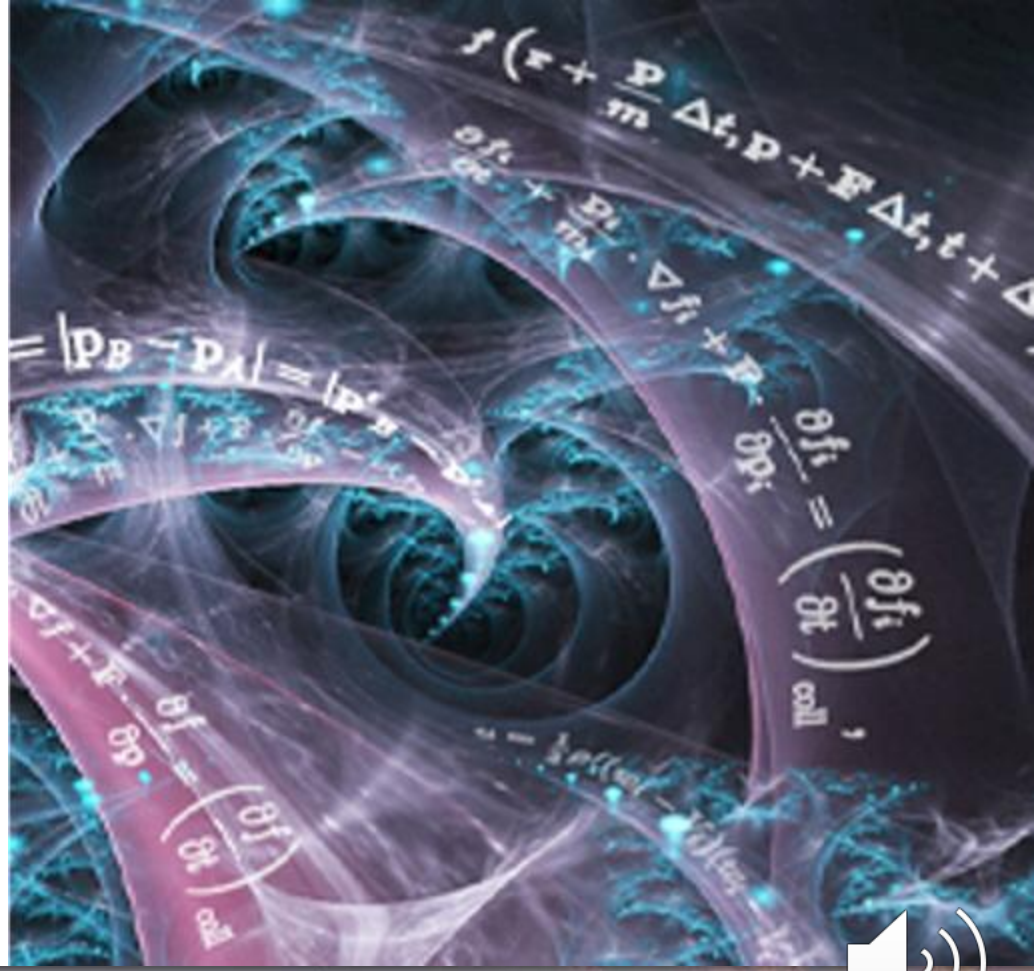
Building around a model: The Critical Illness Digital Twin (CIDT)



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Institution: University of Vermont

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“Teaming4BDT”
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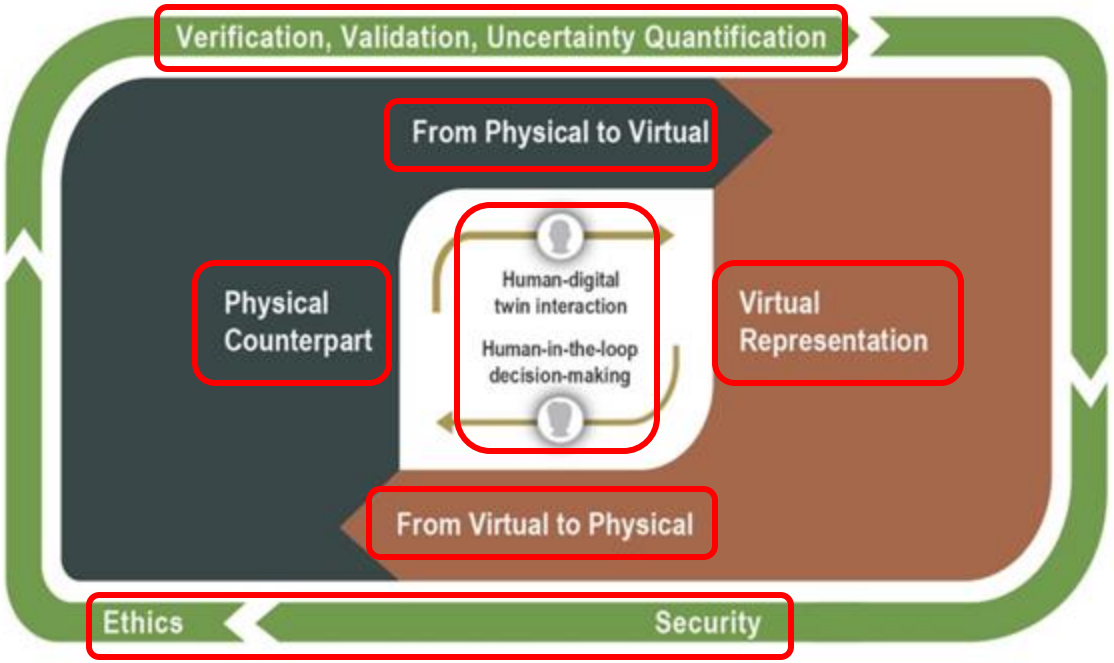
Exercise 1: Filling in the “Loop Diagram”



- Task: Cast a particular BDT project into NASEM Loop: The Critical Illness Digital Twin

“Fit for purpose” => What is the problem?

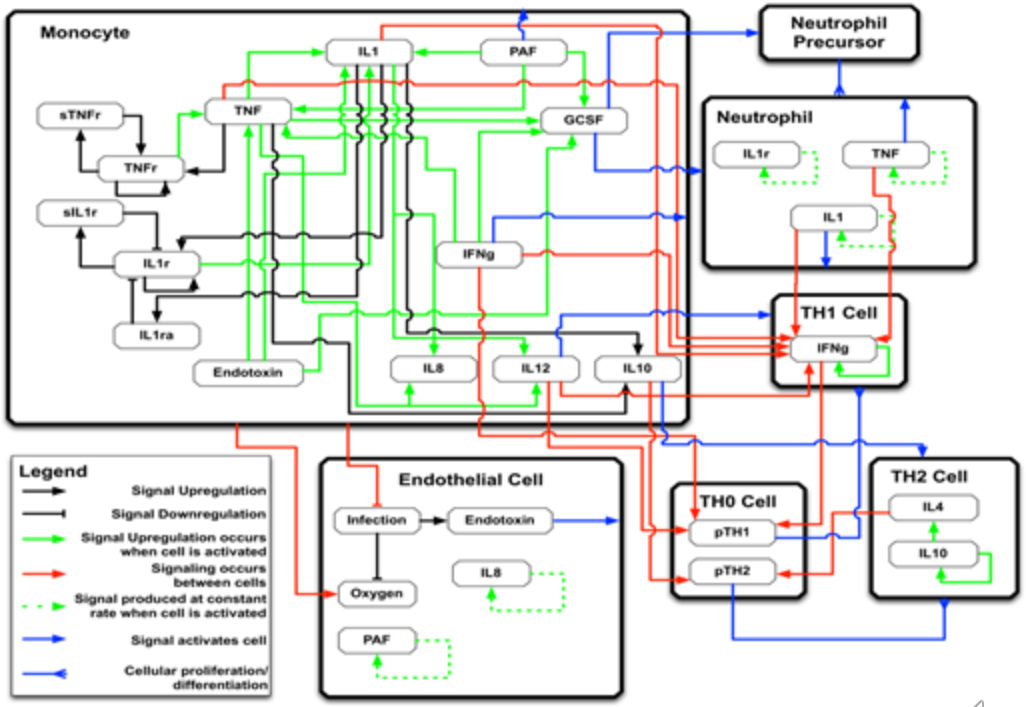
- **Problem to be solved = Sepsis/Acute Inflammation Critical Illness**
  - Leading cause of death in ICU
  - ~ 11 million deaths/year world-wide => WHO Action Item
  - **30-40% Mortality => 2/3 deaths > 72 hrs => “Unexplored state of biology”**
  - Treatment = antibiotics and organ support => **No approved therapies that affect underlying biology**
- What is the time scale/“real time”?
  - Decision Timeframe = Hours at finest resolution

F-f-P cont: Why a BDT for this problem?

- 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
- **REQUIRES capabilities offered by Digital Twins**

What is the virtual asset? = Critical Illness Digital Twin (CIDT)

- Method and Resolution
- Mechanism-based cell-molecular scale agent-based model of acute inflammation: **Innate Immune Response ABM (2004)**
- Simulates systemic inflammation in response to injury/infection
- Protein-mediator based cell-interactions



In silico experiments of existing and hypothetical cytokine-directed clinical trials using agent-based modeling* (Crit Care Med 2004; 32:2050–2060)

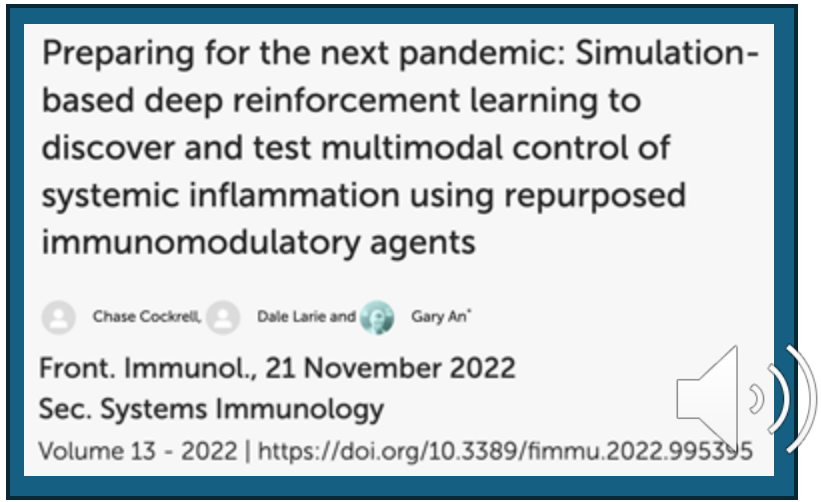
What is the Physical Asset + ongoing bidirectional data link?

- Human to virtual => Source of Data for personalization
- ICU Patients: Measure circulating cytokines/inflammatory mediators => input physical asset state into the virtual asset

- Modalities
  - Existing: Bedside plasma/serum multiplex assay = Ella (Biotechne) 90 min results
  - ***Hypothetical/Future: Aptamer-based continuous monitoring => Potentially Tissue/Organ Specific molecular milieu***

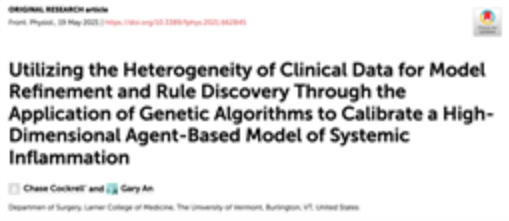
What do you do with the virtual twin output?

- Decision-making/Human in the loop(?) => **Control**
  - Modality: Deep Reinforcement Learning (DRL) on IIRABM to train an AI controller
  - Observation Space = circulating cytokine/mediator levels (obtained via physical asset)
  - Action Space = multi-channel infuser of mediators and monoclonal antibodies (FDA approved biologics)
  - Human in the loop: Time scale 4-6 hours between interventions, can have human in the loop to assess plausibility
  - Theoretical Proof of Concept

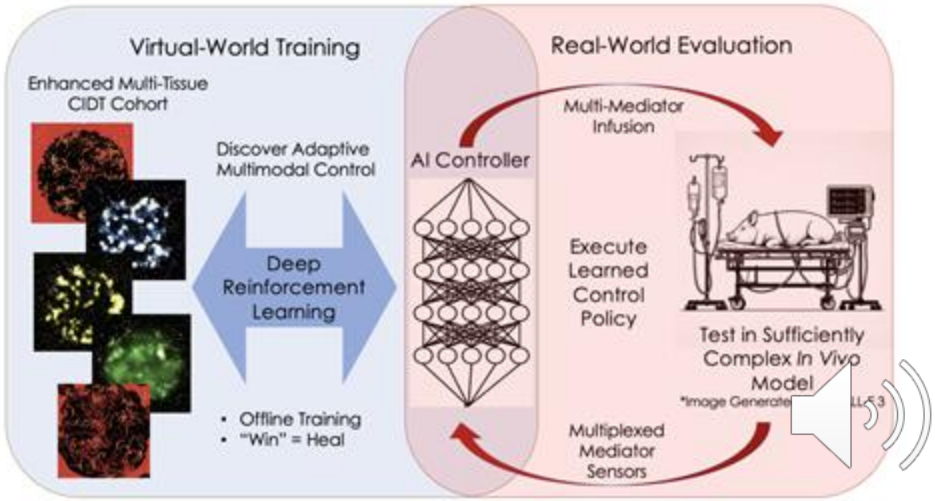


Building Trust => VVUQ

- Validation/UQ: Model-Rule Matrix (MRM) Space
  - ***Novel approach =>*** accounts for perpetual epistemic incompleteness of virtual asset and perpetual uncertainty wrt real-world probability distribution => **Maximal Entropy Principle** in the context of robust control discovery
  - ***Development Gap => benefit from math formalism?***



- For the integrated system?
  - ***Development Gap => Test platform in sufficiently complex in vivo model***



What are the Security/Privacy Issues ?

- None => Rationale:
  - By 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)
  - Control actions individualized based on sub-selection (ensemble) of population-based control policy => time and situation limited (no different than any other lab data)
  - ***Development Gap => Benefit from formal math description of Digital Twin?***

What are the Ethical Issues ?

- No significant issues => Rationale
- Promotes equity by focusing on cytokine/mediator state => agnostic to demographic/ethnicity/sex
- Overcomes lack of representation
- Since AI controller is trained on comprehensive population, there is a very constrained application of specific controls to a specific condition at a specific time, so no ongoing ownership issues

Summary of the “Gaps” Identified?

- Fit-for-purpose => very defined/circumscribed problem
- Virtual Asset => Iterative refinement
- 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

QR Code for PrePrint with Comprehensive Description of CIDT