# Sensitivity Analysis and Uncertainty Quantification for BDT

**Addressing Gaps and Challenges to Successful BDT Implementation:**

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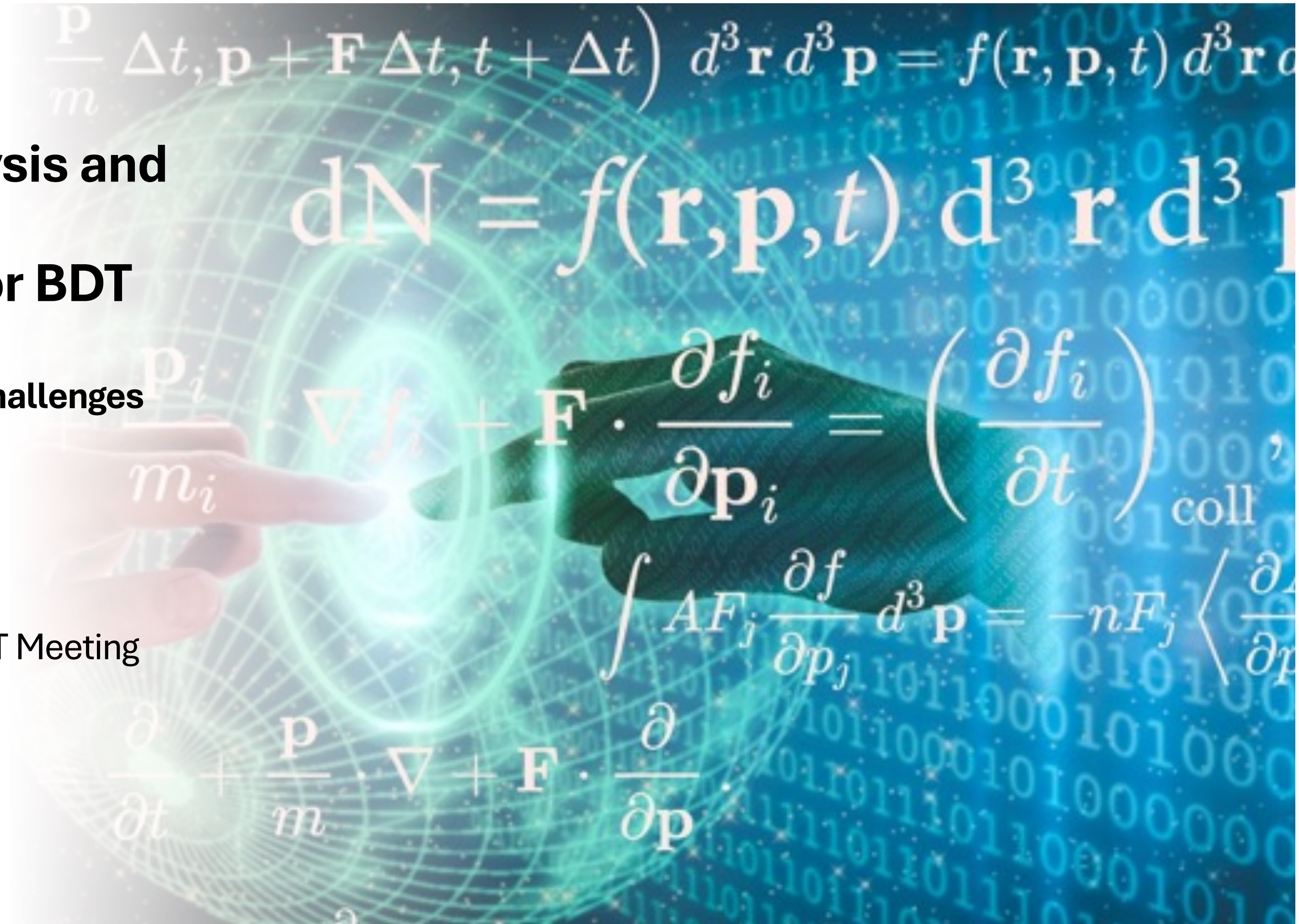
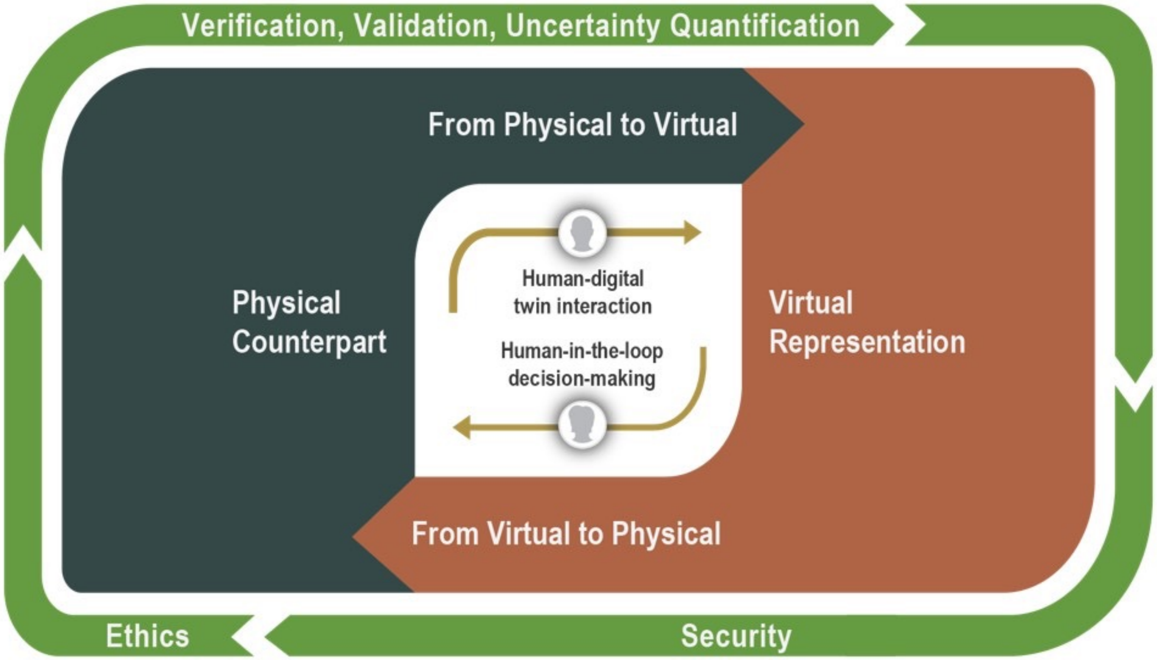


Interagency Modeling and Analysis Group

# NASEM Definition of a Digital Twin

“A digital twin is a set of virtual information constructs that mimics the structure, context, and behavior of a natural, engineered, or social system (or system-of-systems), is dynamically updated with data from its physical twin, has a predictive capability, and informs decisions that realize value. The bidirectional interaction between the virtual and the physical is central to the digital twin."




A Digital Twin is More Than Just Simulation and Modeling

# Biomedical Digital Twin (BDT) Design Challenges

**What needs to be predicted?**
- Levels of complexity
- Levels uncertainty

**What can be modeled and simulated?**
- Mechanistic model development
- AI/ML model development

**What measures need to be captured?**
- For model development
- In real-time

**Is the technology in existence?**
- Appropriate sensors (measurement technologies)
- Computing and storage requirements

**Ethical Issues**
- Privacy, Consent
- Appropriate physiological correlates

“Fit for Purpose”

VVUQ in Dynamic Assets

Bidirectional Real-time Data

Interoperability

Democratized Access

# BDT Design Challenge(s) that can be addressed by this resource

**Sensitivity Analysis (SA) and VVUQ for BDT:**

- Quantify levels of uncertainty in models, parameters and data.
- Quantify role of machine learning in mechanistic models.
- Determine where/when data should be obtained to update models.
- Real-time computing and large-scale storage is continuing challenge.
- Surrogate and reduced-order models critical for real-time implementation – must permit accurate out-of-data predictions.
- Code verification generally necessary for all models.

# My resource

**Sensitivity Analysis/Uncertainty Quantification:**

- Sensitivity analysis employed to determine subsets of influential parameters.
- Model parameters estimated via optimization, statistical inference, or data assimilation techniques.
- Experimental design to guide where to collect future data to best inform models.
- Code verification to establish accuracy; e.g., ”Method of Manufactured Solutions”.
- Uncertainty quantification to guide design, validation, and to assess risk.

# NASEM BDT Design Principles

- Sensitivity analysis provides a broad framework to determine parameters, data, and responses for specific individuals.
- Uncertainty analysis employed to quantify degree to which BDT is effective for considered individuals.
- Associated mathematical/statistical/numerical framework can be scaled based on available data and knowledge.
- Statistical mixed-effects and measure transport provide framework to construct virtual populations.
- Considered framework is inherently modular and can be adapted to accommodate new information, data, and model constructs as they become available.

# “New”math, stats, comp solutions

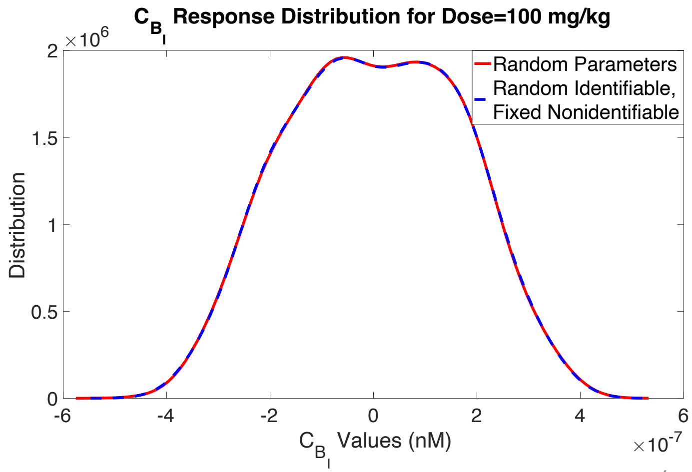
- Highly robust linear algebra and sampling-based sensitivity analysis techniques employed to determine noninfluential model parameters.
- Robust sampling algorithms employed to implement Bayesian inference of model parameters and experimental observation errors.
- Sample from parameter and error distributions to construct prediction intervals for Quantities of Interest; e.g., biomedical response for patient.
- Prediction intervals provide rigorous framework for validating BDTs.
- Prediction Intervals also employed to determine components of mechanistic models to be augmented via data-driven modeling.
- Design of experiments employed to determine where and when to collect additional data to improve predictions for BDTS.
- Reduced-order models employed for real-time implementation of BDTs.

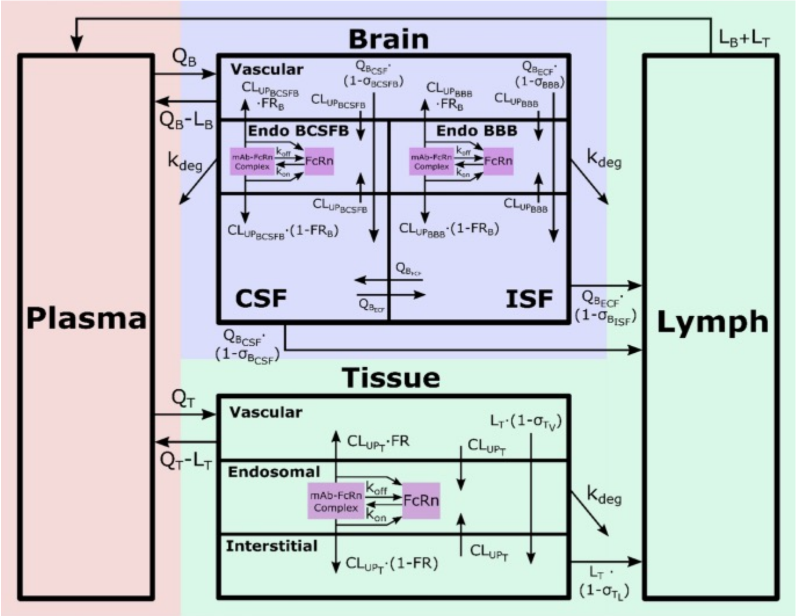
# “New”math, stats, comp solutions

**Example:** Minimal Physiologically-Based Pharmacokinetic (mPBPK) of brain for antibody therapeutics [Bloomingdale, Bakshi, Maass, et al., 2021]

**Note:** 16 ODE, 36 Parameters

**Step 1:** Employ sensitivity analysis to determine and verify 9 identifiable parameters

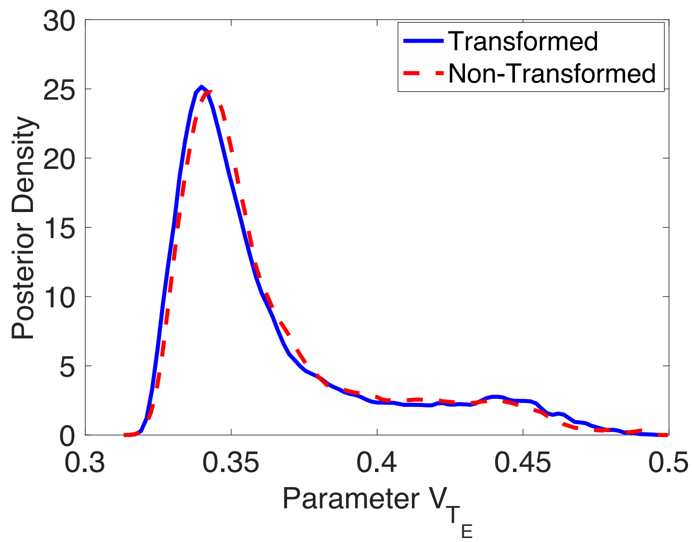


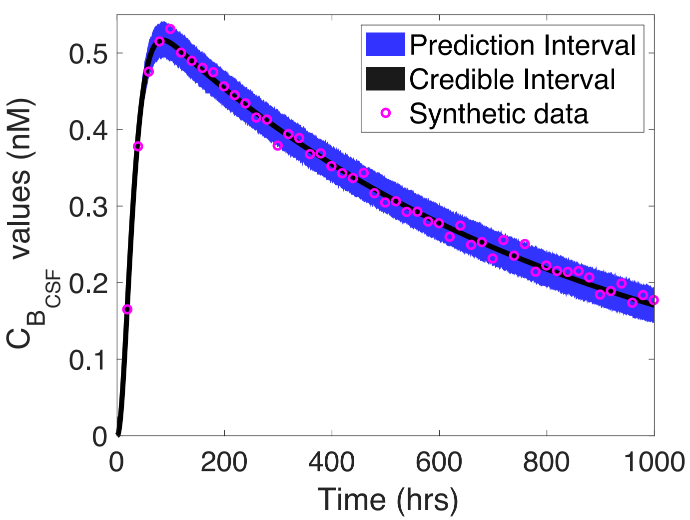
# “New”math, stats, comp solutions

**Step 2:** Compute parameter and response distributions

**Parameter Distribution**




**Prediction Interval for Response**




**Current:** Construct virtual population

# Integrating ethical design

- Use of digital twins may be used to reduce number of clinical trials to those which have proven safe and effective.
- Use of digital twins investigated to test novel and potential high-risk surgery techniques.
- Employ virtual populations to investigate safety, feasibility, and economic viability of considered procedures prior to clinical trials.

# References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# Questions

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