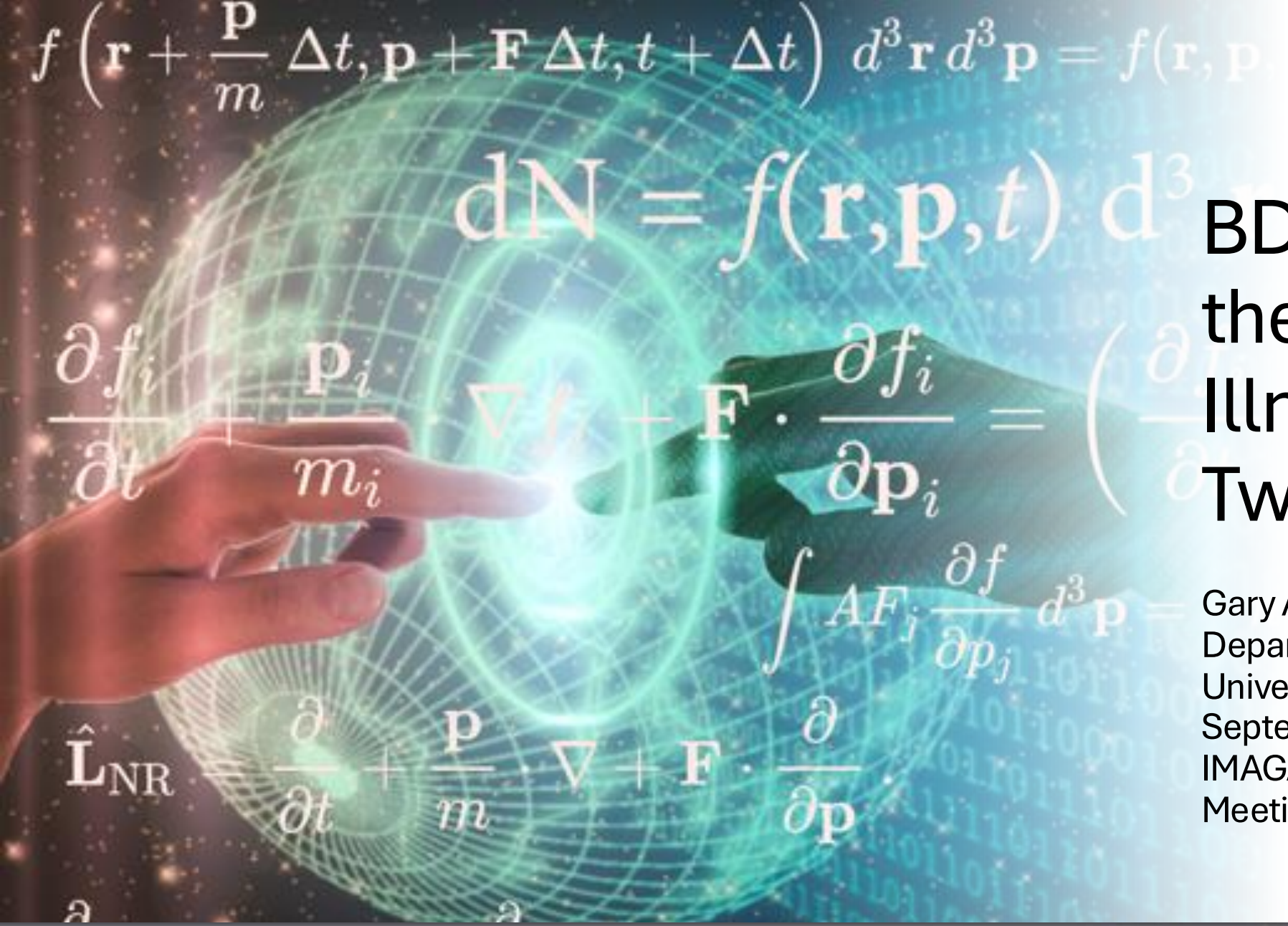

BDT Project: the Critical Illness Digital Twin (CIDT)

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Department of Surgery
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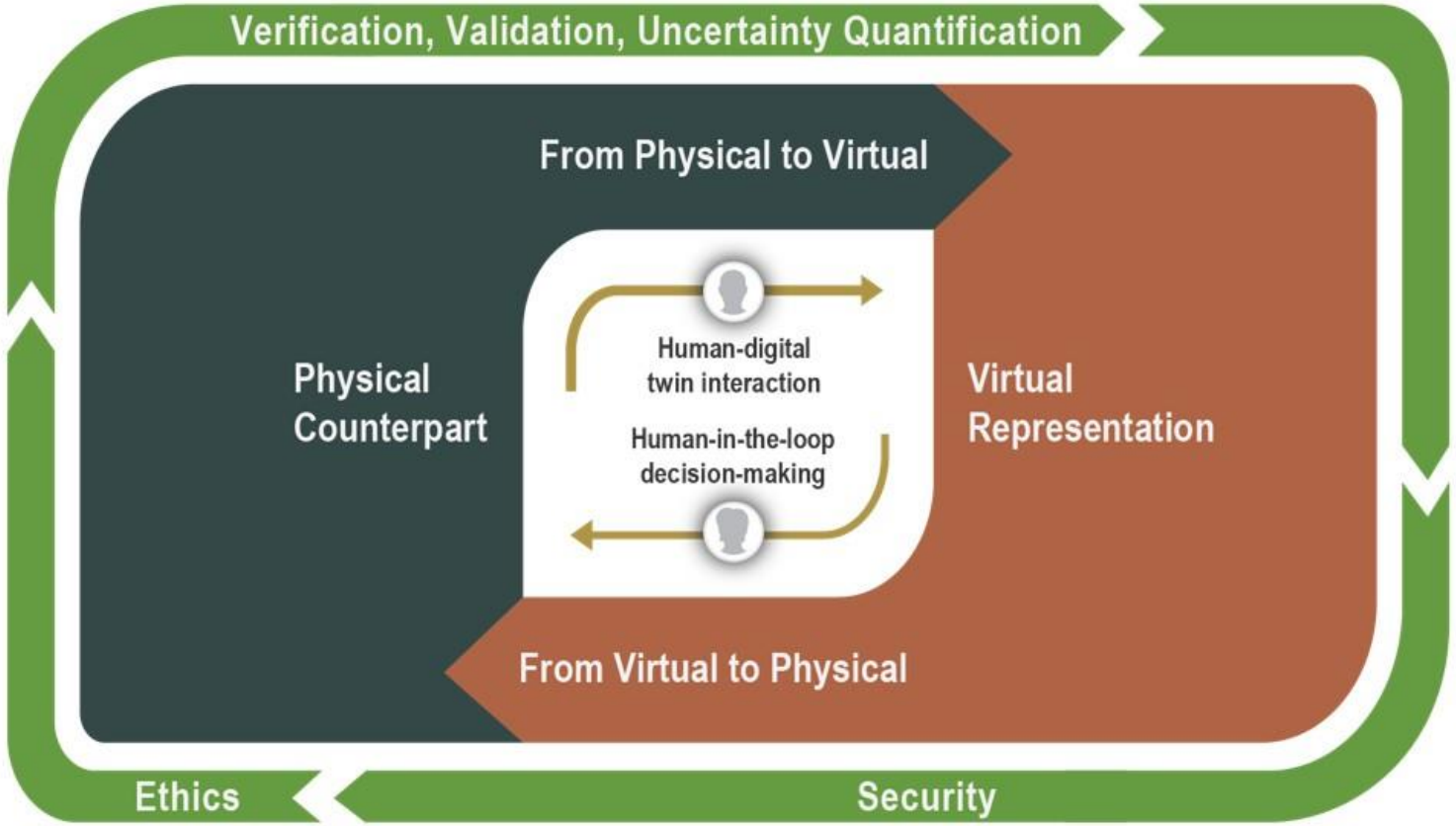
September 30, 2024
IMAG/MSM Teaming4BDT Meeting

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

Problem and BDT Solution: Fit for Purpose

Problem to be solved = Sepsis/Acute Inflammation Critical Illness

- Leading cause of death in ICU
- ~ 11 million deaths/year world-wide => WHO Action Item
- **30-40% Mortality => 2/3 deaths > 72 hrs => "Unexplored state of biology"**
- Treatment = antibiotics and organ support => **No approved therapies that affect underlying biology**

- What is the time scale/"real time"?
  - Decision Timeframe = Hours at finest resolution

Why a BDT for sepsis/acute inflammation driven critical illness?

- No approved therapies for sepsis that affect underlying biology
  - Heterogeneity (between people and time course)
  - Parallel/Redundant Pathways/Processes => Robust
- Rx = Continuous Adaptive Control Problem
  - Updatable sensing of patient state (Bidirectional data flow)
  - Variable multi-model interventions (Control)
  - Computational Guidance

} "Systems of Systems"

- **REQUIRES capabilities offered by Digital Twins**

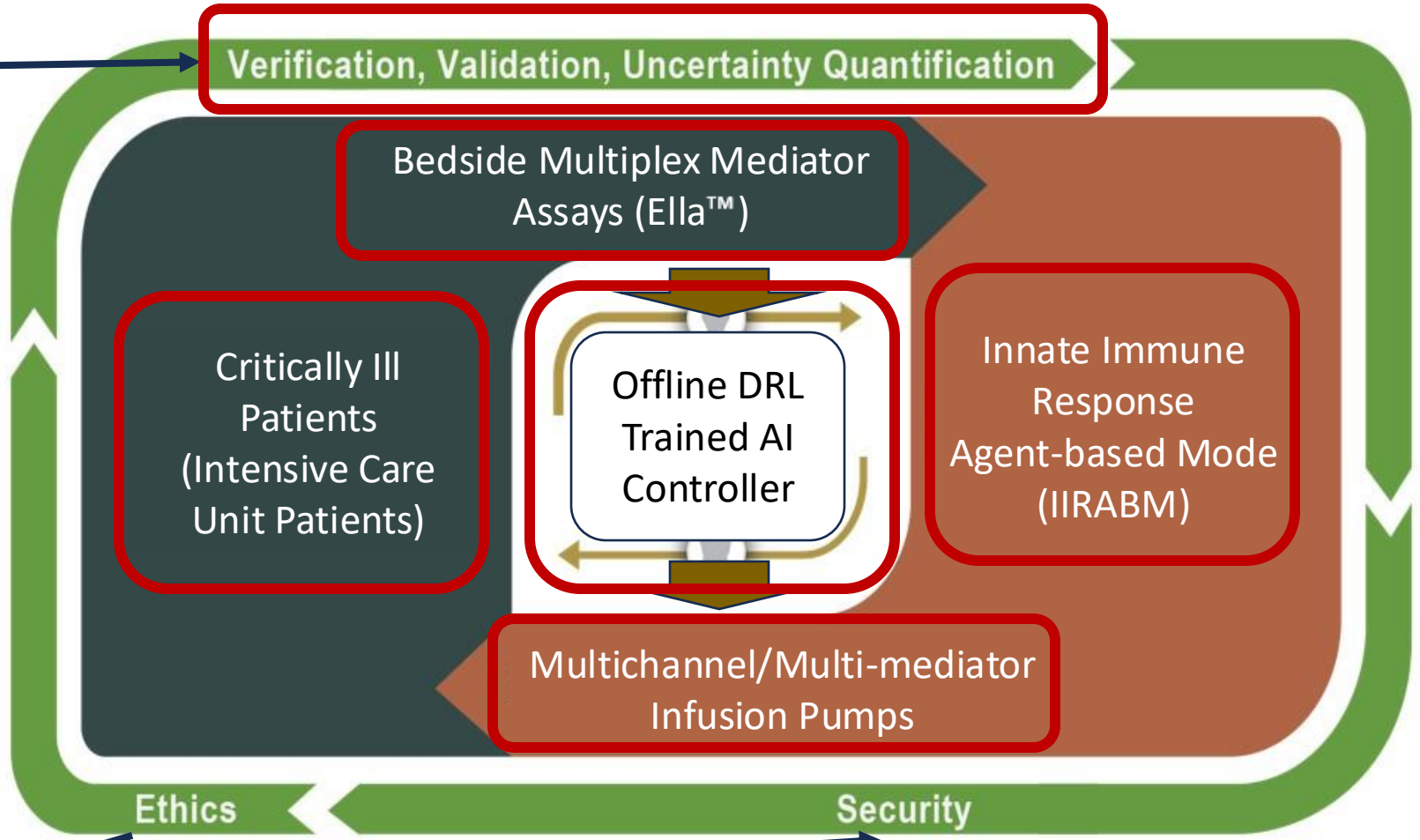
NASEM Loop: Critical Illness Digital Twin

For Virtual Asset:

- Model Rule Matrix (MRM) utilizing Maximal Entropy Principle
- GA/AL Pipeline => Non-falsifiability

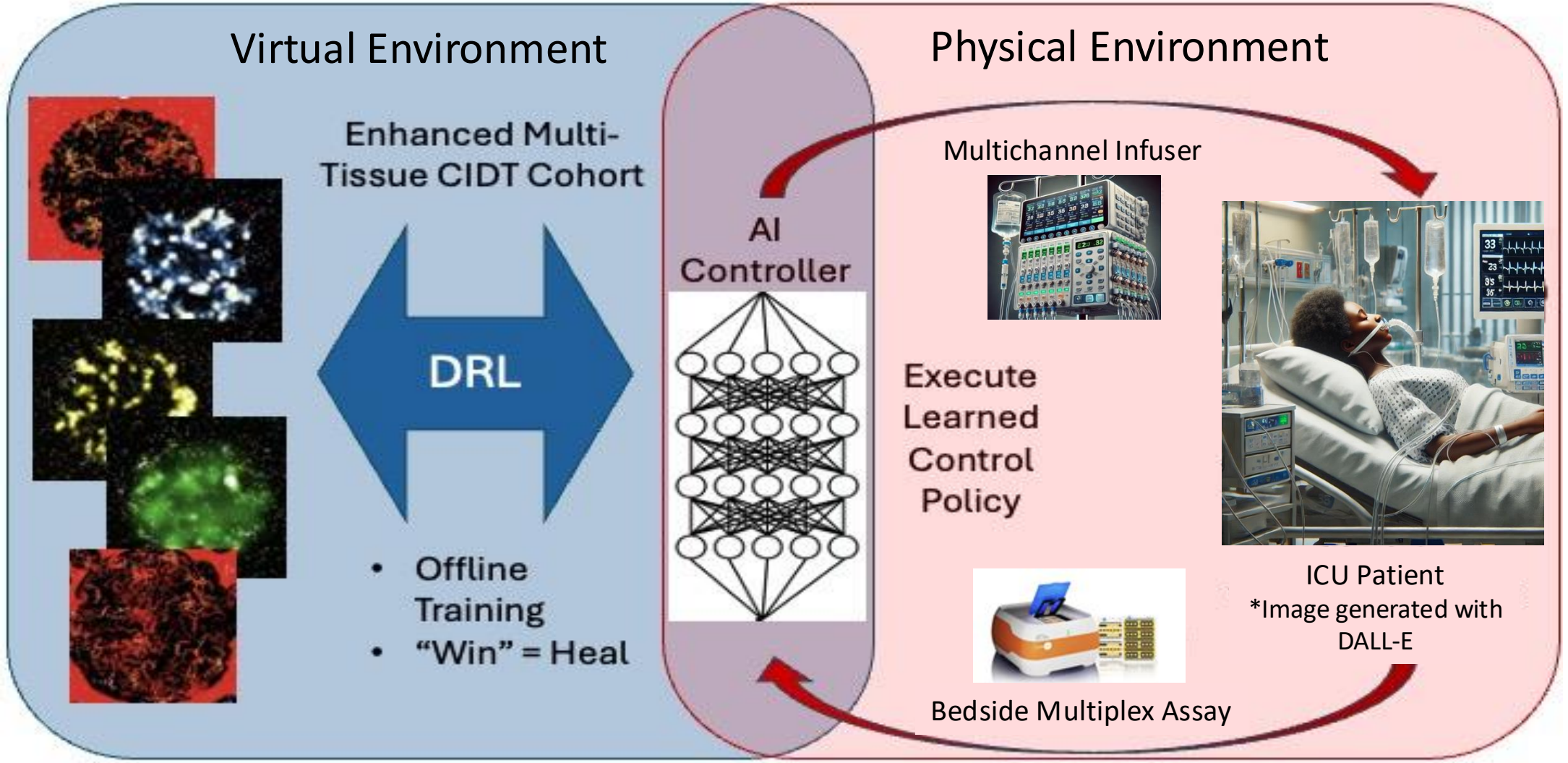
For Overall Cyberphysical System

- Real-world testing in a sufficiently complex animal model that reproduces clinical sepsis



Not relevant to the fit-for-purpose of the CIDT

Physical and Virtual Assets and Their Interaction



Ethical Issues and Team Science Considerations

We do not think Ethical Issues are significant for the CIDT because:

- Data structure focusing on cytokine/mediator state can be separated from HPI
- DRL Control AI pre-trained on simulations representing all possible human states (Maximal Entropy Principle/Shannon Information conservation) => No ownership issues
- Control actions individualized based on sub-selection (ensemble) of population-based control policy => time and situation limited (no different than any other lab data)

Team Science Issues

- Model-driven assay requirements => Physical asset developments (Aptamer, etc.) => Modular sustainability
- Acceptance of novel VUQ approach could be enhanced by formal mathematical description

Summary of "Gaps" Identified

- Fit-for-purpose => very defined/circumscribed problem
- Virtual Asset => Iterative refinement as with any computational model
- Physical Asset ***Future Development Area***=> enhanced tissue specific aptamer sensors (2nd Generation CIDT)
- Trustworthiness => VVUQ =>
  - Of Virtual Asset: ***Development Area = Acceptance of method?*** => may be aided by mathematical formalism of computational workflow?
  - Of entire BDT/cyberphysical system: ***Development Area*** = Real-world testing of theoretical effectiveness => large animal models of sufficient complexity (late-stage sepsis)
- Security and Ethics => Not relevant

Questions

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Resources: For comprehensive description of CIDT see:

arXiv > q-bio > arXiv:2405.05301

Quantitative Biology > Other Quantitative Biology

[Submitted on 8 May 2024 (v1), last revised 16 Jun 2024 (this version, v2)]

A design specification for Critical Illness Digital Twins to cure sepsis: responding to the National Academies of Sciences, Engineering and Medicine Report: Foundational Research Gaps and Future Directions for Digital Twins

Gary An, Chase Cockrell