* 2015;26:092003. doi:10.1088/0957-0233/26/9/092003.
- [25] Thompson A, Senin N, Giusca C, Leach R. Topography of selectively laser melted surfaces: A comparison of different measurement methods. *CIRP Ann - Manuf Technol* 2017;66:543–6. doi:10.1016/j.cirp.2017.04.075.
- [26] Townsend A, Senin N, Blunt L, Leach RK, Taylor JS. Surface texture metrology for metal additive manufacturing: a review. *Precis Eng* 2016;46:34–47. doi:10.1016/j.precisioneng.2016.06.001.
- [27] Todhunter LD, Leach RK, Lawes SDA, Blateyron F. Industrial survey of ISO surface texture parameters. *CIRP J Manuf Sci Technol* 2017;19:84–92. doi:10.1016/j.cirpj.2017.06.001.
- [28] Triantaphyllou A, Giusca CL, Macaulay GD, Roerig F, Hoebel M, Leach RK, et al. Surface texture measurement for additive manufacturing. *Surf Topogr Metrol Prop* 2015;3:024002. doi:10.1088/2051-672X/3/2/024002.
- [29] International Organization for Standardization. ISO 25178-2:2012 - Geometrical product specifications (GPS) -- Surface texture: Areal -- Part 2: Terms, definitions and surface texture parameters 2012.
- [30] Townsend A, Pagani L, Blunt L, Scott PJ, Jiang X. Factors affecting the accuracy of areal surface texture data extraction from X-ray CT. *CIRP Ann - Manuf Technol* 2017;66:547–50. doi:10.1016/j.cirp.2017.04.074.
- [31] Senin N, Thompson A, Leach RK. Feature-based characterisation of signature topography in laser powder bed fusion of metals. *Meas Sci Technol* 2017. doi:10.1088/1361-6501/aa9e19.
- [32] Quinsat Y, Lartigue C, Brown CA, Hattali L. Characterization of surface topography of 3D printed parts by multi-scale analysis. *Int J Interact Des Manuf IJIDeM* 2017;1–8. doi:10.1007/s12008-017-0433-9.