

NIST Advanced Manufacturing Series
NIST AMS 100-85

**On Methods of Uncertainty
Quantification in Computational
Modeling and Simulation**

Harmonizing Modeling and Metrology Practices

Vijay Srinivasan

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Abstract

As Computational Modeling and Simulation (CMS) increasingly drives critical engineering and regulatory decisions, establishing model credibility has become paramount. This report presents a comprehensive approach to harmonizing the uncertainty quantification (UQ) methods within the computational modeling standards of the American Society of Mechanical Engineers (ASME) with the empirical metrology practices of the Joint Committee for Guides in Metrology (JCGM). We explain a standardized, risk-based approach to credibility assessment, demonstrating how Verification, Validation, and Uncertainty Quantification (VVUQ) efforts can be scaled in proportion to model risk, which is determined by model influence and decision consequence. To navigate the modern CMS landscape, we categorize models across creation, logic, and transparency perspectives, contrasting mechanistic first-principles approaches with empirical data-driven techniques. Furthermore, this work details the mathematical methods of UQ, comparing the propagation of variances against the propagation of distributions, and highlights recent developments in the physical interpretation of adjoint methods to overcome computational bottlenecks in sensitivity analysis. Finally, we look ahead to the challenges of UQ in Artificial Intelligence (AI) models and the integration of UQ practices into digital twin ecosystems and industrial ontologies. Ultimately, this work provides a unified framework for bridging the gap between computational predictions and physical reality.

Keywords

Adjoint Methods; Computational Modeling and Simulation (CMS); Credibility Assessment; Digital Twins; Metrology; Ontologies; Risk-Based Framework; Sensitivity Analysis; Uncertainty Quantification (UQ); Verification and Validation (V&V).

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1. Introduction

Over the past decade, the credibility assessment of computational modeling and simulation (CMS) has become an active topic for standardization and regulatory guidance. Taking the lead on standardization, the American Society of Mechanical Engineers (ASME) has published a series of standards for the verification, validation, and uncertainty quantification (VVUQ) of CMS. Within these standards, ASME formally defines a computational model as “the representation of the mathematical model such that it can be executed on a computer,” with a simulation being “the act of executing the model” [1, 3]. Table 1Q presents the formal definitions for this hierarchy of modeling terms, progressing from the initial conceptual abstraction down to the final simulation. The practical implementation of these standards, including their extension to emerging technologies like *in silico* clinical trials and data-driven models, has been comprehensively detailed in recent literature [7].

Table 1.Q Formal definitions of modeling and simulation terms according to ASME VVUQ 1-2022 [1].

Term	Formal Definition
Conceptual Model	A collection of assumptions and process descriptions representing a specific system behavior.
Mathematical Model	The mathematical relationships needed to describe the conceptual model.
Computational Model	The representation of the mathematical model such that it can be executed on a computer.
Simulation	The act of executing the model.

On the regulatory front, the U.S. Food and Drug Administration (FDA) recognizes such industry consensus standards and encourages the use of CMS to generate evidence supporting the safety and effectiveness of medical devices [4]. This regulatory outlook extends beyond medical devices into pharmaceutical manufacturing, where the FDA has successfully evaluated and approved numerous applications utilizing process models for drug substance and product process development, monitoring, and real-time control [8]. As the stakes for these CMS-based predictions rise, establishing trust in their outputs has become an imperative, and their credibility assessment has taken center stage.

The ASME series of standards on VVUQ provides a rigorous framework for building this trust and executing the necessary credibility assessment processes for CMS. Verification ensures that the mathematical problems are solved correctly, validation ensures that the correct physical, chemical, or biological phenomena are being mathematically modeled, and uncertainty quantification (UQ) assesses how input variations affect the simulation outputs [1]. However, CMS validation is not an isolated exercise; it intrinsically requires comparing virtual simulation outputs against empirical data gathered from real-world experiments.

This intersection of virtual simulation and physical experimentation is where a disconnect can be perceived. The collection, characterization, and expression of empirical data fall under the domain of metrology—the scientific study of measurement. Metrology is governed by its own strict set of international guidelines, most notably the Guide to the Expression of Uncertainty in Measurement (GUM) maintained by the Joint Committee for Guides in Metrology (JCGM) [9]. For decades, the computational modeling community and the metrology community have operated in parallel, often using different vocabularies and philosophical approaches to handle uncertainty [10]. The central objective of this report is to examine how these two communities view UQ, with the goal of harmonizing the predictive power of computational modeling with the rigorous, empirical foundations of metrology.

To achieve this objective, this report details a comprehensive approach to establishing model credibility. Specifically, this work makes five primary contributions: (1) it examines the conceptual relationship between computational UQ and metrological uncertainty; (2) it demonstrates how VVUQ efforts in CMS can be practically scaled using a risk-based credibility assessment framework; (3) it clarifies the underlying mathematical methods of UQ, highlighting the physical interpretation of adjoint methods to overcome computational bottlenecks; (4) it identifies how the VVUQ paradigm can be extended from mathematical models to classical data models and digital-twin ecosystems; and (5) it identifies opportunities for representing VVUQ information using semantic models and industrial ontologies.

The remainder of this paper is organized as follows. Section 2 introduces the ASME standards and terminologies for VVUQ, establishing the flowchart for computational credibility. Section 3 reviews the JCGM’s foundational guidelines on the expression of measurement uncertainty (GUM) to highlight the metrological viewpoint. Section 4 explores the risk-based credibility assessment framework, illustrating how VVUQ efforts can be scaled in proportion to model risk, which is determined by model influence and decision consequence. Section 5 offers three distinct perspectives on CMS—creation, logic, and transparency. Section 6 details the primary mathematical methods for conducting UQ, specifically the propagation of variances and the propagation of distributions. Section 7 examines sensitivity analysis and recent efforts on the physical interpretation of adjoint methods for overcoming computational bottlenecks. Section 8 looks ahead to the interplay between UQ and the emerging digital twin ecosystem and industrial ontologies. Finally, Section 9 provides concluding remarks on the challenges and future of harmonizing modeling and metrology practices.

2. ASME Standards for VVUQ

Since the early 2000s, ASME has led the development of guidelines and standards for VVUQ across various computational disciplines, from solid mechanics to medical devices. To harmonize the vocabulary across these diverse fields, ASME published the foundational standard *ASME VVUQ 1-2022: Verification, Validation, and Uncertainty Quantification Ter-*

minology in Computational Modeling and Simulation [1]. Table 2 provides the formal definitions of some of the core VVUQ concepts as established in this standard.

Table 2. Formal definitions of core VVUQ terms from the ASME VVUQ 1-2022 [1].

Term	ASME VVUQ 1-2022 Formal Definition
Referent	A reference value (or set of values) against which simulation results or empirical data are compared.
Verification	The process that establishes the mathematical correctness of the computational model with respect to a referent.
Validation	The process of determining the degree to which a model represents the empirical data from the perspective of the context of use.
Uncertainty Quantification (UQ)	The process of generating and applying mathematical models to provide a measure of uncertainty in the empirical data or simulation results.
Quantity of Interest (QOI)	A quantity that provides important information about the system state.
Question of Interest (?OI)	The specific question, decision, or concern that is being addressed.
Context of Use (COU)	The specification of the role and scope of the computational model used to address the question of interest.

While the formal definitions in Table 2 are essential for strict standardization, it is highly instructive to interpret these concepts through practical, engineering-focused language. In doing so, it is important to note that the CMS software system under consideration typically solves algebraic, differential, or integral equations using various symbolic and numerical methods.

2.1. Verification: Solving the Equations Right

In plain terms, verification is performed to determine if the computational model fits the intended mathematical description. It asks the question: *Are we solving the equations right?* To answer this, the process relies on a *referent*—which, in the context of verification, is typically a known exact analytical solution or a highly accurate mathematical benchmark, rather than physical data. For example, if a model simulates heat conduction, the referent for code verification might be the exact mathematical solution to a linear one-dimensional heat equation under specific boundary conditions; the software’s output is then compared against this referent to prove the equations were programmed correctly. Verification is largely a mathematical and software engineering exercise. It is often subdivided into *code verification* (identifying bugs and ensuring the mathematics is correctly im-

plemented in the software) and *solution verification* (estimating numerical accuracy, such as errors introduced by mesh discretization or finite computer precision).

2.2. Validation: Solving the Right Equations

While verification checks the mathematics, validation checks the physics (or chemistry, or biology). Validation is implemented to determine if the model accurately represents the real-world application. It asks the question: *Are we solving the right equations?* This process fundamentally relies on comparing the simulation results against a physical referent—typically empirical data measured from a real-world system.

Every modeling effort begins with a *question of interest*—the specific engineering decision or regulatory concern the simulation is intended to address. Crucially, a computational model in engineering is never universally valid; it is only validated for a specific *context of use* (COU) tailored to answer that question. The COU defines the exact scope, environmental conditions, and operational boundaries within which the model's predictions can be trusted. For example, if the question of interest is, “Will a cardiovascular stent survive ten years of use?”, the intended COU would encompass predicting fatigue life under normal blood pressure pulsations. A structural model might be highly accurate and fully validated for this specific scenario. However, that same model cannot automatically be trusted to answer a different question of interest—such as how the stent will deform if subjected to an extreme, external crush load—because that scenario falls outside its validated context. Ultimately, if the computational model accurately captures the relevant real-world phenomena within its defined COU, it is considered validated for that specific application.

2.3. Uncertainty Quantification: “No Validation Without UQ”

Uncertainty quantification is conducted to determine how variations in the numerical and physical parameters ultimately affect the simulation outcomes. In ASME VVUQ process illustrated in Fig. 1, UQ is not merely an optional add-on; it is the linchpin of the entire credibility assessment [5].

This ASME VVUQ process dictates a powerful underlying philosophy: *there is no validation without UQ*. As illustrated concisely in Fig. 1, to truly validate a model, one must execute parallel branches of investigation: a computational models and simulations branch, and a physical experiments branch. More details on these two branches can be found in [5].

One cannot simply compare a single deterministic simulation output to a single experimental data point. Because both the simulation and the physical experiment possess inherent variations, imperfect knowledge, and measurement limitations, UQ must be rigorously applied to the outputs of *both* branches. Validation, therefore, is achieved only by the rigorous comparison of the computational outputs and the empirical outputs *along with their respective uncertainties*.

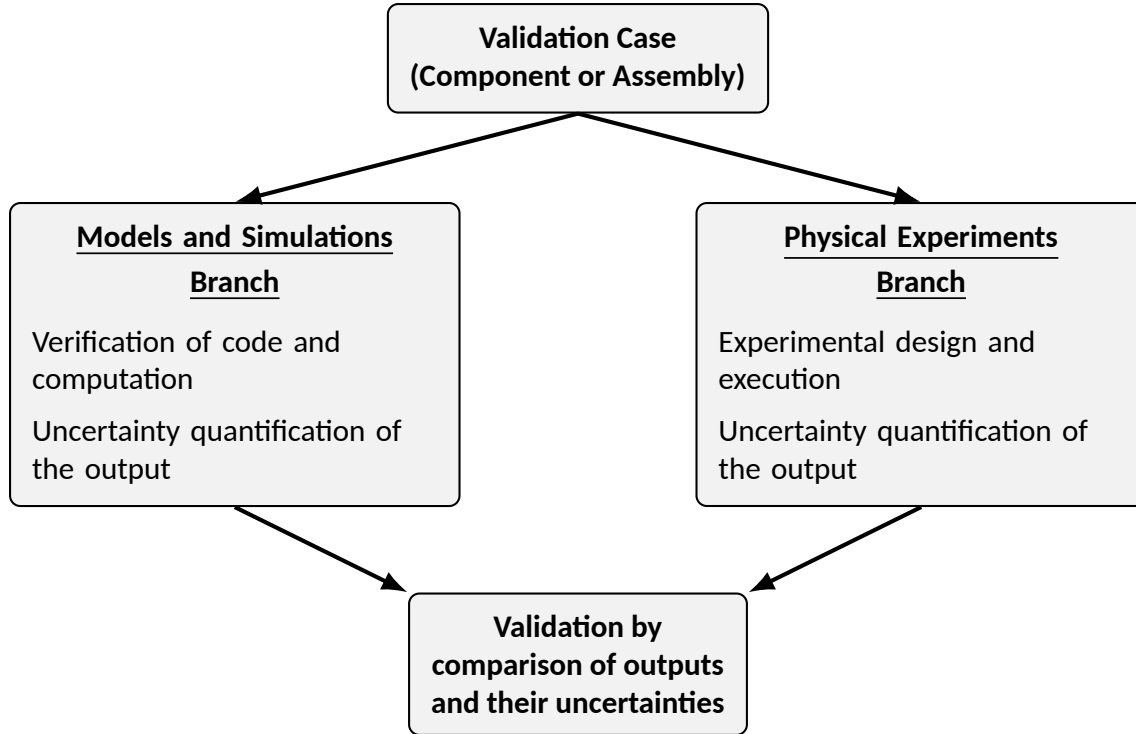


Fig. 1. The ASME VVUQ process workflow. Validation requires the rigorous comparison of outputs *and* their respective uncertainties from both the computational and experimental branches. Adapted from ASME VVUQ 10.2-2021 [5].

Executing this comprehensive validation process can be highly resource-intensive. A practical solution to this challenge is to scale the rigor of the VVUQ activities in proportion to the risk associated with the CMS's intended use. This approach is discussed in detail in Section 4 on the risk-based credibility assessment of CMS. First, however, it is necessary to examine the right branch of Fig. 1, which addresses UQ from the perspective of experiments and metrology.

3. JCGM on GUM

While the ASME VVUQ standards provide a rigorous framework from the perspective of computational modeling, physical experiments and empirical data collection have long been governed by the strict principles of metrology. To meaningfully compare simulation outputs with empirical data as required by the ASME VVUQ process, we must have a unified, harmonized way to express uncertainty across both domains. Methods for this harmonization can be found in the guidelines established by the Joint Committee for Guides in Metrology (JCGM) [9].

3.1. Background, Scope, and Rationale

The JCGM is an international committee chaired by the Director of the Bureau International des Poids et Mesures (BIPM) and formed by several international organizations, including ISO (International Organization for Standardization) and IEC (International Electrotechnical Commission). In 1997, the JCGM assumed responsibility for maintaining two foundational metrology documents: the *International Vocabulary of Metrology* (VIM) [2] and the *Guide to the Expression of Uncertainty in Measurement* (GUM) [9]. While the GUM serves as the overarching international framework, national metrology institutes have adapted its principles for practical application. For instance, NIST Technical Note 1297 was originally established to standardize the reporting of NIST’s own measurement results, but it has since become a widely adopted guide for evaluating and expressing uncertainties across industry and academia in the United States [11].

The primary rationale for the GUM is to establish general rules for evaluating and expressing uncertainty in measurement across a broad spectrum of applications, ranging from the shop floor to fundamental research. Because measurement results are used to make informed decisions in health, safety, commerce, and science, providing a standardized statement of credibility—expressed as measurement uncertainty—is strictly required. Crucially for the computational modeling community, the GUM explicitly lists the “comparison of model outputs and experiments” and “evaluating the validity of models” as key situations where measurement uncertainty is of critical importance.

3.2. Formal Definitions in Metrology

Just as ASME strictly defines VVUQ terminology, the JCGM relies on the VIM to define core metrological concepts. Table 3 provides the formal definitions of some of these fundamental terms as summarized in VIM [2].

Table 3. Formal definitions of some core metrology terms [2].

Term	JCGM VIM Formal Definition
Measurand	Quantity intended to be measured.
Measurement	Process of experimentally obtaining one or more quantity values that can reasonably be attributed to a quantity.
Measurement Uncertainty	Non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used.
Measurement Model	Mathematical relation among all quantities known to be involved in a measurement.

While these definitions originate from physical metrology, the GUM [9] takes a broad view of “measurement,” explicitly recognizing instances where the process is essentially

computational. According to the GUM, measurement uncertainty is the doubt about the true value of the measurand that remains after making a measurement. This uncertainty can be formally expressed in various ways. Commonly used ways include:

- *A standard uncertainty*: The uncertainty of the result of a measurement expressed simply as a standard deviation. It provides a baseline statistical measure of the dispersion of the values that could reasonably be attributed to the measurand.
- *An expanded uncertainty with a coverage factor*: This is obtained by multiplying the standard uncertainty by a coverage factor (often denoted as k). It scales the uncertainty to define an interval expected to encompass a large fraction of the distribution of values.
- *A coverage interval with a stated coverage probability*: An interval constructed around the measurement result that is intended to contain the true value of the measurand with a specific, stated probability (for example, a 95% coverage probability).
- *A probability distribution describing the knowledge about the measurand, often expressed as a probability density function (PDF)*: The most comprehensive expression of uncertainty. Rather than just a single variance or interval, it characterizes the complete state of knowledge by mathematically defining the probabilities for all possible values of the measurand.

3.3. Two Methods of Propagation

To determine the uncertainty of an output quantity (the measurand), the GUM offers methods for propagating the uncertainties associated with the input quantities through the measurement model. The GUM provides two principal methods for propagating this measurement uncertainty:

1. *The Law of Propagation of Uncertainty*: [9] This is an approach that takes the estimates and standard uncertainties of the input quantities and propagates them through a linearized form of the measurement model. In mathematical terms this is actually the *propagation of variances*. Because it relies on linearization, it requires the computation of local sensitivities (the derivatives of the model with respect to its inputs).
2. *Propagation of Distributions*: [12] Often implemented via the Monte Carlo method, this approach takes the joint probability density function (PDF) assigned to the input quantities and propagates them through the measurement model to obtain an approximation of the PDF for the measurand. Unlike the previous method, it does not strictly rely on linearizing the model, nor does it require the explicit computation of local sensitivities.

These two methods—the propagation of variances and the propagation of distributions—form the current metrological bedrock of uncertainty quantification. In Section 6, we will detail the mathematical methods for these two approaches and discuss how they can be practically deployed in CMS.

4. Risk-Based Credibility Assessment of CMS

While the ASME V&V 1-2022 standard provides the vocabulary for computational modeling, and the JCGM GUM provides the mathematical framework for uncertainty, a critical practical question remains for the practitioner: *How much effort should be expended on the V&V process?*

To address this, the ASME V&V 40-2018 standard introduced a risk-based (also known as risk-informed) credibility assessment framework, originally tailored for medical devices [3]. This framework has become highly influential because it has been officially recognized by the U.S. Food and Drug Administration (FDA) which subsequently issued guidance in 2023 to assist industry in applying these concepts to regulatory submissions [4]. By endorsing this standard, regulatory bodies have actively nudged the industry to adopt a risk-based approach to scaling their V&V efforts.

4.1. Formal Definitions of Risk

The ASME V&V 40 framework is anchored by three foundational concepts about model risk. Table 4 provides the formal definitions of some of these terms.

Table 4. Formal definitions of some of risk assessment terms from ASME V&V 40 standard and FDA guidance [3, 4].

Term	Formal Definition
Model Influence	The contribution of the computational model relative to other contributing evidence in addressing the question of interest.
Decision Consequence	The significance of an adverse outcome resulting from an incorrect decision concerning the question of interest.
Model Risk	The possibility that the computational model and the simulation results may lead to an incorrect decision that would lead to an adverse outcome.

4.2. Scaling the V&V Effort

Intuitively, model risk is a combination of model influence and decision Consequence. If a computational model is the sole source of evidence used to make a critical engineering decision, its *model influence* is high. If an error in that decision could result in catastrophic

failure or severe patient harm, the decision consequence is also high. Together, these yield a high *model risk*. As illustrated by the two-dimensional matrix in Fig. 2, the overall model risk scales upward as both influence and consequence increase.

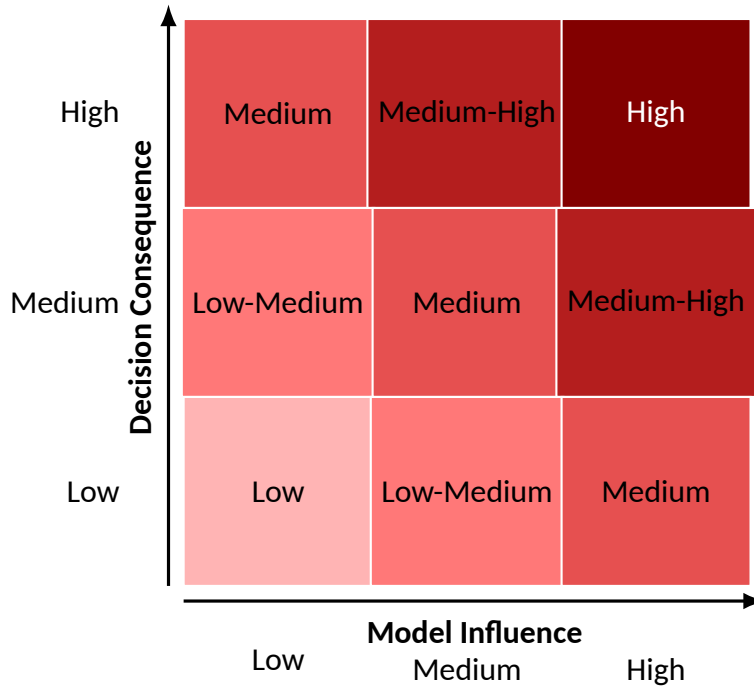


Fig. 2. An illustration of how Model Influence and Decision Consequence combine to determine overall Model Risk. Adapted from FDA guidelines [4].

The core philosophy of this framework is that *model credibility assessment must be commensurate with model risk*. If a model falls into the “Low” risk category, a lighter deployment of the VVUQ processes (such as relying on basic software verification and limited validation with experimental data) may be sufficient. However, if the model falls into the “High” risk category, the practitioner must execute the full, rigorous ASME VVUQ process shown previously in Fig. 1, including exhaustive uncertainty quantification and extensive validation against physical experiments.

4.3. Extension to Artificial Intelligence (AI)

The power of this risk-based credibility paradigm has recently transcended mechanistic, physics-based modeling and seeped into the assessment of purely data-driven models. In January 2026, the FDA and the European Medicines Agency (EMA) jointly published ten *guiding principles of good AI practice in drug development* [13].

As AI models become increasingly prevalent in predicting toxicity, efficacy, and post-market safety, the regulatory consensus is that these technologies must also be scaled according to their specific context of use. Principle 2 of this EMA & FDA joint document

explicitly recommends a “risk-based approach,” requiring that the development and use of AI technologies undergo “proportionate validation, risk mitigation, and oversight based on the context of use and determined model risk.”

This foundational concept of model risk is again put into practice in Principle 8, which calls for “risk-based performance assessments.” This principle recommends that evaluating an AI model means assessing the complete system—including human-AI interactions—“using fit-for-use data and metrics that are appropriate for the intended context of use.” It further requires that this assessment be supported by the “validation of predictive performance through appropriately designed testing and evaluation methods.” Thus, the risk-based VVUQ philosophy pioneered by the computational mechanics community continues to set the standard for establishing trust in broader digital ecosystems.

5. Three Perspectives on CMS

To effectively apply UQ and establish credibility, one must first clearly understand the nature of the computational model being evaluated. Within the modern engineering ecosystem, CMS can be categorized through three distinct perspectives: how the model is created, the underlying logic driving it, and its level of transparency.

5.1. Perspective 1: How the Model is Created

This perspective examines the foundational building blocks of the model:

- *Mechanistic Models*: These are built upon scientific laws and first principles (e.g., physics, chemistry, biology).
- *Data-Driven Models*: These are built empirically, relying on AI or machine learning (ML) algorithms to identify patterns in existing data.

As engineering problems become more complex, the community is increasingly turning to *hybrid models* that occupy the middle ground, leveraging first principles where the physics are well-understood, and using data-driven techniques to model highly complex, highly non-linear material behaviors.

5.2. Perspective 2: The Logic Behind the Model

The creation method directly dictates the logical reasoning the model employs:

- *Deductive Logic*: Mechanistic models are inherently deductive. They start with general, universally accepted laws (like the Navier-Stokes equations for fluid dynamics) and make predictions for specific cases in given scenarios.
- *Inductive Logic*: Data-driven models are inherently inductive. They study several special cases with specific observations (e.g., the training data) and make predictions about other special cases.

5.3. Perspective 3: Transparency of the Model

The third perspective depends on how much access the practitioner has to the inner workings of the CMS solver:

- *White Box (Glass Box)*: The internal equations, algorithms, and mathematical structures are fully accessible and visible to the user.
- *Black Box*: The internal workings are entirely hidden. The user can only observe the outputs generated from a specific set of inputs.
- *Gray Box*: The user has partial access to and knowledge of the internal mechanisms.

A Crucial Distinction: It is a common misconception that all mechanistic models are "glass boxes" and all data-driven models are "black boxes." In reality, these are independent axes. A highly rigorous, first-principles-based mechanistic model can be—and often is—a strict "black box" to the end-user if it is deployed via proprietary commercial software where the vendor restricts access to the source code and internal algorithms. Conversely, a data-driven linear regression model might be a perfectly transparent "white box." Understanding model transparency is vital, as it governs which mathematical methods are available to perform Sensitivity Analysis and UQ.

5.4. Comparing Mechanistic and Data-Driven Models

Table 5 outlines the key differences between pure mechanistic and pure data-driven models across several critical features.

Table 5. Comparison of Mechanistic and Data-Driven Models.

Feature	Mechanistic (Physics-Based)	Data-Driven (Empirical/AI/ML)
Source of Truth	Scientific laws / First Principles	Correlations in Data
Data Requirement	Low volume (for calibration)	High volume (for training)
Interpretability	High (Parameters have physical meaning)	Low (Parameters are abstract weights)
Generalizability	High (Can extrapolate to new conditions)	Low (Interpolation only; may fail outside the "Training Domain")
Validation Focus	Correct physics, chemistry, or biology implementation	Data quality & separation of Training/Test sets

The reliance on different "sources of truth" fundamentally alters how these models are validated and deployed in practice. Because mechanistic models are anchored by physical

laws, their parameters possess physical meaning (e.g., thermal conductivity, elastic modulus), making them highly interpretable. This grounding in physics allows them to confidently extrapolate and make predictions in new conditions that have not been explicitly tested. Consequently, their data requirements are relatively low, typically limited to small datasets needed for baseline calibration.

In stark contrast, data-driven models rely entirely on the correlations found within their data sets. This requires high volumes of data for training. Because the model is building mathematical relationships rather than physical ones, its parameters are abstract weights, resulting in low interpretability. Most importantly, data-driven models possess low generalizability: they are highly effective at interpolating within their training domain, but generally fail when asked to extrapolate outside of those established bounds. Therefore, the validation of an AI model relies heavily on ensuring impeccable data quality and strict separation between the training and testing datasets.

6. Mathematical Methods for Uncertainty Quantification

To bridge the modeling and metrology practices, we must dive into the underlying mathematics of UQ. While the JCGM GUM encompasses various techniques, the propagation of measurement uncertainty generally relies on a measurement model that relates input parameters to a specific output, which we can designate as the Quantity of Interest (QOI).

In practice, there are two principal mathematical approaches to propagate this uncertainty: the propagation of variances (which the GUM formally refers to as the Law of Propagation of Uncertainty) and the propagation of distributions.

6.1. Propagation of Variances

The method of propagation of variances relies on a linear approximation of how parameter variations affect the QOI. Let the QOI, denoted as Q , be a function of k input parameters, $p_1, \dots, p_k$. At the nominal (mean) values of these parameters, the QOI evaluates to Q_0 .

The variation in the QOI, $Q - Q_0$, can be expressed as a linear approximation:

$$Q - Q_0 = \sum_{i=1}^k S_i \cdot \Delta p_i \quad (1)$$

where S_i represents the *sensitivity* of Q with respect to the parameter p_i , assuming all other parameters are held constant. These individual sensitivities form the Sensitivity Vector, $S = [S_1, \dots, S_k]^T$.

If we know the input covariance matrix, Σ , of the parameters:

$$\Sigma = \begin{bmatrix} \text{Var}(p_1) & \dots & \text{Covar}(p_1, p_k) \\ \vdots & \ddots & \vdots \\ \text{Covar}(p_k, p_1) & \dots & \text{Var}(p_k) \end{bmatrix} \quad (2)$$

we can calculate the variance of the QOI as:

$$\text{Var}(Q) = S^T \Sigma S \quad (3)$$

The standard uncertainty is simply $u(Q) = \sqrt{\text{Var}(Q)}$. The final result is typically expressed as $Q_0 \pm k' \cdot u(Q)$, where the coverage factor k' is usually 2 or 3 (representing approximately 95% or 99% coverage probabilities, respectively, if a Gaussian PDF is assumed for Q).

In summary, executing the propagation of variances successfully requires two mathematical components: the Input Covariance Matrix (Σ) and the Sensitivity Vector (S).

6.2. Propagation of Distributions

An alternative approach to UQ is the propagation of distributions, which entirely avoids the need for computing sensitivities. The Monte Carlo Method (MCM) is the most prominent example of this approach [12].

Instead of a covariance matrix and a linear approximation, MCM begins with a known joint probability density function (PDF) that characterizes the uncertainty of all input parameters. The method proceeds by randomly sampling m points within this k -dimensional parametric space, strictly in accordance with the joint PDF.

For each of the m sampled points, a call is made to the CMS solver. Because the solver is treated purely as a “black box,” the internal physics and sensitivities do not need to be accessible. The m resulting outputs are then compiled into a histogram, which directly approximates the PDF of the QOI. The descriptive statistics of this histogram provide a comprehensive capture of how parametric variability influences the uncertainty of the QOI.

6.3. Comparison of UQ Methods

Both mathematical methods provide valid avenues for UQ, but they rely on fundamentally different assumptions and computational burdens. Table 6 summarizes the comparison between the two approaches.

The primary advantage of the propagation of variances is its computational speed, provided the sensitivity vector can be obtained efficiently; however, its reliance on a linear approximation may falter for highly non-linear models. Conversely, MCM captures non-linear behaviors naturally and requires no access to the solver’s internal sensitivities, but it can be computationally prohibitive due to the high number of calls (m) required to converge on a smooth histogram.

Given these trade-offs, a “good UQ practice” in CMS is to employ both methods when computationally feasible. Using the propagation of variances for estimating the standard uncertainty and the propagation of distributions to cross-check the results ensures both efficiency and rigor in the credibility assessment.

Table 6. Comparison of Sensitivity Analysis and Monte Carlo Method for UQ.

Propagation of Variances (using Sensitivity Analysis)	Propagation of Distributions (using Monte Carlo Method)
Depends on the covariance matrix of the input parameters	Depends on the joint PDF of the input parameters
Requires the explicit computation of sensitivities	Does not need computation of sensitivities
Assumes a linear model for the variation in the QOI	Does not assume a linear model for the variation in the QOI
Assumes a PDF-type (e.g., Gaussian) for the QOI to express coverage probability	Outputs a histogram approximating the actual PDF of the QOI
Does not depend on random sampling	Strongly depends on sampling in the parametric space

7. Sensitivity Analysis and Adjoint Methods

While we have established that sensitivity analysis (SA) is the mathematical engine enabling the propagation of variances for UQ in CMS, its utility extends far beyond UQ. In engineering practice, SA is a highly versatile tool because:

- It provides critical gradient information required for product and process optimization, an application that has historically driven much of the methodological development in SA.
- It acts as a diagnostic tool to identify which parameters dominate the system's behavior, highlighting parameters that must be controlled carefully, while isolating parameters that have negligible impact. Research in this area has extended local sensitivity analysis to "global" sensitivity analysis, which evaluates the influence of parameters over their full plausible range of variation within the input parametric space.
- It facilitates the creation of reduced-order or surrogate models, which can replace computationally expensive simulations for rapid, real-time analysis.

7.1. The Computational Bottleneck of Black-Box SA

The practical challenge of SA lies in its computational cost. When a CMS solver operates as a "black box," the analyst has no access to the internal equations and must approximate the sensitivity vector, S , using finite difference methods. To compute the rate of change of the QOI with respect to each parameter p_i , the solver must be executed once at the nominal state, and then executed again for a small perturbation of each parameter. For a model with k parameters, this requires $k + 1$ calls to the CMS solver. In modern systems possessing

thousands of parameters, this brute-force approach can quickly become computationally prohibitive.

7.2. Adjoint Methods for Mechanistic Glass-Box Models

For mechanistic models that are also transparent models—often referred to as “glass box” models—the internal computational methods may be accessible. In these cases, local sensitivities can be computed exactly by differentiating the governing equations. This transparency unlocks the ability to use the *Adjoint Method*, a mathematically elegant technique that bypasses the computational bottleneck of finite differences [14].

The adjoint method is an analytical superpower in computational mechanics: it allows the user to compute the entire local sensitivity vector, S , in a single computational pass, regardless of the parameter count. By solving the primary equation once, and then solving the corresponding adjoint equation once, the sensitivities for every input parameter can be extracted simultaneously.

7.3. Physical Interpretation of Adjoint Methods

While the adjoint method is highly efficient, its mathematical formulation can often seem abstract to practicing engineers. To bridge this gap, NIST has started publishing a series of Advanced Manufacturing Series (AMS) reports aimed at providing interpretability and explainability to adjoint methods.

This series translates the abstract mathematics of adjoint operators into well-known physical principles:

1. *Part I: Self-Adjoint Linear Systems* [15] explores linear steady-state systems like static elasticity and homogeneous heat diffusion, demonstrating how sensitivities can be viewed through the lens of reciprocity. A dominant theme in this report is how the symmetry in mathematical expressions (which is the defining feature of self-adjointness) can be connected to physical principles, such as Maxwell’s reciprocity theorem.
2. *Part II: Non-Self-Adjoint Linear Systems* [16] addresses transient and convective systems, observing how the mathematical development shows that information in the adjoint system flows backward in time or against the physical flow. This phenomenon is acknowledged, more often implicitly, in computational techniques that solve a “final value problem” in adjoint formulations. The laws of thermodynamics can offer some insight here, because the informational entities in adjoint systems behave more like physical entities in the original (forward) systems.
3. *Part III: Nonlinear Systems* [17] extends the methodology to generalized nonlinear natural phenomena, detailing how the adjoint equations operate on the linearized

tangent models of the nonlinear system. This effectively reduces the adjoint formulation for nonlinear systems back to the linear frameworks discussed in the previous two reports [15, 16].

These reports serve a dual purpose in the modern digital ecosystem:

1. They provide the foundational “materials and methods” for software developers building CMS tools. Starting from scratch, they explain the elegant mathematical techniques and the resulting computational efficiencies in detail for CMS software development.
2. They also offer the theoretical explainability required for regulatory and engineering trust when AI-assisted systems write software under human supervision. This is perhaps the most serious need that has emerged in recent times, as more and more programming tasks are carried out by AI systems.

These reports are envisioned to be only the beginning. More explanatory documents are expected in the near future, with an eye towards harmonizing UQ methods for new and emerging modeling and metrology practices.

8. Looking Ahead

One major development awaiting further investment and investigation is the UQ in data-driven systems, led by the explosive growth of AI/ML models in CMS. The urgency of this need is palpable in the recent “good AI practice” guidance jointly issued by EMA and FDA [13]. It is also felt keenly by standards development organizations that are gearing up to take up the credibility assessment of AI models as soon as they complete the task with mechanistic models.

There are also other areas and problems that need more research in UQ. These include the enduring interest in digital twins and the emergence of industrial ontologies. These two areas will now be explored in some detail.

8.1. The Digital Twin Ecosystem

A digital twin is defined as a set of virtual information constructs that mimics the structure, context, and behavior of a natural, engineered, or social system [6]. Crucially, it goes beyond traditional, static simulation by being dynamically updated with data from its physical counterpart, possessing a predictive capability, and informing decisions that realize value. The defining characteristic of a digital twin is the bidirectional interaction between the virtual and the physical.

In 2023, the National Academies of Sciences, Engineering, and Medicine mapped out the core elements of the digital twin ecosystem [6]. Figure 3 illustrates this architecture. It relies on sensor fusion, data assimilation, and inverse problems to drive the flow of information from the physical counterpart to the virtual representation. Conversely, automated

control and decision-making drive the flow of information from the virtual representation back to the physical system. At the center of this loop sits human-in-the-loop decision making, ensuring that computational insights are contextualized by human expertise.

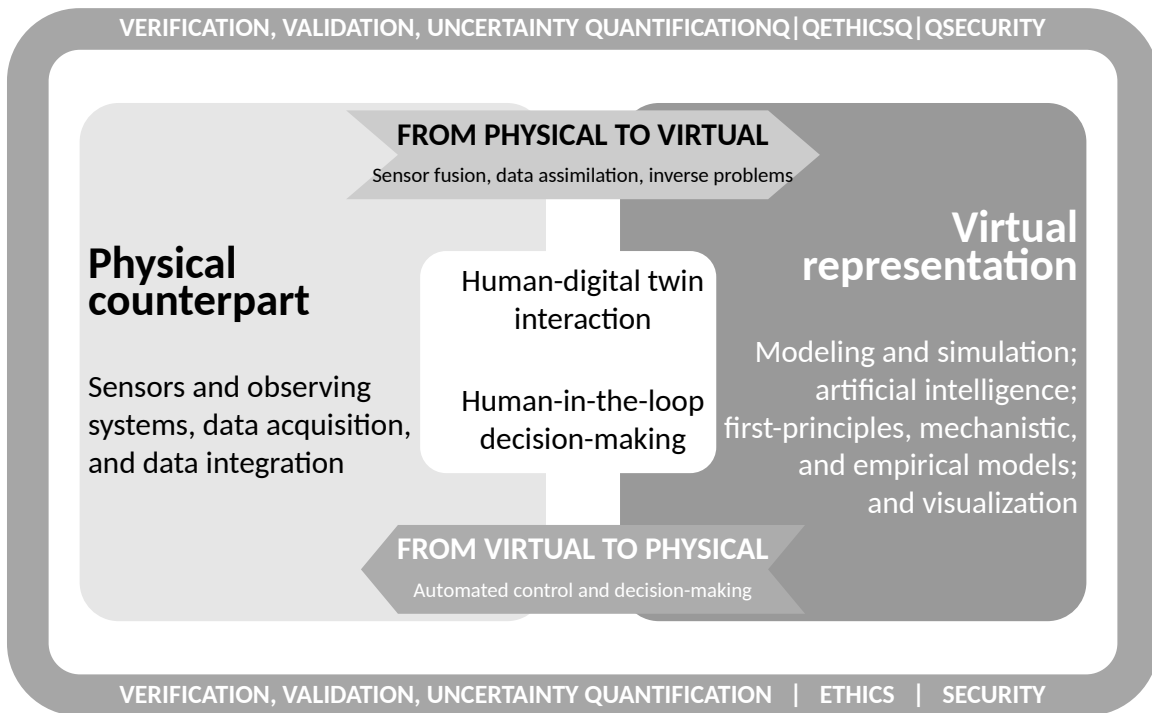


Fig. 3. Elements of the digital twin ecosystem. The framework encompasses a continuous loop of bidirectional interaction between the physical counterpart and its virtual representation, enveloped entirely by Verification, Validation, and Uncertainty Quantification (VVUQ). Recreated and adapted from the National Academies of Sciences, Engineering, and Medicine [6].

Crucially, the National Academies note that because digital twins drive high-stakes decision-making, the entire ecosystem must be structurally enveloped by VVUQ. They have designated VVUQ as one of the four key elements of a digital twin “to build confidence and trust in the digital twin and establish boundaries for the use of simulations.” All the terminology and concepts developed for the credibility assessment of CMS can now be applied to the credibility assessment of the digital twin ecosystem depicted in Fig. 3. As we undertake this exercise, two topics capture our attention, as described below.

8.1.1. VVUQ for Digital Twin Control Systems

One application of a digital twin is to use the bidirectional interaction between the physical and virtual entities to form a “sense-compute-actuate” loop for control of the physical entity. For example, a digital twin of a bioreactor may be used to control the bioreactor by

sensing the state of the physical bioreactor, running a CMS system in its virtual representation, and actuating a pump to feed the necessary nutrients to the bioreactor.

As observed in Section 7, performing a sensitivity analysis of the “open loop plant” will identify the most sensitive parameters that need to be controlled, and this will enable the design of a good control policy for the bioreactor. In general, V&V of control systems is an important topic that deserves more attention.

8.1.2. V&V of Classical Data Models

There has been a flurry of standardization activities around the digital twin framework for manufacturing. ISO has so far published six parts of its ISO 23247 series on this topic [18, 19]. An important feature of this series of ISO standards is the classification of eight types of *observable manufacturing elements* (OME), for which classical data models are defined to enable the creation of Extensible Markup Language (XML) or JavaScript Object Notation (JSON) schemas and their instances. The standardized data for the OMEs can then be exchanged across supply chains and over the lifecycle. They serve as the important metadata for digital twins for manufacturing applications. We refer to such data models as *classical* data models to distinguish them from *semantic* data models defined using ontologies in Section 8.2.

This then raises an important question: *Are classical data models also computational models?* The definitions presented in Table 1 seem to indicate that the answer should be yes, even though no mathematical equation may be solved and the U methods we have discussed thus far do not apply. So we are left with the situation where validation has to be undertaken without any explicit emphasis on U.

To resolve this apparent dilemma, we must broaden our perspective of what constitutes verification and validation for software artifacts that do not solve mathematical equations describing physical phenomena. Fortunately, the advanced manufacturing community has acted on this problem. In establishing guidelines for manufacturing systems, the ASME V&V 50 subcommittee explicitly broadens the V&V scope in its standard [20] by relying on definitions from both ASME V&V 1 [1] and the systems engineering standard ISO/IEC 15288 [21].

Under ISO/IEC 15288, verification is defined as the confirmation that “specified requirements have been fulfilled,” while validation is the confirmation that “the requirements for a specific intended use or application have been fulfilled.” As defined by ASME V&V 50.1, these systems-level definitions apply generically to all artifacts, components, and subsystems—including classical data models.

This critical distinction offers a pathway forward: it shifts the focus of V&V away from the comparison of mathematical and computational outputs against experimental measurements, and toward the rigorous fulfillment of *requirements*. For a classical data model, verification becomes the objective confirmation of structural and syntactic compliance (e.g., verifying that an XML or JSON instance strictly conforms to its schema definitions and data types). Validation, correspondingly, assesses whether the data model fulfills the

requirements of its specific intended use within the digital ecosystem—ensuring it accurately and sufficiently represents the OMEs to support enterprise decision-making.

Through this approach, credibility is established via rigorous requirements engineering and schema validation, circumventing the need for the probabilistic UQ methods traditionally reserved for physics-based solvers. This opens additional research and standardization opportunities in VVUQ for digital twins.

8.2. Industrial Ontologies

As manufacturing systems scale in complexity, the rigid schema structures of classical data models often become insufficient for capturing the dynamic, interconnected nature of modern digital ecosystems. To address this, the community is increasingly turning to semantic data models driven by ontologies. A major catalyst in this space is the Industrial Ontologies Foundry (IOF), which provides a suite of interoperable ontologies specifically designed for industrial applications (e.g., manufacturing) [22, 23]. By aligning with top-level standards such as the Basic Formal Ontology (BFO) [24], the IOF establishes a standardized vocabulary that distinguishes between material entities that persist through time (continuants) and processes that unfold over time (occurents). This semantic foundation allows for the tracking of a product's lifecycle, providing a much richer, machine-readable knowledge graph than traditional XML or JSON schemas.

8.2.1. Ontologies for Metrology and VVUQ

While industrial ontologies excel at knowledge representation, they currently exhibit a significant limitation: they function primarily as metadata layers without intrinsic support for VVUQ. Existing standards can define what a physical parameter represents, but they cannot express the provenance of its uncertainty or link a variance estimate to the specific computational workflow used to generate it.

Addressing this gap represents a challenge for the CMS community. A formal ontology for metrology and VVUQ frameworks—such as the VIM, the GUM, and the terms and concepts established in ASME VVUQ 1-2022—requires translating the philosophical and mathematical definitions of uncertainty, error, calibration, and referents into rigorous, machine-readable logic. This is an immense undertaking that demands consensus across international standards bodies. Yet, this effort is absolutely critical; without machine-readable metadata for risk-based credibility, digital ecosystems for engineering and manufacturing may not provide the traceability, reproducibility, and regulatory readiness required for high-stakes decision-making.

8.2.2. Practical Integration: Semantic Placeholders for UQ

Fortunately, the implementation of CMS does not need to wait for the completion of a formal VVUQ ontology. In parallel with the community-wide challenge, researchers are

developing pragmatic, immediate engineering solutions to capture UQ data. A recent advancement in the biomanufacturing sector exemplifies this approach. Choy et al. (2026) introduced a Biological Systems-of-Systems (Bio-SoS) ontology that explicitly integrates UQQ into process modeling and simulation [25].

Rather than attempting to define a universal ontology of uncertainty, this approach creates semantic “placeholders” for sensitivity analysis (SA) and parameter variances directly within the simulation ontology. Crucially, it treats traceability as a tangible data object within the knowledge graph. It links simulation metrics, such as mean and variance, to their originating input perturbations using explicit semantic properties (e.g., *has Associated Data Structure*). By doing so, this approach elevates UQ and sensitivity analysis from a post-hoc, manual assessment into an automated, intrinsic property of CMS. This practical integration allows the CMS software to self-report its own limitations and uncertainty, offering an effective blueprint for incorporating VVUQ into industrial ontologies today.

9. Concluding Remarks

The increasing reliance on CMS across critical engineering and medical applications has fundamentally shifted how we evaluate safety, efficacy, and performance. As we transition from using simulations as mere design aids to deploying them as primary evidence for regulatory and operational decisions, the question of credibility of CMS becomes paramount. Building that credibility requires harmonizing the dynamic, predictive capabilities of computational modeling (guided by ASME VVUQ standards) with the rigor of metrology (governed by JCGM GUM), in evaluating and expressing UQ.

As we have explored in this report, establishing model credibility is not a one-size-fits-all endeavor. The risk-based credibility assessment paradigm—pioneered by the ASME V&V 40 framework and recognized by regulatory bodies like the FDA—provides a necessary compass. By scaling the rigor of VVUQ to the specific model risk (the intersection of model influence and decision consequence), practitioners can efficiently allocate computational and experimental resources where they matter most.

Furthermore, understanding the nature of the model—whether it is a deductive, glass-box mechanistic model or an inductive, black-box data-driven model—dictates the mathematical tools at our disposal. Whether utilizing the propagation of distributions via Monte Carlo methods, or unlocking the computational efficiency of the propagation of variances through adjoint methods, rigorous methods of UQ ensure that our virtual predictions are grounded in sound mathematics.

Looking forward, the integration between the physical and virtual worlds will continue to evolve. The horizon of engineering and applied science is defined by the digital twin ecosystem, where continuous, bidirectional data flows connect physical assets to their virtual representations in real-time. Simultaneously, the rapid integration of AI/ML into these workflows introduces new layers of complexity. To manage this scale, rigorous VVUQ must serve as both a vital safeguard and the primary mechanism for establishing credibility. Only through this rigor can we instill the trust required for high-stakes decision-making.

Ultimately, harmonizing modeling and metrology practices is not just a regulatory requirement or an academic exercise; it is the foundational requirement for the next generation of scientific discovery and technological innovation. Only through the disciplined application of the UQ methods can we confidently step into an era where digital predictions match physical realities.

References

- [1] ASME VVUQ Standards Committee. *ASME VVUQ 1-2022: Verification, Validation, and Uncertainty Quantification Terminology in Computational Modeling and Simulation*. The American Society of Mechanical Engineers, New York, NY, 2022.
- [2] JCGM. *JCGM 200:2012 International vocabulary of metrology - Basic and general concepts and associated terms (VIM)*. Joint Committee for Guides in Metrology (JCGM), 3rd edition, 2012.
- [3] ASME V&V 40 Subcommittee. *ASME V&V 40-2018: Assessing credibility of computational modeling through verification and validation: Application to medical devices*, 2018.
- [4] U.S. Food and Drug Administration (FDA). *Assessing the credibility of computational modeling and simulation in medical device submissions: Guidance for industry and food and drug administration staff*. Technical report, Center for Devices and Radiological Health, 2023.
- [5] ASME VVUQ 10 Subcommittee. *ASME VVUQ 10.2-2021: The Role of Uncertainty Quantification in Verification and Validation of Computational Solid Mechanics Models*. The American Society of Mechanical Engineers, New York, NY, 2021.
- [6] National Academies of Sciences, Engineering, and Medicine. *Foundational research gaps and future directions for digital twins: Consensus study report highlights*. Technical report, The National Academies Press, Washington, DC, 2023.
- [7] Marc Horner, Jeff Bischoff, and Payman Afshari, editors. *Computational Modeling and Simulation of Medical Devices: Verification, Validation, and Uncertainty Quantification*. Springer, 2026.
- [8] Adam C. Fisher, Sharmista Chatterjee, Rapti Madurawe, Geng Tian, Russi Tran, and Sau L. Lee. FDA regulatory experience with drug manufacturing process models in approved applications. *International Journal of Pharmaceutics*, 702:127249, 2026.
- [9] JCGM. *JCGM GUM-1:2023 Guide to the expression of uncertainty in measurement - Part 1: Introduction*. Guidance document, Joint Committee for Guides in Metrology (JCGM), 2023.
- [10] Ralph C. Smith. *Uncertainty Quantification: Theory, Implementation, and Applications*. Society for Industrial and Applied Mathematics (SIAM), Philadelphia, PA, 2nd edition, 2024.
- [11] Barry N. Taylor and Chris E. Kuyatt. *Guidelines for evaluating and expressing the uncertainty of NIST measurement results*. Technical Report NIST Technical Note 1297, National Institute of Standards and Technology, Gaithersburg, MD, USA, 1994.

- [12] Joint Committee for Guides in Metrology (JCGM). Evaluation of measurement data - Supplement 1 to the "Guide to the expression of uncertainty in measurement" - Propagation of distributions using a Monte Carlo method. Technical Report JCGM 101:2008, BIPM, 2008.
- [13] European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA). Guiding principles of good AI practice in drug development. Technical report, January 2026.
- [14] Michael B Giles and Niles A Pierce. An introduction to the adjoint approach to design. *Flow, turbulence and combustion*, 65(3):393–415, 2000.
- [15] Vijay Srinivasan. On the physical interpretation of adjoint methods for sensitivity analysis, Part I: Self-adjoint linear systems. Technical report, National Institute of Standards and Technology, February 2026. NIST AMS 100-77. <https://doi.org/10.6028/NIST.AMS.100-77>.
- [16] Vijay Srinivasan. On the physical interpretation of adjoint methods for sensitivity analysis, Part II: Non-self-adjoint linear systems. Technical report, National Institute of Standards and Technology, May 2026. NIST AMS 100-79. <https://doi.org/10.6028/NIST.AMS.100-79>.
- [17] Vijay Srinivasan. On the physical interpretation of adjoint methods for sensitivity analysis, Part III: Nonlinear systems. Technical report, National Institute of Standards and Technology, August 2026. NIST AMS 100-84. <https://doi.org/10.6028/NIST.AMS.100-84>.
- [18] Guodong Shao, Simon Frechette, and Vijay Srinivasan. An analysis of the new ISO 23247 series of standards on digital twin framework for manufacturing. In *Proceedings of the ASME 2023 Manufacturing Science and Engineering Conference (MSEC2023)*, New Brunswick, NJ, USA, June 12–16 2023. MSEC2023-101127.
- [19] Guodong Shao, Simon Frechette, and Vijay Srinivasan. Advancements in the ISO 23247 series: Digital thread integration and digital twin composition for smart manufacturing. In *Proceedings of the ASME 2026 International Design Engineering Technical Conference and Computers and Information in Engineering Conference (IDETC-CIE2026)*, Houston, TX, USA, August 23–26 2026. DETC2026-194319.
- [20] ASME VVUQ 50 Committee. Verification and validation of computational modeling for advanced manufacturing. Standard ASME VVUQ 50.1-2025, The American Society of Mechanical Engineers, New York, NY, USA, 2025.
- [21] ISO/IEC/IEEE. Systems and software engineering — system life cycle processes. Standard ISO/IEC/IEEE 15288:2023, International Organization for Standardization, Geneva, Switzerland, 2023.
- [22] Industrial Ontologies Foundry (IOF). Industrial ontologies foundry: Semantic standards for manufacturing. <https://www.industrialontologies.org/>, 2026. Accessed: 2026-09-02.
- [23] Industrial Ontologies Foundry (IOF). IOF ontologies repository. <https://github.com/iofoundry/ontology>, 2026. Accessed: 2026-09-02.

- [24] Robert Arp, Barry Smith, and Andrew D. Spear. *Building Ontologies with Basic Formal Ontology*. MIT Press, 2015.
- [25] Keilung Choy, Keqi Wang, Wei Xie, Ana Nikolov, Jinxiang Pei, Milos Drobnjakovic, Vijay Srinivasan, Fuqiang Cheng, and Boonserm Kulvatunyou. A biological systems-of-systems ontology for multi-scale biomanufacturing process modeling and simulation. In *Proceedings of the ASME 2026 International Design Engineering Technical Conferences and Computers and Information in Engineering Conference (IDETC-CIE2026)*, Houston, TX, USA, August 23–26 2026. DETC2026-193858.