

# Mathematical Technology for Agent-Based Digital Twins

Workshop on “Mathematics of Cancer: Open Mathematical Problems”

Institute for Pure and Applied Mathematics  
University of California, Los Angeles

Los Angeles, CA  
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## Laboratory for Systems Medicine

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UF Mehrad Lab

Kitware

RDA Working Group on Building Immune Digital Twins

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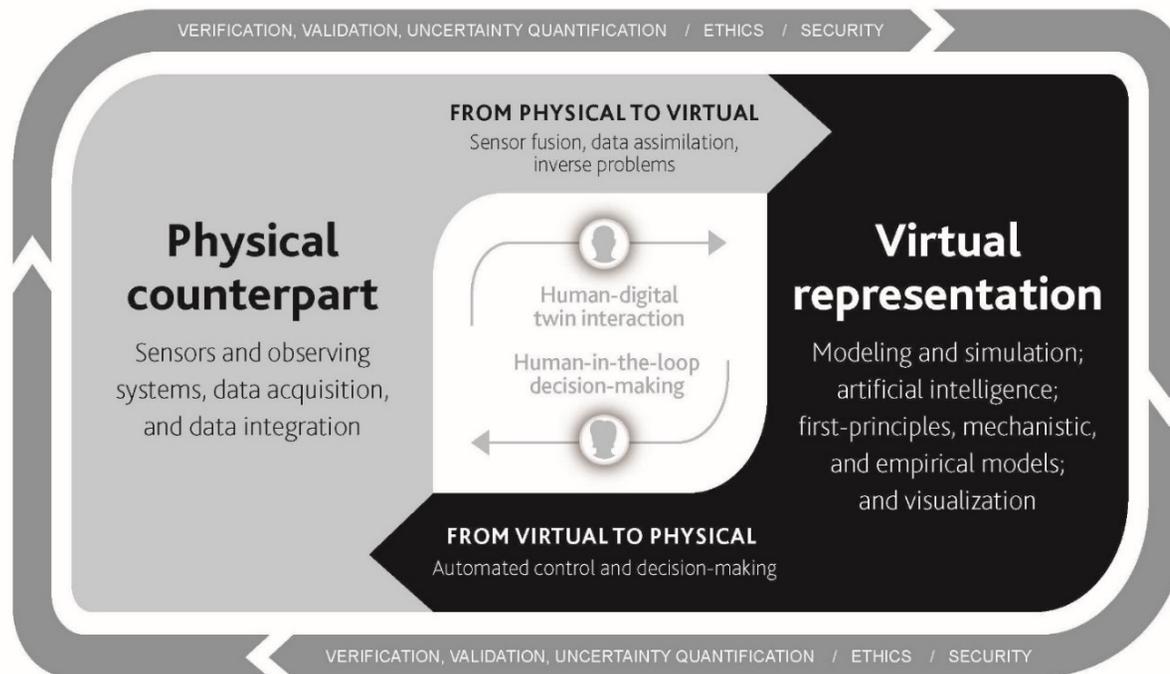
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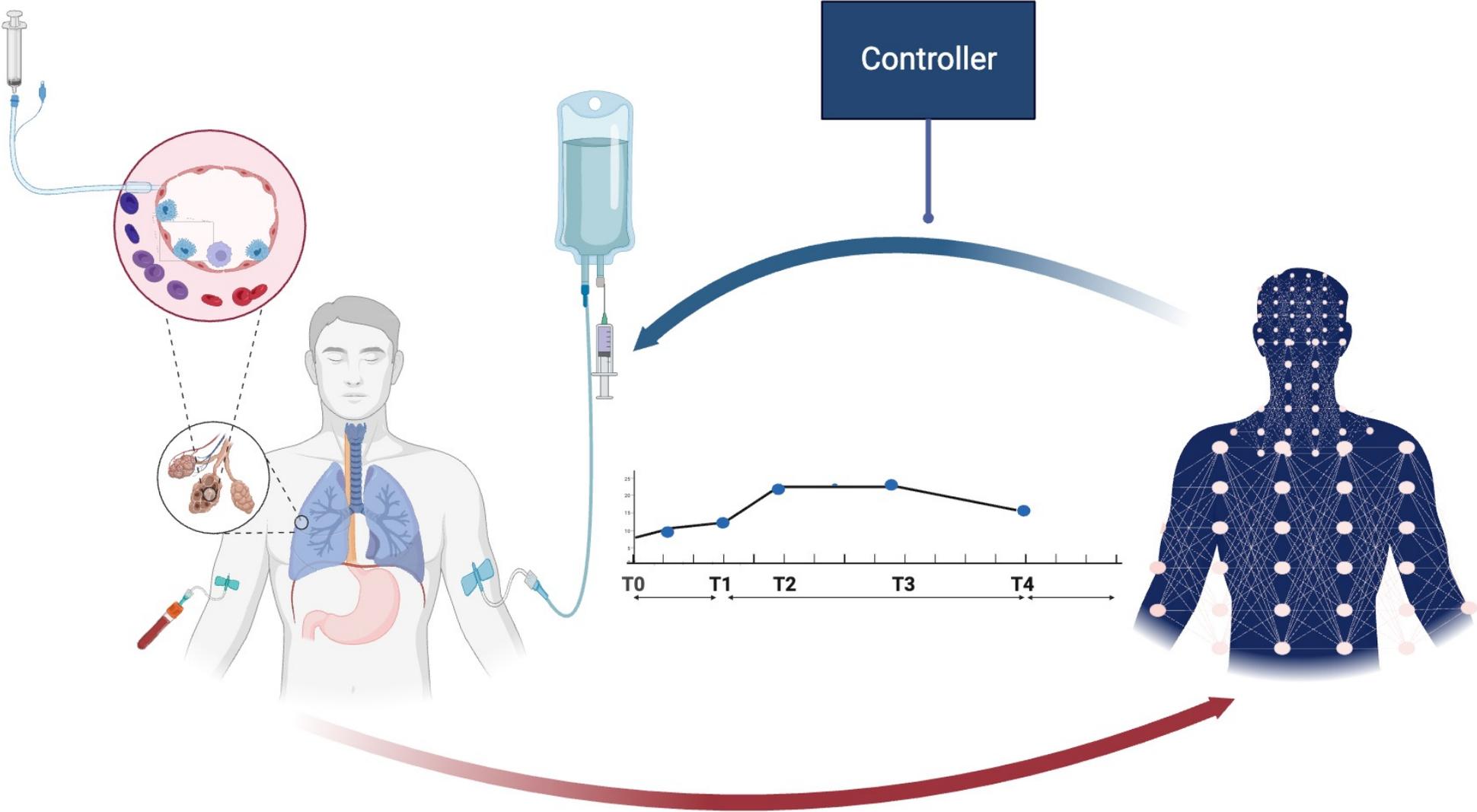
# Digital Twins



National Academies of Sciences, Engineering, and Medicine. 2023. *Foundational Research Gaps and Future Directions for Digital Twins*. <https://doi.org/10.17226/26894>



# Precision Care



## Insulin Pump Therapy

Like a healthy pancreas, insulin pumps deliver one type of insulin. Using your personal pump settings, insulin is delivered continuously (basal) and in larger doses for meals (bolus).

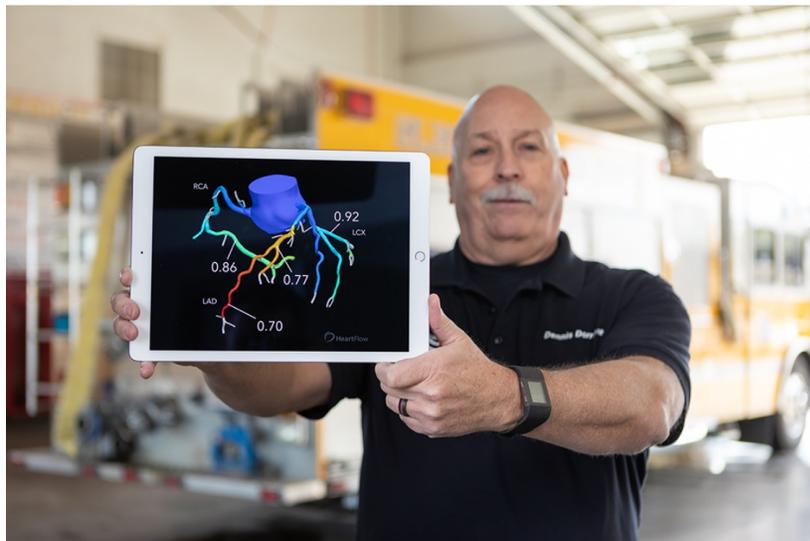


- 1 LARGE TOUCHSCREEN**  
Insulin delivery is personalized using a simple pump touchscreen.
- 2 TUBING**  
Insulin flows through thin, flexible tubing (variety of lengths available).
- 3 INFUSION SET**  
The tubing leads to an adhesive patch and fine tube under the skin.

BENEFITS OF PUMPING



Eviola  
diagnosed  
2012



Bringing together human ingenuity and advanced technology to help combat heart disease, the #1 cause of death.

HeartFlow's non-invasive personalized cardiac test provides unprecedented visualization of each patient's coronary arteries, enabling physicians to create more effective treatment plans for their patients.

# Digital twins in medicine

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Perspective

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## Forum on immune digital twins: a meeting report

Check for updates

Reinhard Laubenbacher<sup>1</sup>✉, Fred Adler<sup>2</sup>, Gary An<sup>3</sup>, Filippo Castiglione<sup>4</sup>, Stephen Eubank<sup>5</sup>, Luis L. Fonseca<sup>1</sup>, James Glazier<sup>6</sup>, Tomas Helikar<sup>7</sup>, Marti Jett-Tilton<sup>8</sup>, Denise Kirschner<sup>9</sup>, Paul Macklin<sup>6</sup>, Borna Mehrad<sup>1</sup>, Beth Moore<sup>9</sup>, Virginia Pasour<sup>10</sup>, Ilya Shmulevich<sup>11</sup>, Amber Smith<sup>12</sup>, Isabel Voigt<sup>13</sup>, Thomas E. Yankeelov<sup>14,15</sup> & Tjalf Ziemssen<sup>13</sup>

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Check for updates

### OPEN ACCESS

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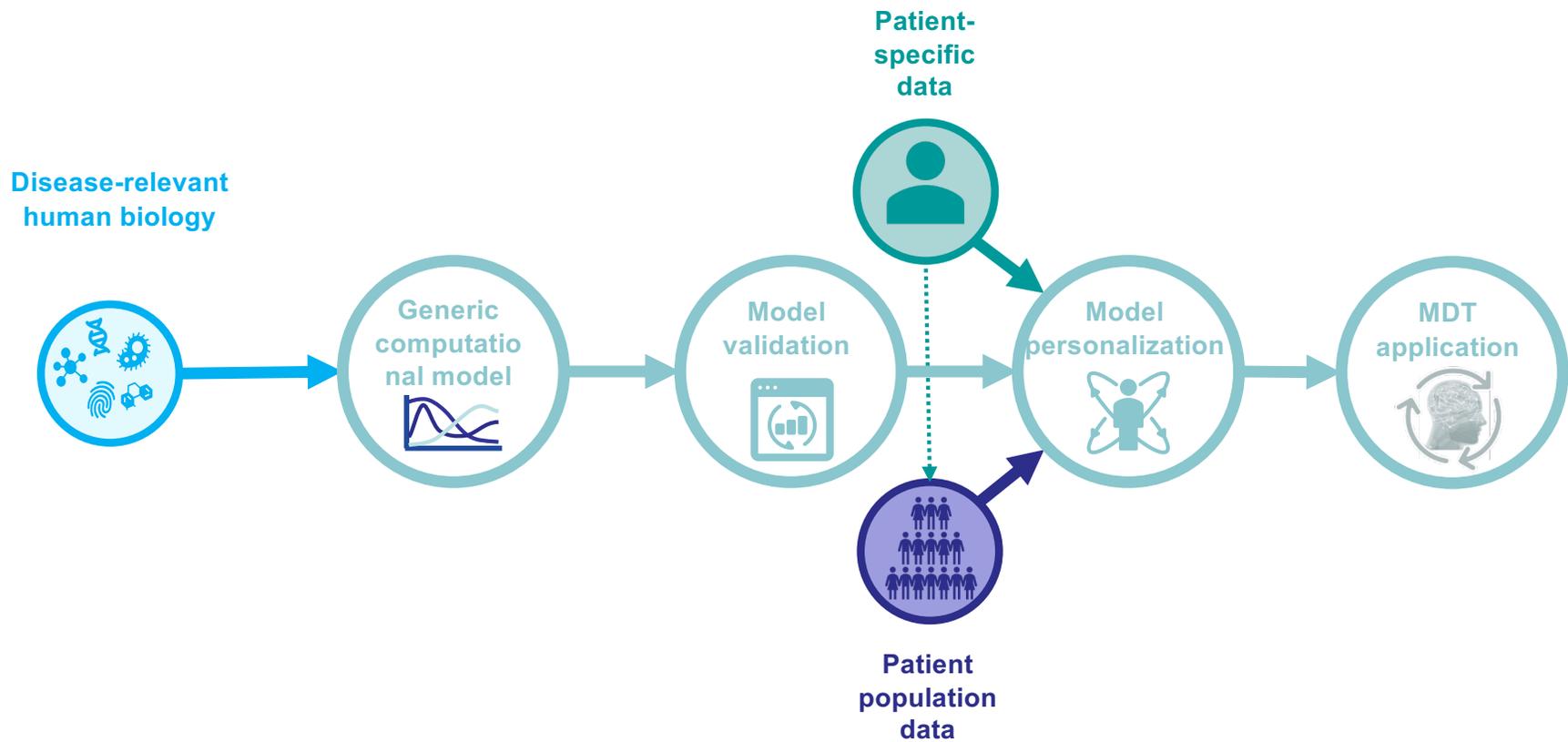
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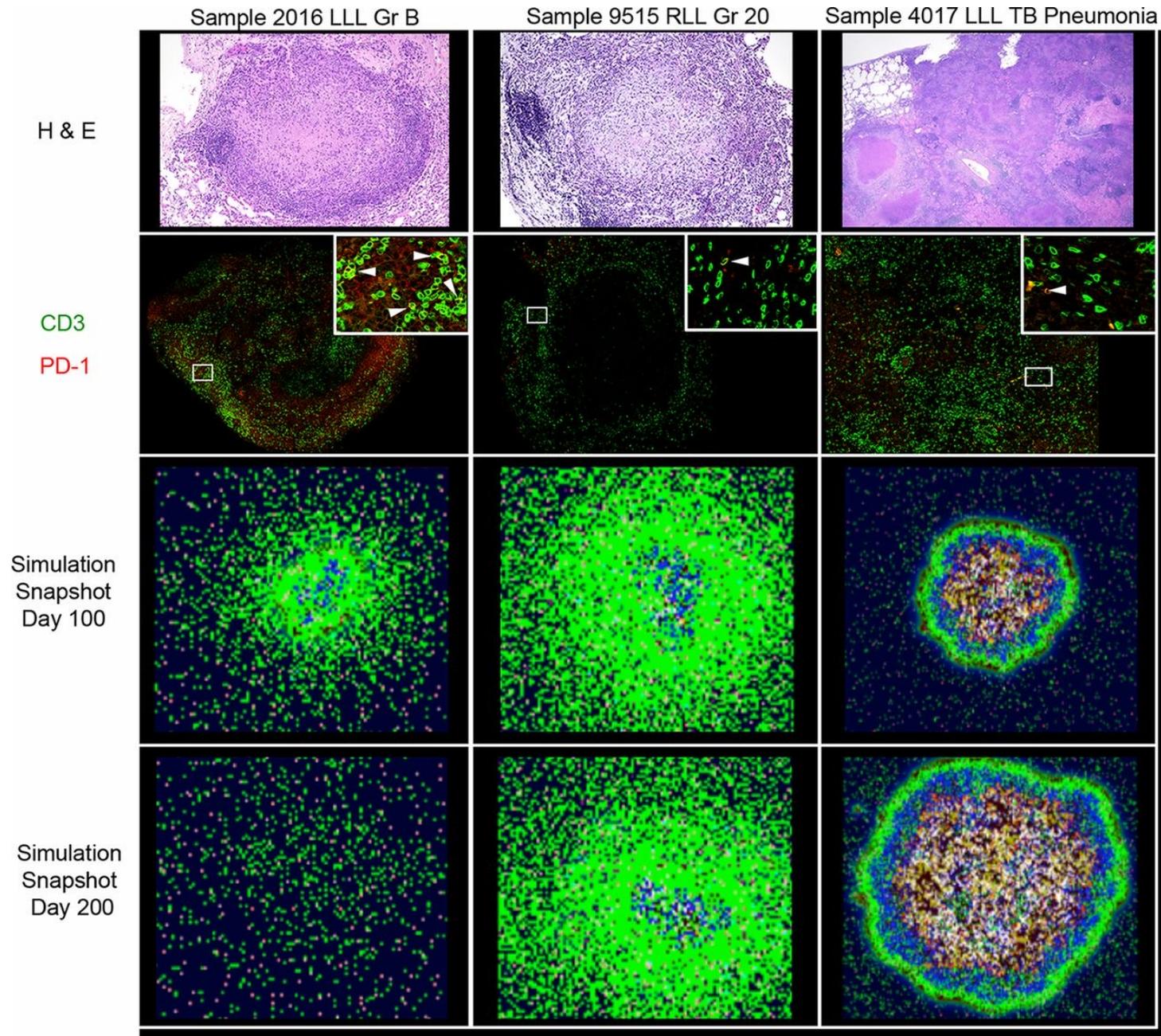
## Toward mechanistic medical digital twins: some use cases in immunology

Reinhard Laubenbacher<sup>1\*</sup>, Fred Adler<sup>2</sup>, Gary An<sup>3</sup>, Filippo Castiglione<sup>4</sup>, Stephen Eubank<sup>5</sup>, Luis L. Fonseca<sup>1</sup>, James Glazier<sup>6</sup>, Tomas Helikar<sup>7</sup>, Marti Jett-Tilton<sup>8</sup>, Denise Kirschner<sup>9</sup>, Paul Macklin<sup>6</sup>, Borna Mehrad<sup>1</sup>, Beth Moore<sup>9</sup>, Virginia Pasour<sup>10</sup>, Ilya Shmulevich<sup>11</sup>, Amber Smith<sup>12</sup>, Isabel Voigt<sup>13</sup>, Thomas E. Yankeelov<sup>14,15,16</sup> and Tjalf Ziemssen<sup>13</sup>





# Agent-based models



# Toward a pneumonia digital twin

## INTERFACE

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### Research



**Cite this article:** Ribeiro HAL, Vieira LS, Scindia Y, Adhikari B, Wheeler M, Knapp A, Schroeder W, Mehrad B, Laubenbacher R. 2022 Multi-scale mechanistic modelling of the host defence in invasive aspergillosis reveals leucocyte activation and iron acquisition as drivers of infection outcome. *J. R. Soc. Interface*

## Multi-scale mechanistic modelling of the host defence in invasive aspergillosis reveals leucocyte activation and iron acquisition as drivers of infection outcome

Henrique AL Ribeiro<sup>1</sup>, Luis Sordo Vieira<sup>1,2</sup>, Yogesh Scindia<sup>1,3</sup>, Bandita Adhikari<sup>4</sup>, Matthew Wheeler<sup>1</sup>, Adam Knapp<sup>1</sup>, William Schroeder<sup>5</sup>, Borna Mehrad<sup>1,†</sup> and Reinhard Laubenbacher<sup>1,†</sup>

<sup>1</sup>Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of Florida, Gainesville, FL, USA

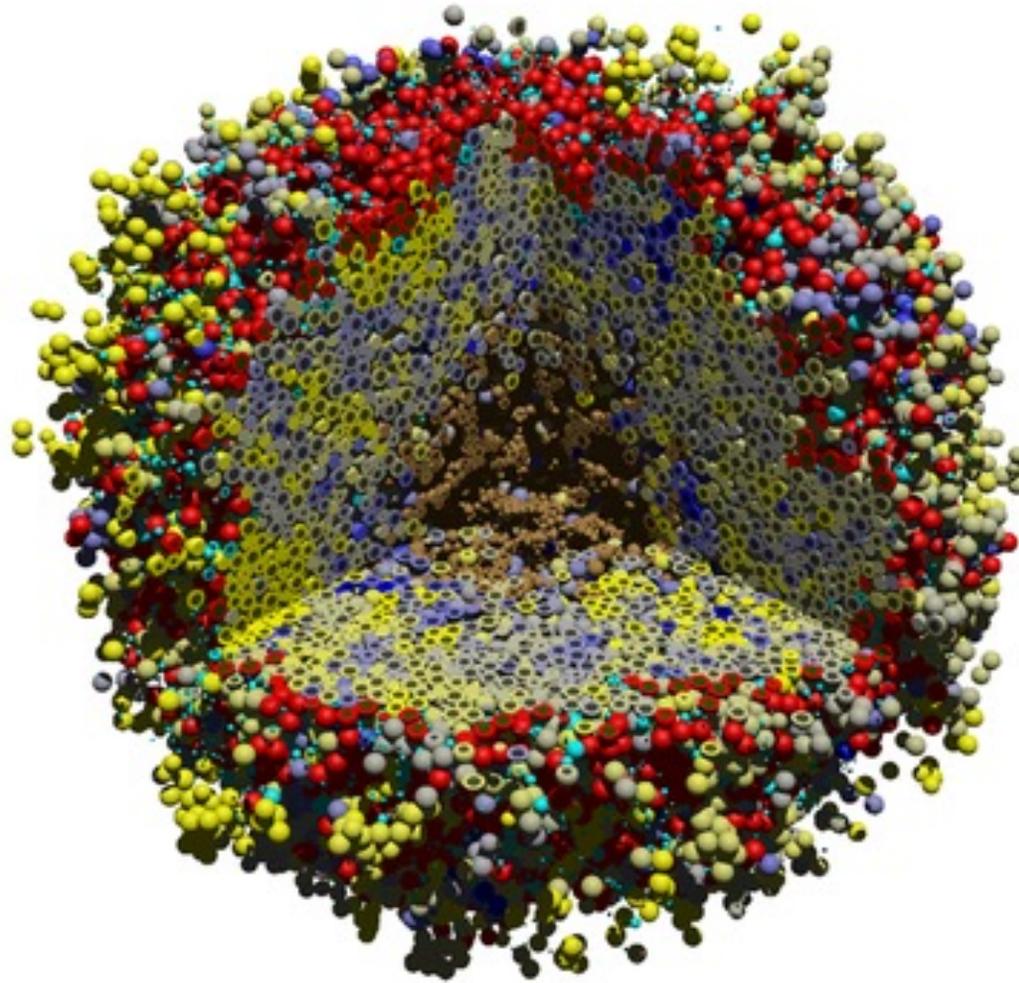
<sup>2</sup>Department of Psychiatry, University of Florida, Gainesville, FL, USA

<sup>3</sup>Department of Pathology, University of Florida, Gainesville, FL, USA

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<sup>5</sup>Kitware Inc., Clifton Park, NY, USA

PhysiCell ([physicell.org](http://physicell.org))



# Control

”Modern control theory, based on differential equations, is not an adequate tool for solving the problems of complex control systems. It is necessary to construct differential equations to trace the input-output paths, that is, to apply a deductive deterministic approach. But it is impossible to use this approach for complex systems because of the difficulty in finding these paths.”

Alexey Ivakhnenko

IEEE Transactions on Systems, Man, and Cybernetics, 1971

METHODS

## Optimal control of agent-based models via surrogate modeling

Luis L. Fonseca<sup>1</sup> <sup>\*</sup>, Lucas Böttcher<sup>1,2</sup> <sup>\*</sup>, Borna Mehrad<sup>1</sup> , Reinhard C. Laubenbacher<sup>1</sup>

**1** Laboratory for Systems Medicine, Department of Medicine, University of Florida, Gainesville, Florida, United States of America, **2** Department of Computational Science and Philosophy, Frankfurt School of Finance and Management, Frankfurt am Main, Germany

PHILOSOPHICAL  
TRANSACTIONS A

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Research

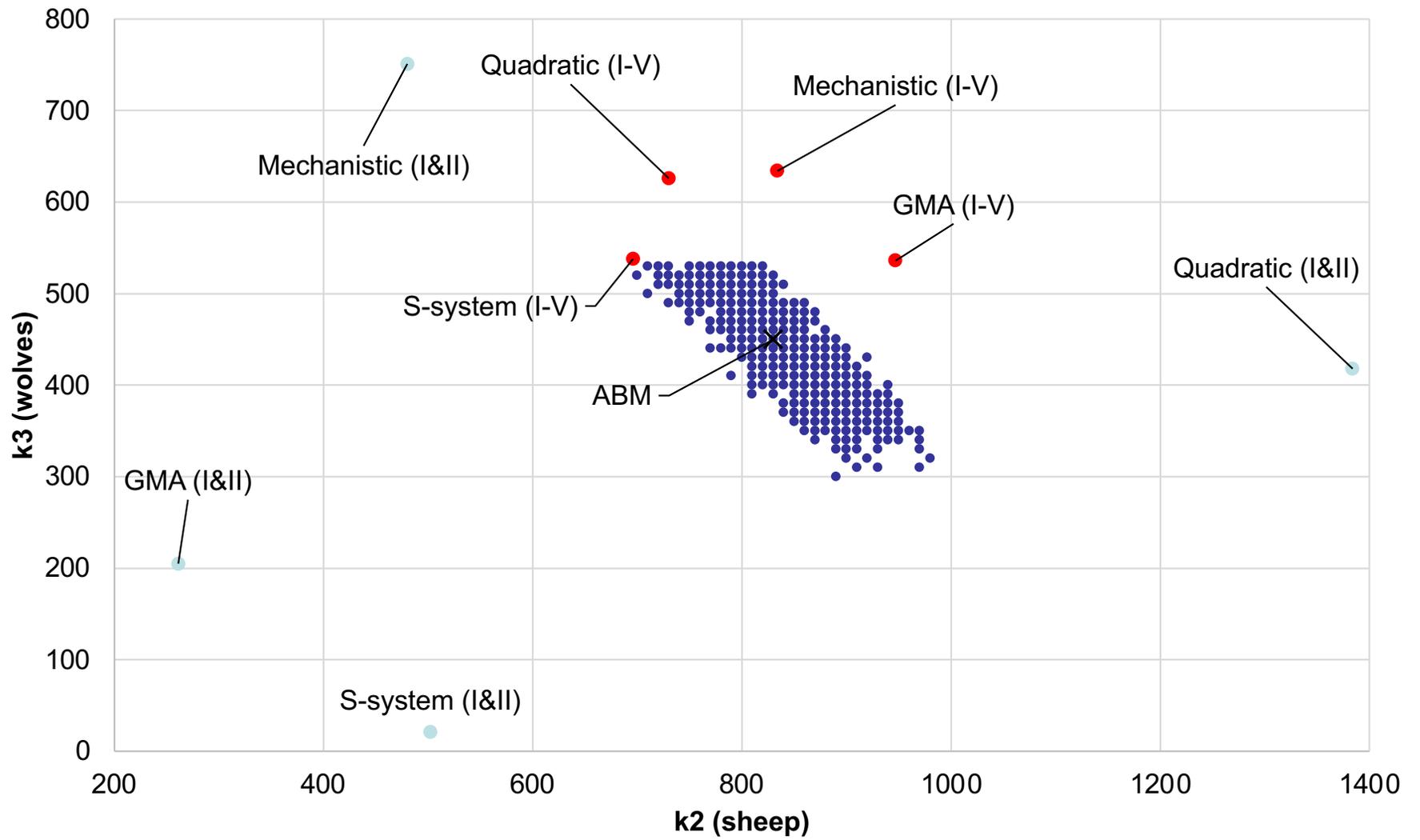


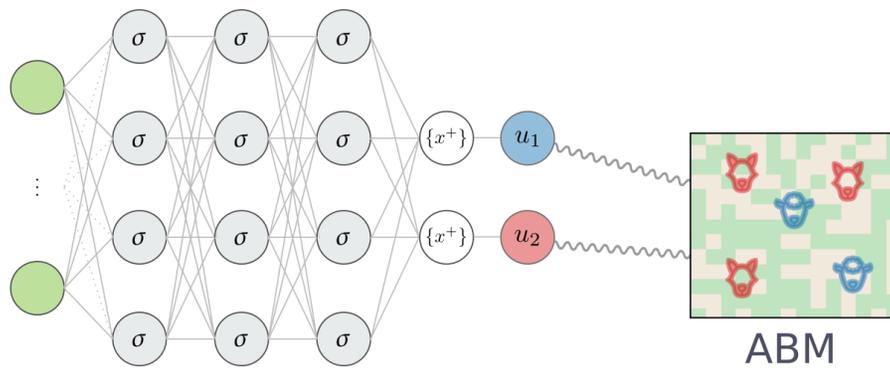
Control of medical digital  
twins with artificial neural  
networks

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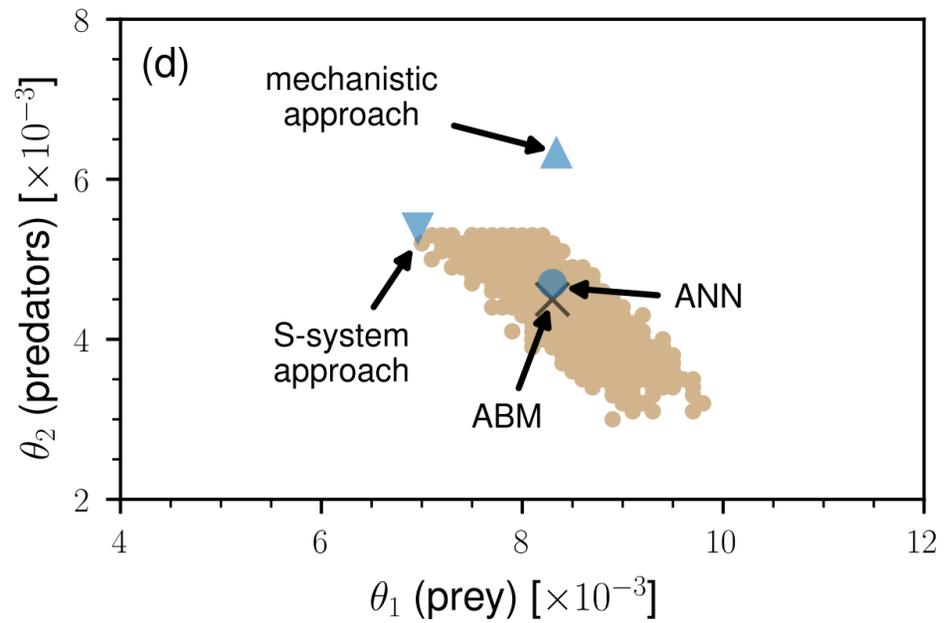
Lucas Böttcher<sup>1,2,\*</sup>, Luis L. Fonseca<sup>2,\*</sup>  
and Reinhard C. Laubenbacher<sup>2</sup>

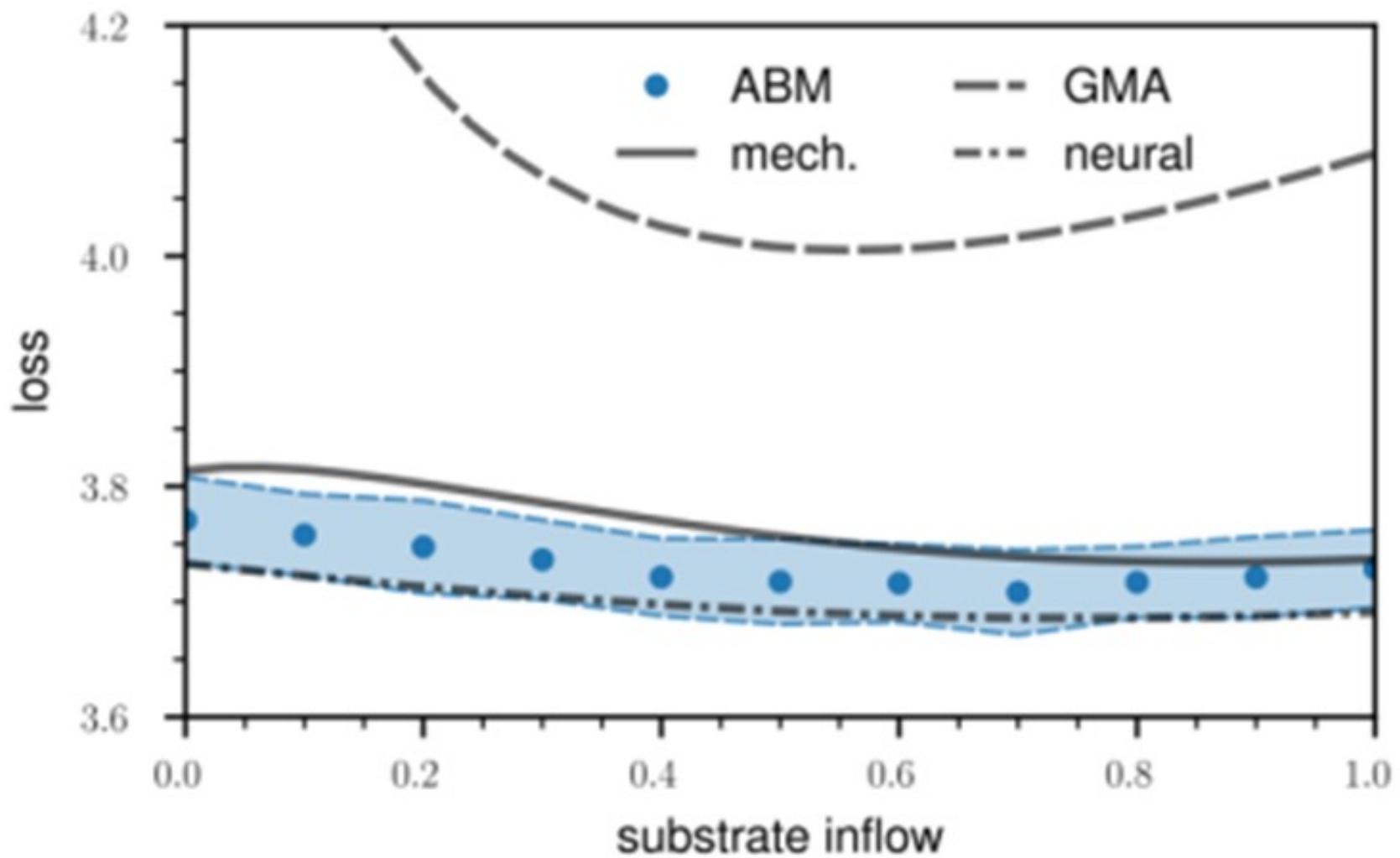
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inputs hidden layers controls





# INTERFACE

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**Cite this article:** Knapp A, Cruz DA, Mehrad B, Laubenbacher RC. 2025 Personalizing computational models to construct medical digital twins. *J. R. Soc. Interface* **22**: 20250055. <https://doi.org/10.1098/rsif.2025.0055>

## Personalizing computational models to construct medical digital twins

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Adam Knapp, Daniel A. Cruz, Borna Mehrad and Reinhard C. Laubenbacher

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Department of Medicine, University of Florida, Gainesville, FL, USA

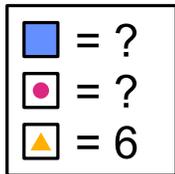
**Model microstate:** a full initialization of the ABM

**Model macrostate:**

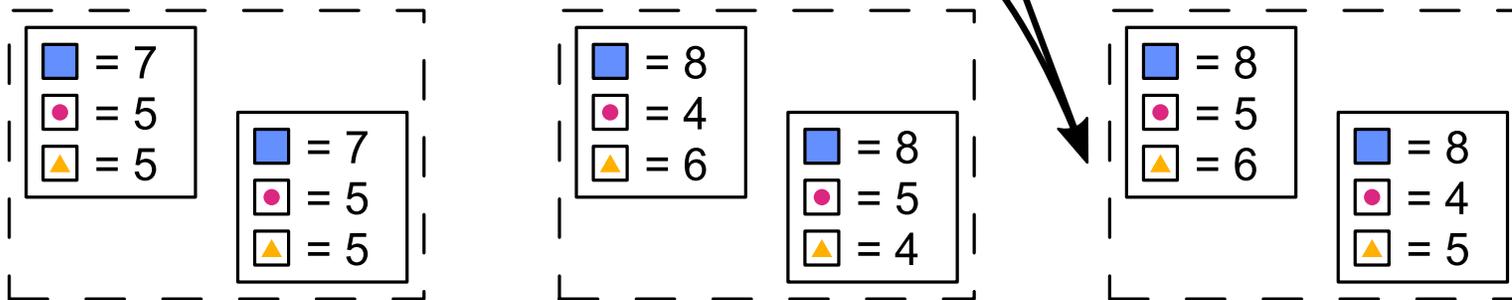
- Model parameters;
- Model states that are global states of system components, such as molecule concentrations in a blood compartment;
- Summaries of microstates;

**Mathematical Problem:** Given repeated partial measurements of model macrostates, how can one calibrate the ABM and simulate it to forecast its likely trajectory?

Observations

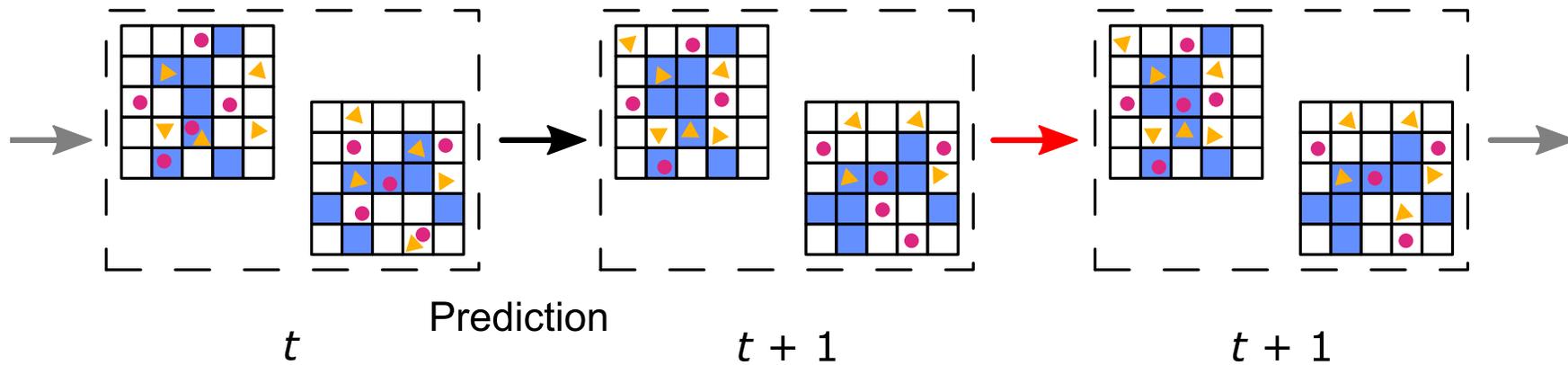


Macro-states



KF + Resample

Micro-states



Summarize

Synthesize

$t$

Prediction

$t + 1$

$t + 1$

## Open mathematical problems

- Develop new generations of these methods for more complex multi-scale ABMs using generative AI tools, e.g., variational autoencoders
- Uncertainty quantification
- Digital twins based on large quantitative models combining mechanisms and multimodal data, e.g., EHR, omics, imaging data
- Develop a general digital twin platform



<https://www.wsj.com/articles/intensive-care-gets-friendlier-with-apps-devices-1426535128>