



University of Idaho
College of Science



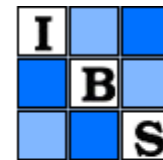
**Systems Medicine
of Infectious Diseases**
Research and Consulting Group

Parameter Inference in Immune Digital Twins: A Stochastic Adaptive Filtering Approach

Juan E. Sereno, E.A. Hernandez-Vargas

Department of Mathematics and Statistical Science
University of Idaho

Tuesday, June 16, 2026



WNAR

The Western North American
Region of The International Biometric Society

WNAR 2026, Pullman, WA

Panel 1. A 52-year-old male with a history of stroke and hemiplegia is found confused in his prison cell.



Taken, and adapted with Gemini, from:

[1] Laubenbacher, R., Mehrad, B., Shmulevich, I., & Trayanova, N. (2024). **Digital twins in medicine.** Nature Computational Science, 4(3), 184-191.

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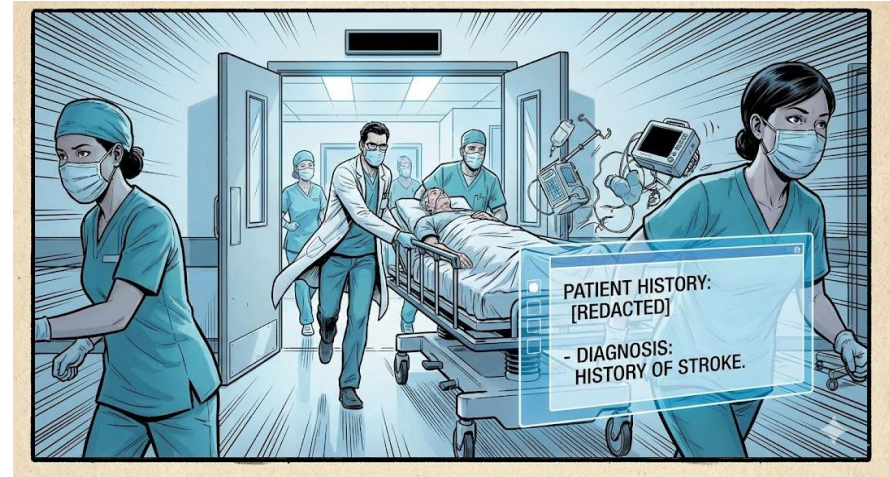
Panel 2. At ED, patient presents hypotension, mild renal insufficiency, and bilateral airspace disease on chest X-ray.



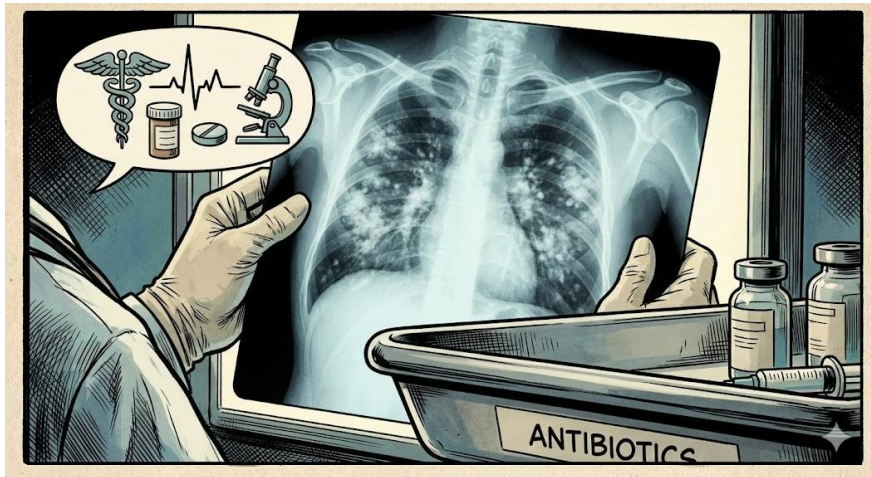
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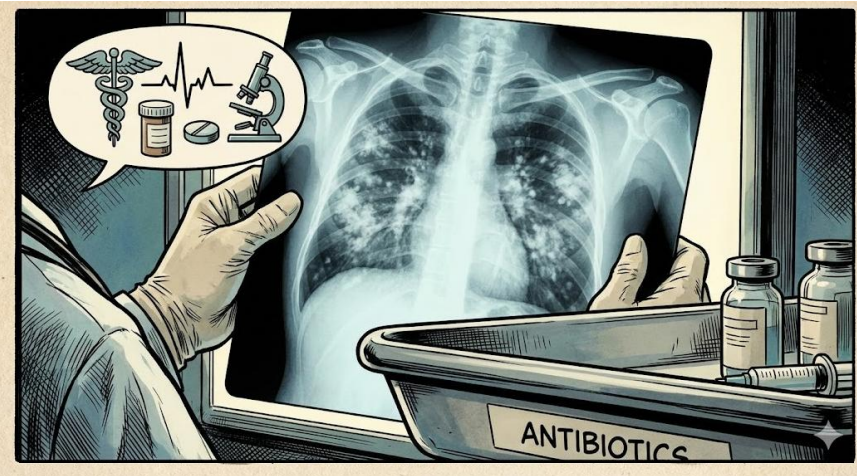
Panel 3. Pneumonia diagnosed and empiric severe pathogen antibiotics started.



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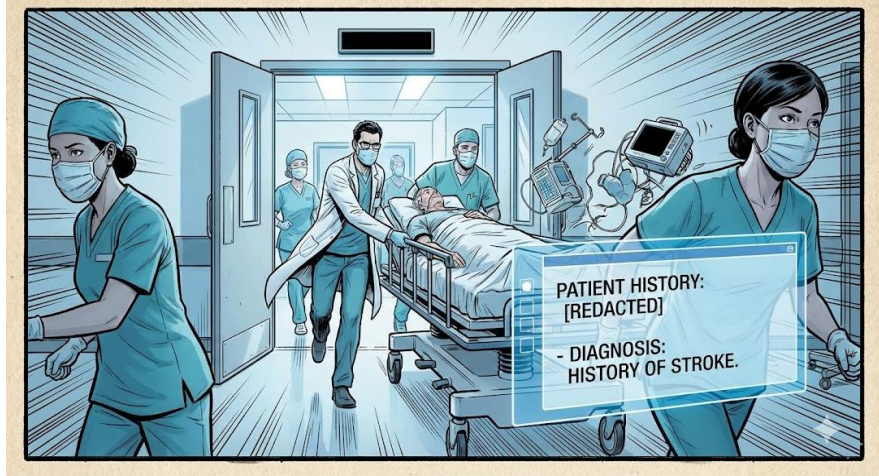


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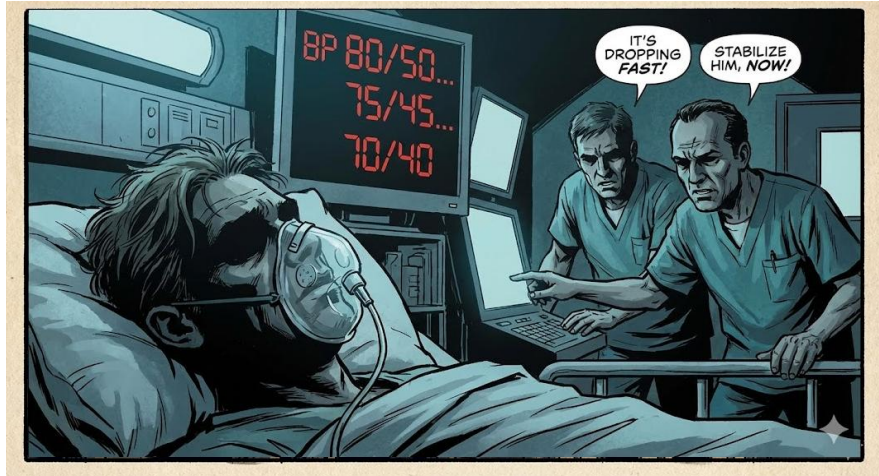


Suspected pathogen:
Klebsiella pneumoniae

Panel 2. At ED, patient presents hypotension, mild renal insufficiency, and bilateral airspace disease on chest X-ray.



Panel 4. 6 h later, recurrent hypotension requiring intravenous pressors and escalating supplemental oxygen.



Panel 5. 3 h after deterioration, requires endotracheal intubation and mechanical ventilation for ARDS-induced hypoxic respiratory failure.



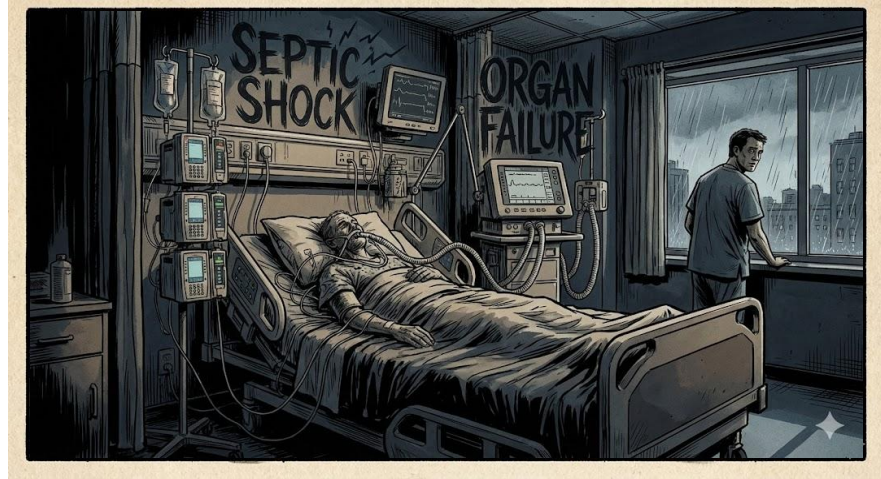
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Panel 6. Condition progress to refractory septic shock and acute kidney injury **despite receiving antibiotics to which the *Klebsiella pneumoniae* was sensitive.**



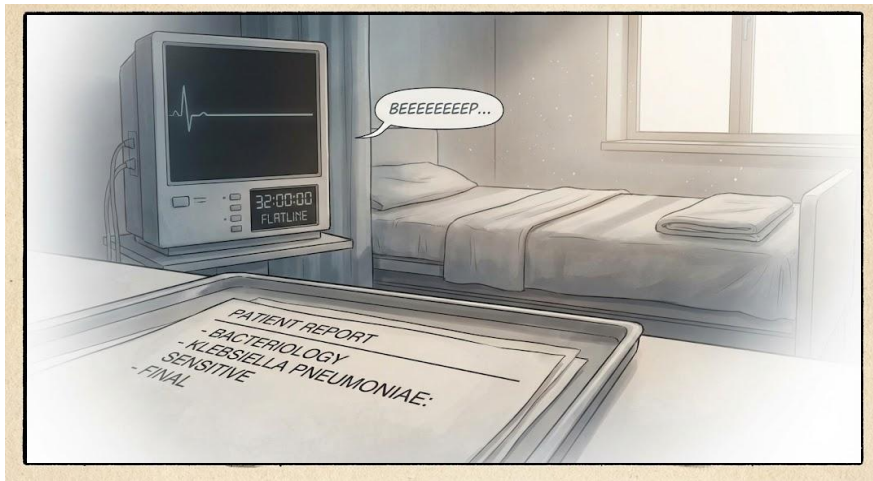
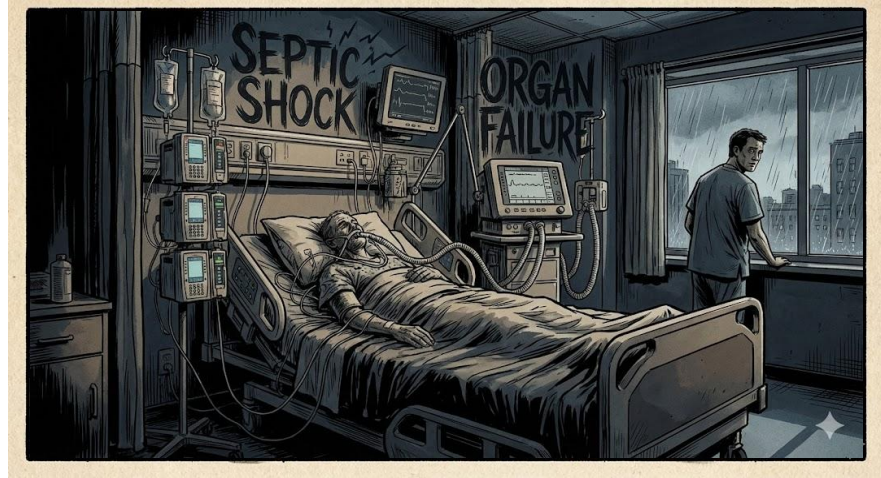
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Panel 7. Patient dies of multi-organ failure 32 hours after presentation.

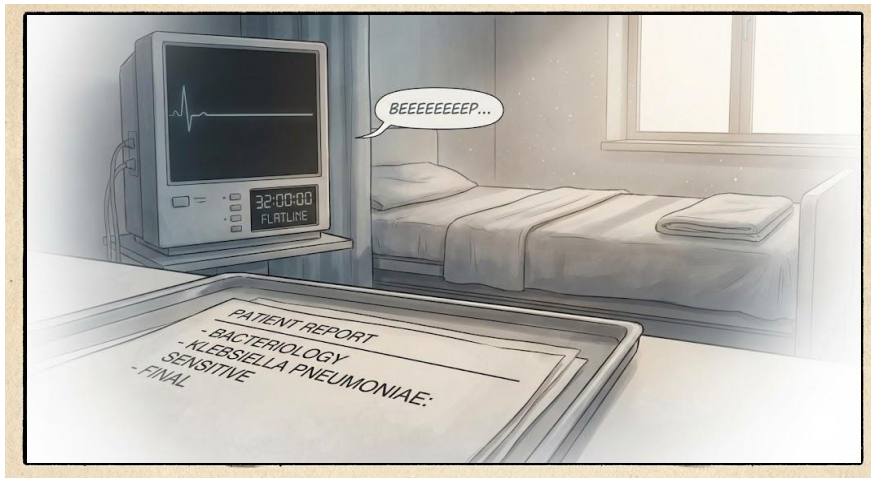
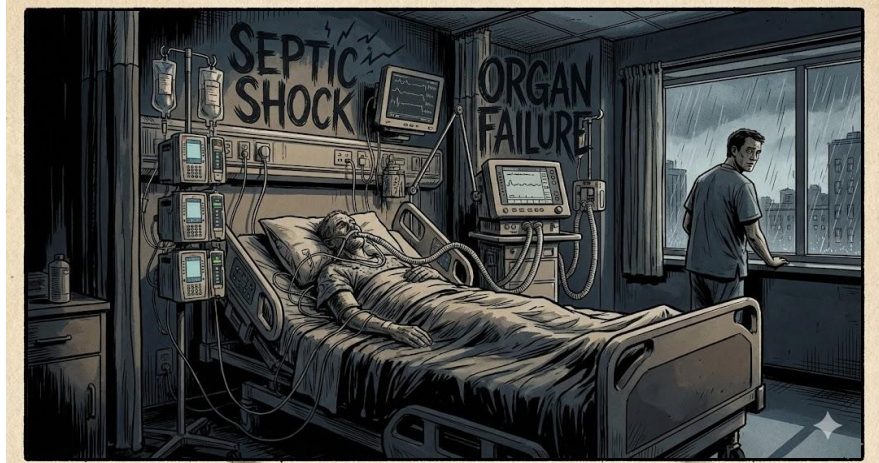
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What is a Digital Twin in Medicine?

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Digital Twin [2]:

1. A model of the physical twin.
2. An evolving set of data relating to the object, and
3. A means of dynamically updating or adjusting the model in accordance with data.

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Medical Digital Twin [1,3]:

A computational model of the system to be twinned (heathy or sickness processes) that is connected to the physical twin in a bidirectional fashion over time, periodically recalibrated with patient data, and provides patient predictions over time to prevent or treat diseases.

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[2] Wright, L., & Davidson, S. (2020). **How to tell the difference between a model and a digital twin**. *Advanced Modeling and Simulation in Engineering Sciences*, 7(1), 13.

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

Digital Twins in Medicine

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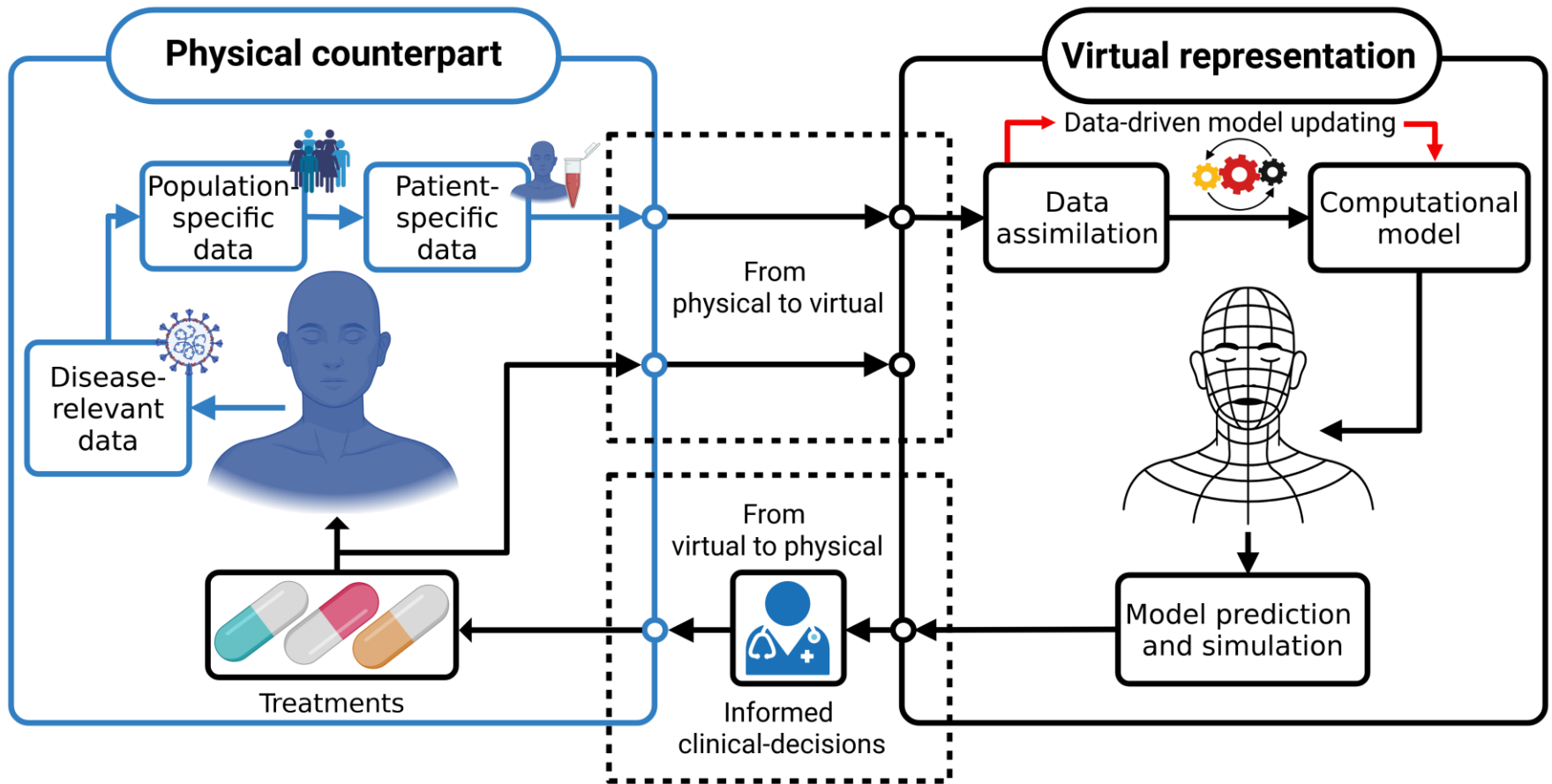


Figure 1. The standard Digital Twin Framework [5] .

Digital Twins in Medicine

Old fashion batch-based identification process!

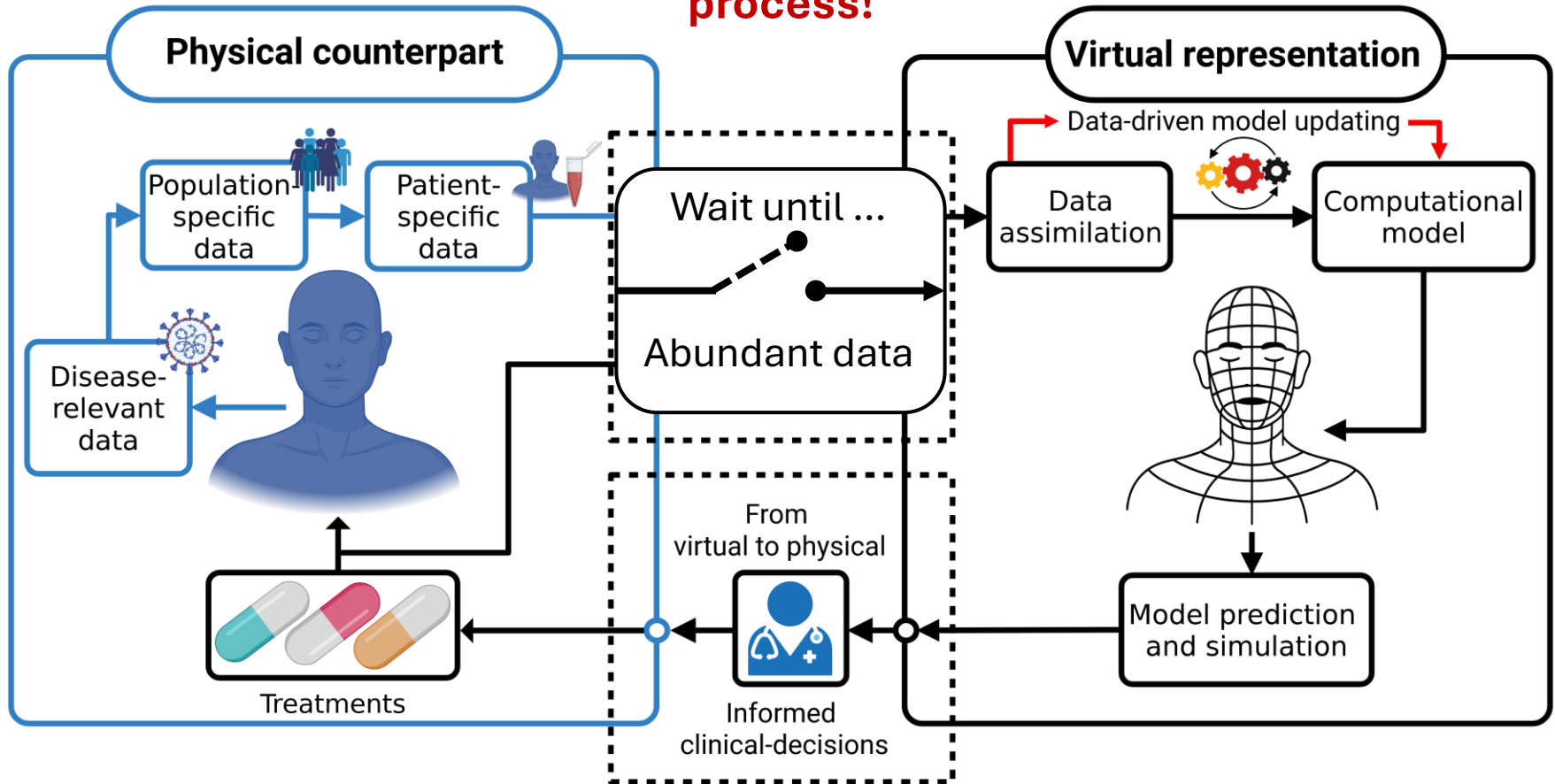


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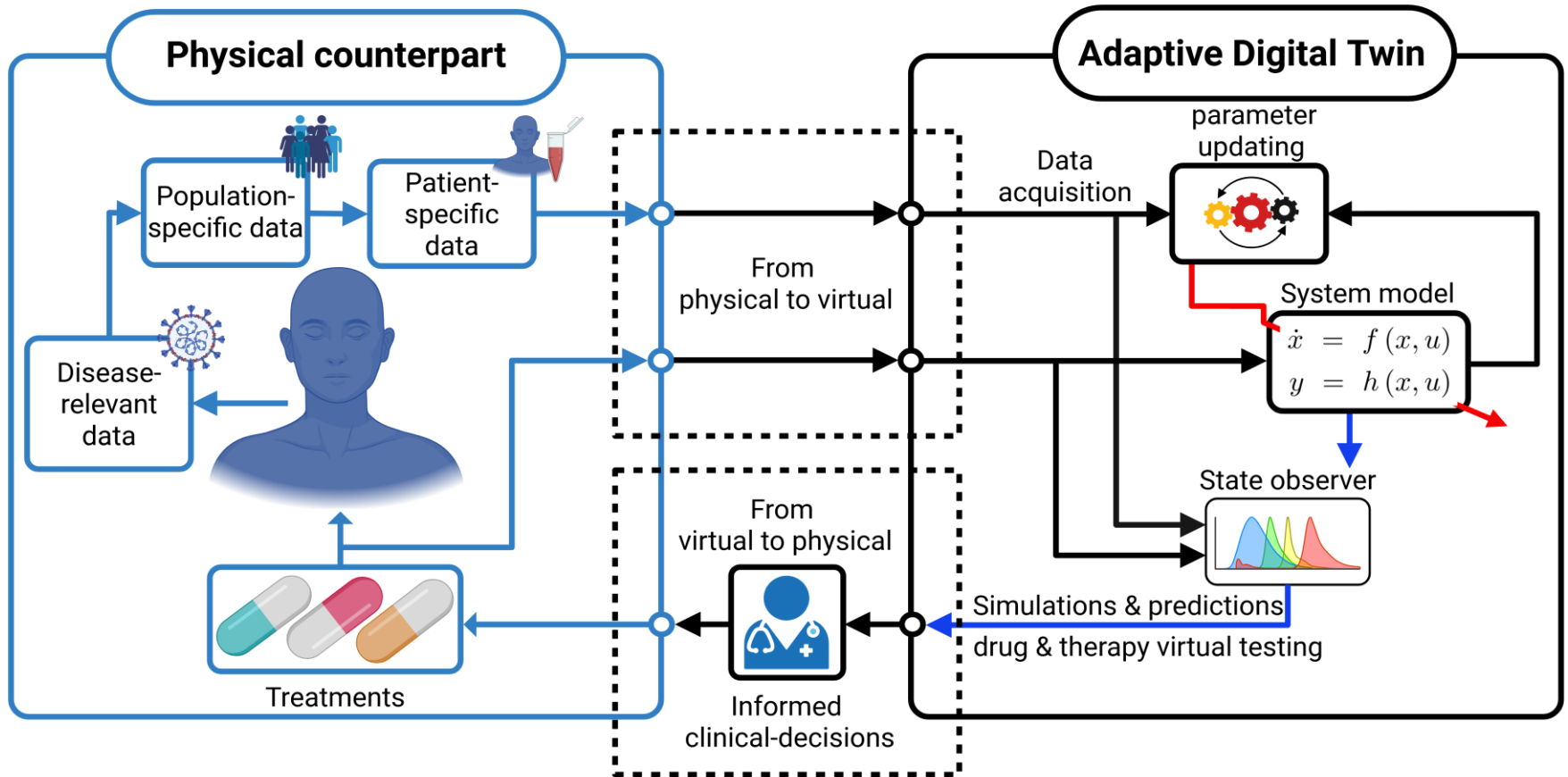


Figure 2. Our Adaptive Digital Twin Framework [5] .

Digital Twins in Medicine

Adaptive fashion, parameters are updated
as new data became available!

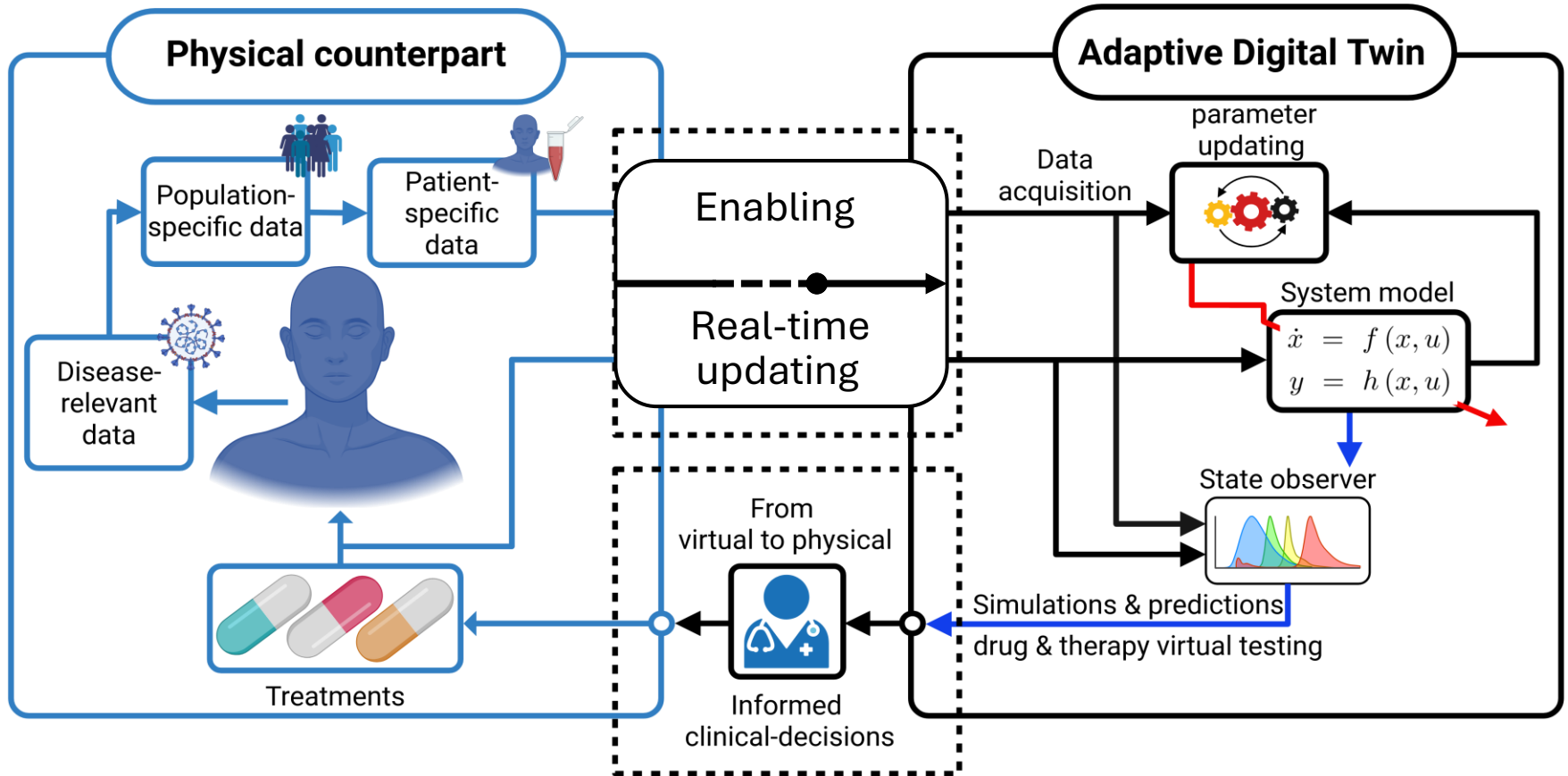


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Modeling HIV Infection

HIV mutation model

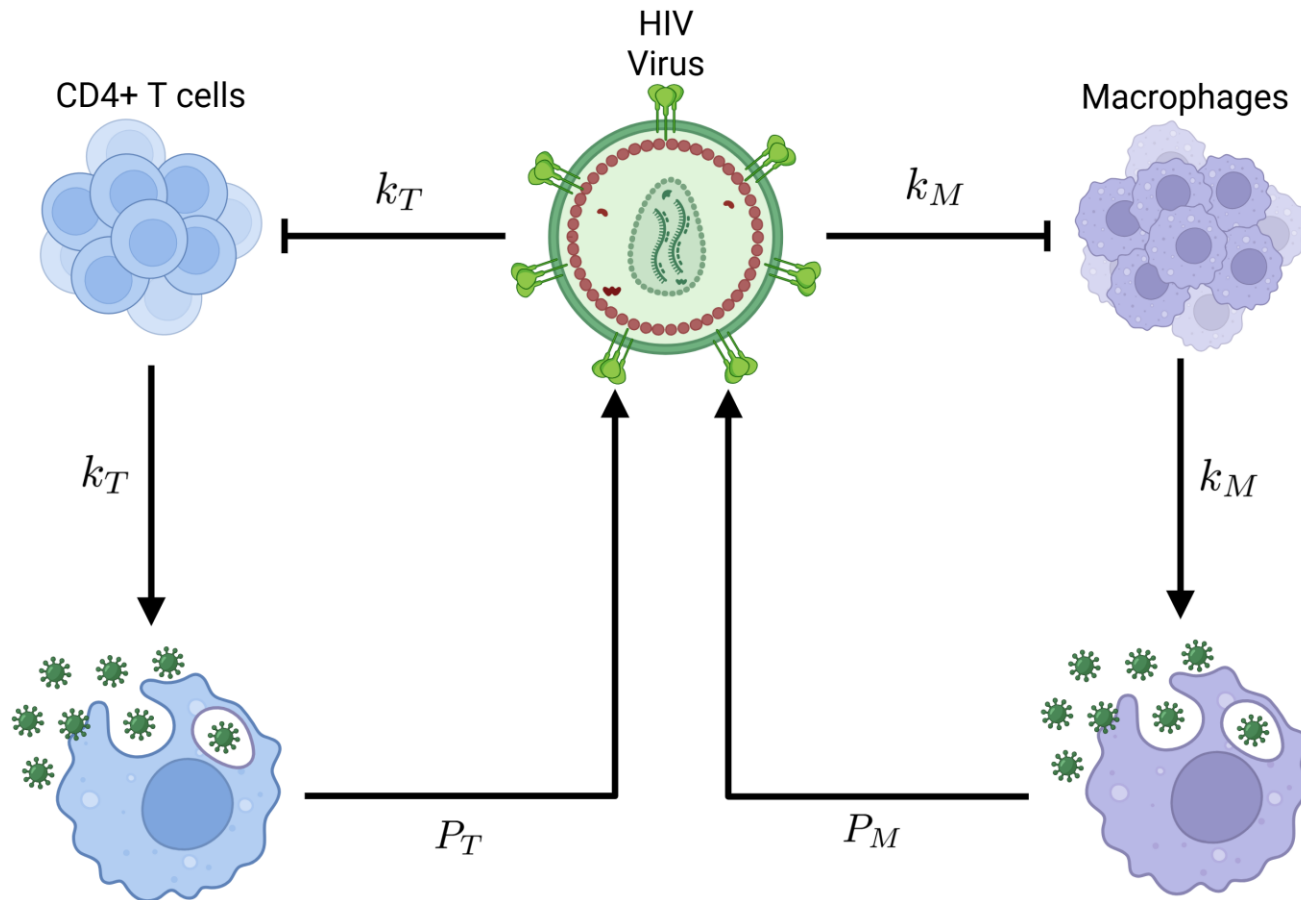


Figure 3. HIV infection scheme, taken from [8].

HIV mutation model

$$\dot{T} = s_T + \frac{\rho_T}{C_T + V_T} T V_T - \sum_{i=1}^n k_{T,\sigma}^i T V_i - \delta_T T$$

$$\dot{M} = s_M + \frac{\rho_M}{C_M + V_T} M V_T - \sum_{i=1}^n k_{M,\sigma}^i M V_i - \delta_M M$$

$$\dot{T}_i^* = k_{T,\sigma}^i T V_i + \sum_{j=1}^n \mu m_{i,j} V_j T - \delta_{T^*} T_i^*$$

$$\dot{M}_i^* = k_{M,\sigma}^i M V_i + \sum_{j=1}^n \mu m_{i,j} V_j M - \delta_{M^*} M_i^*$$

$$\dot{V}_i = p_{T,\sigma}^i T_i^* + p_{M,\sigma}^i M_i^* - \delta_V V_i.$$

HIV mutation model

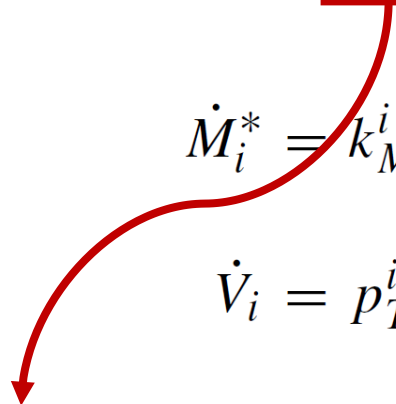
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$$\dot{M}_i^* = k_{M,\sigma}^i M V_i + \sum_{j=1}^n \mu m_{i,j} V_j M - \delta_{M^*} M_i^*$$

$$\dot{V}_i = p_{T,\sigma}^i T_i^* + p_{M,\sigma}^i M_i^* - \delta_V V_i. \quad (1)$$



Can we update model parameters to estimate infections rates and uncovered states such as the number of infected cells from available measures?

HIV mutation scenario

4 genotype – 4 parameter

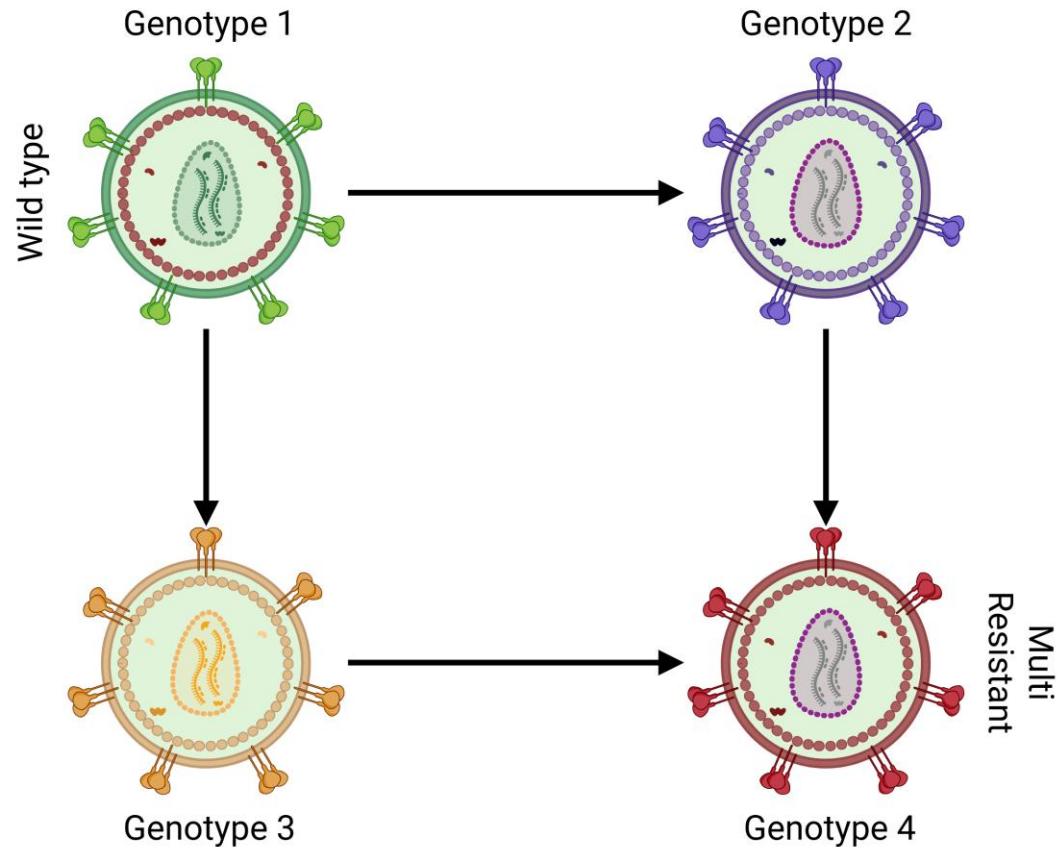


Figure 4. HIV mutation model scheme, 4 genotypes.

Taken from:

[10] Hernandez-Vargas, E. A., Colaneri, P., & Middleton, R. H. (2013). **Switching strategies to mitigate HIV mutation**. *IEEE Transactions on Control Systems Technology*, 22(4), 1623-1628.

On Hybrid Extended Kalman Filtering for Parameter Inference

Hybrid Extended Kalman Filtering

Taken from:

[7] Simon, D. (2006). *Optimal state estimation: Kalman, H infinity, and nonlinear approaches*. John Wiley & Sons.

Hybrid Extended Kalman Filtering

1. Consider the stochastic system equations given by:

$$\begin{aligned}\dot{x} &= f(x, u, t) + w(t) \\ y_k &= h_k(x_k) + v_k \\ w(t) &\sim (0, Q) \\ v_k &\sim (0, R_k)\end{aligned}\tag{2}$$

2. Initialize the filter as follows:

$$\begin{aligned}\hat{x}_0^+ &= E[x_0] \\ P_0^+ &= E[(x_0 - \hat{x}_0^+)(x_0 - \hat{x}_0^+)^T]\end{aligned}\tag{3}$$

Hybrid Extended Kalman Filtering

3. *In a recursive manner*, for $k = 1, 2, \dots$, perform the following.

(a) Integrate from time $(k - 1)^+$ to time k^- as follows:

$$\begin{aligned}\dot{\hat{x}} &= f(\hat{x}, u, 0, t) \\ \dot{P} &= AP + PA^T + LQL^T\end{aligned}\tag{4}$$

where A and L are defined by:

$$A = \left. \frac{\partial f}{\partial x} \right|_{\hat{x}} \quad L = \left. \frac{\partial f}{\partial w} \right|_{\hat{x}}\tag{5}$$

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(b) At time k , update with the measurement y_k :

$$\begin{aligned}K_k &= P_k^- H_k^T (H_k P_k^- H_k^T + M_k R_k M_k^T)^{-1} \\ \hat{x}_k^+ &= \hat{x}_k^- + K_k (y_k - h_k(\hat{x}_k^-, 0, t_k)) \\ P_k^+ &= (I - K_k H_k) P_k^- (I - K_k H_k)^T + K_k M_k R_k M_k^T K_k^T\end{aligned}\tag{6}$$

H_k and M_k are the partial derivatives of $h_k(x_k, v_k)$ with respect to x_k and v_k , and are both evaluated at $\hat{x}_k^-$.

Hybrid Extended Kalman Filtering

Joint State - parameter estimation

For inference of the parameter p , first augment the state vector x' as,

$$x'_k = \begin{bmatrix} x_k \\ p_k \end{bmatrix}. \quad (7)$$

Secondly, model $p_{k+1} = p_k + w_{pk}$, where w_{pk} is a small artificial noise term.

Results on adaptive parameter updating

Numerical Results

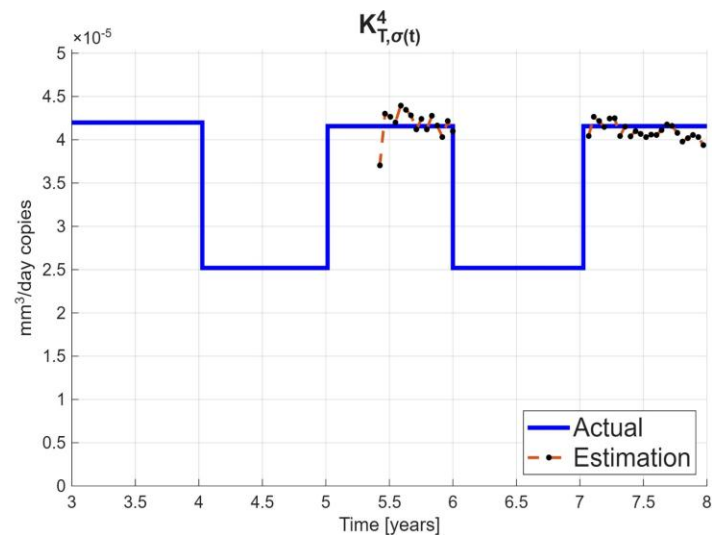
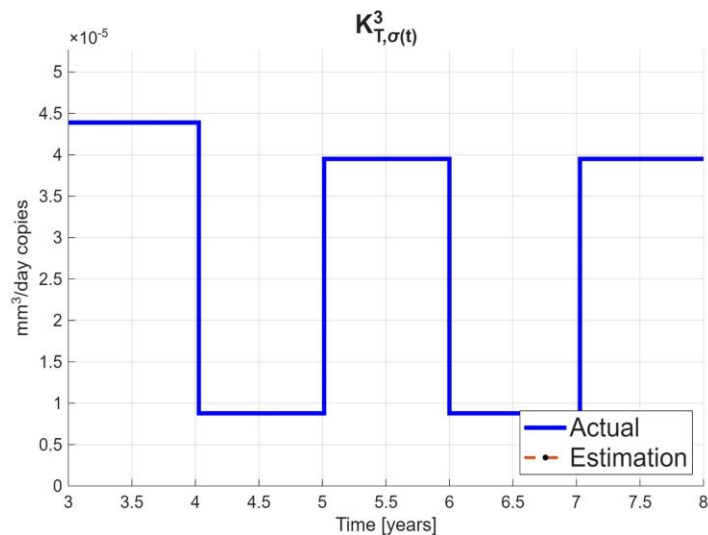
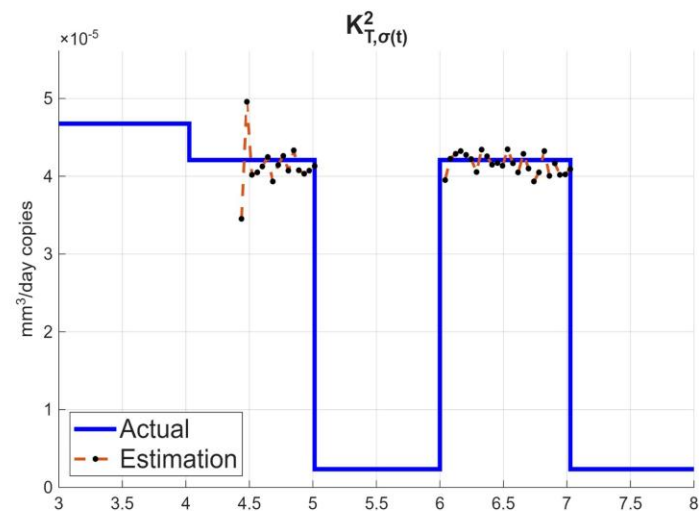
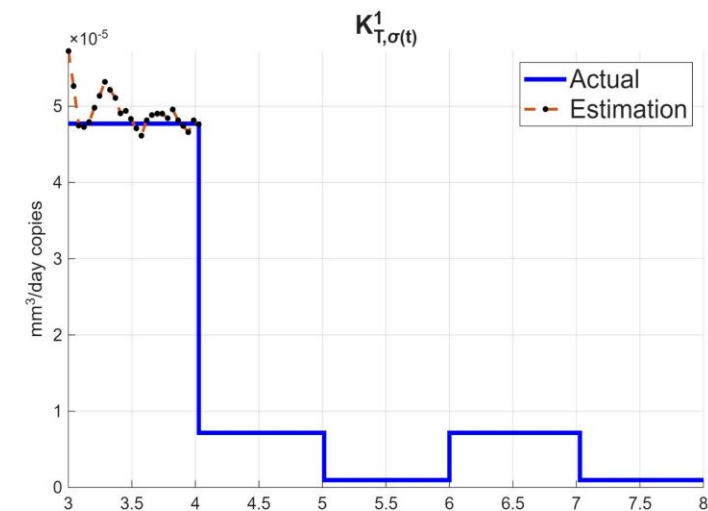


Figure 5. Parameter estimation of $K_{T,\sigma}^{i=1,2,3,4}$.

Numerical Results

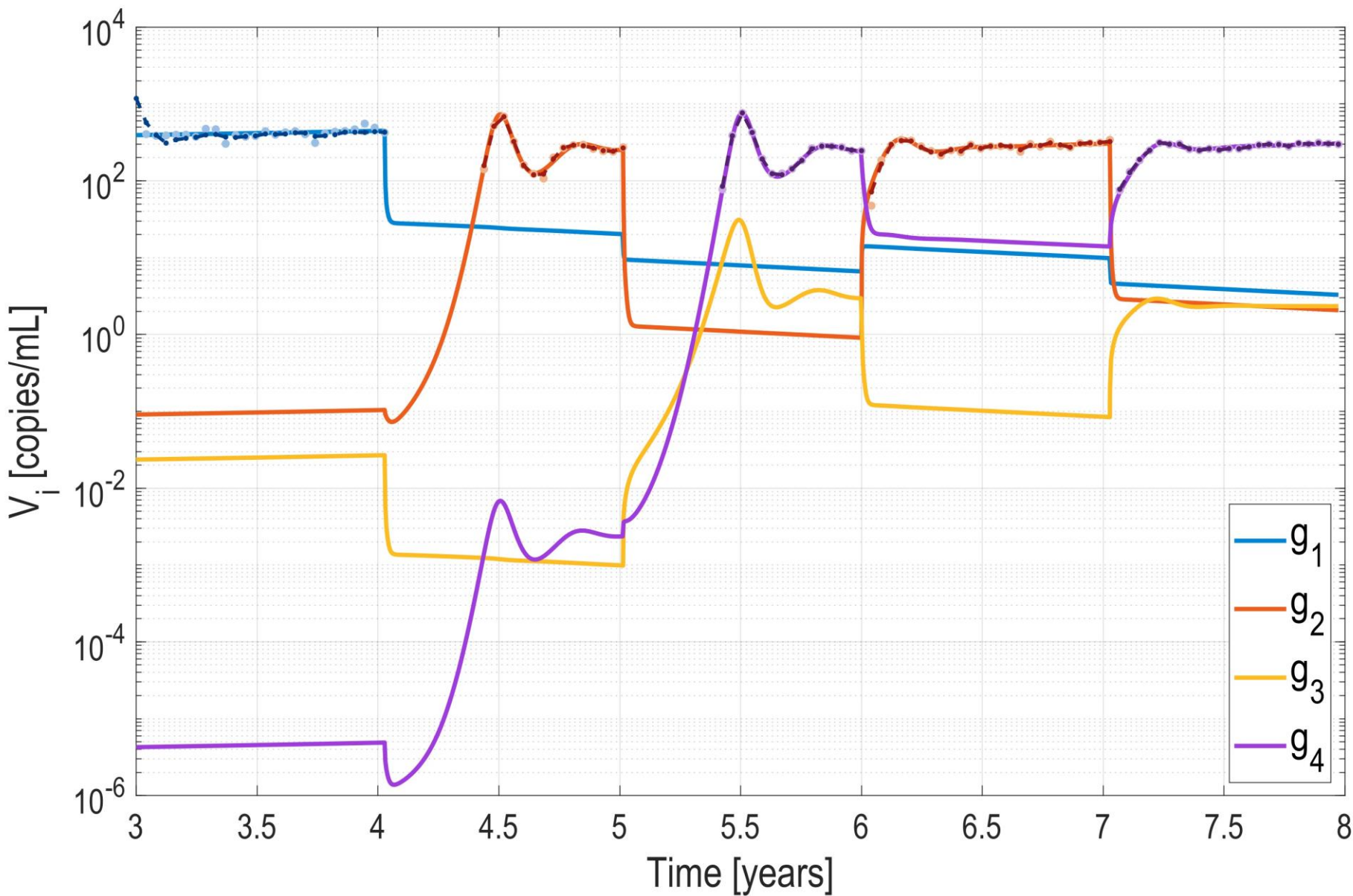


Figure 6. State estimation of each Virus genotype.

Numerical Results

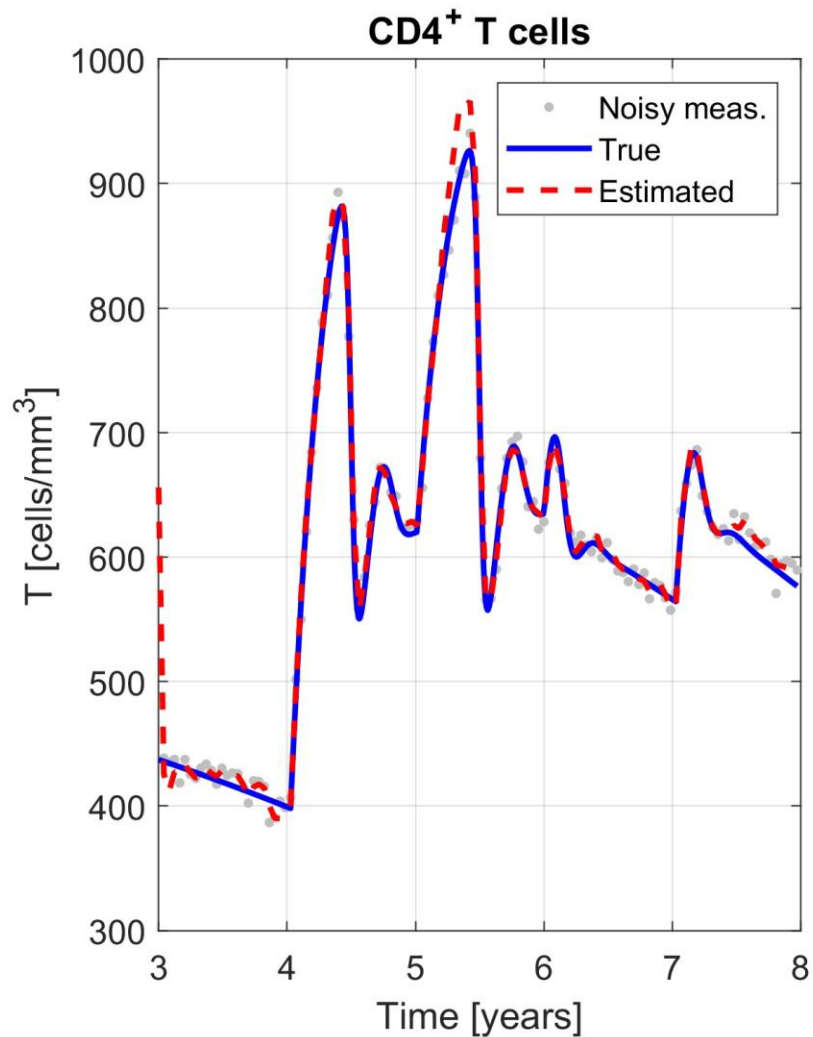


Figure 7. State estimation of CD4⁺ T cells.

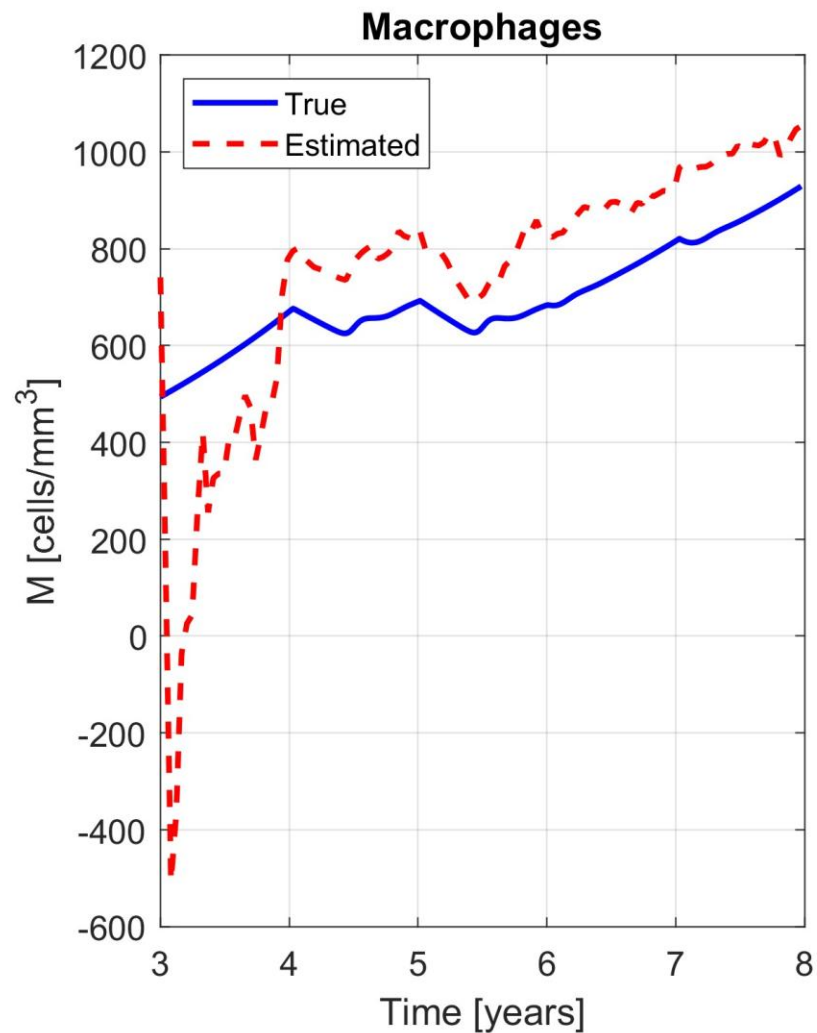


Figure 8. State estimation of Macrophages.

Numerical Results

Infected T^* cells

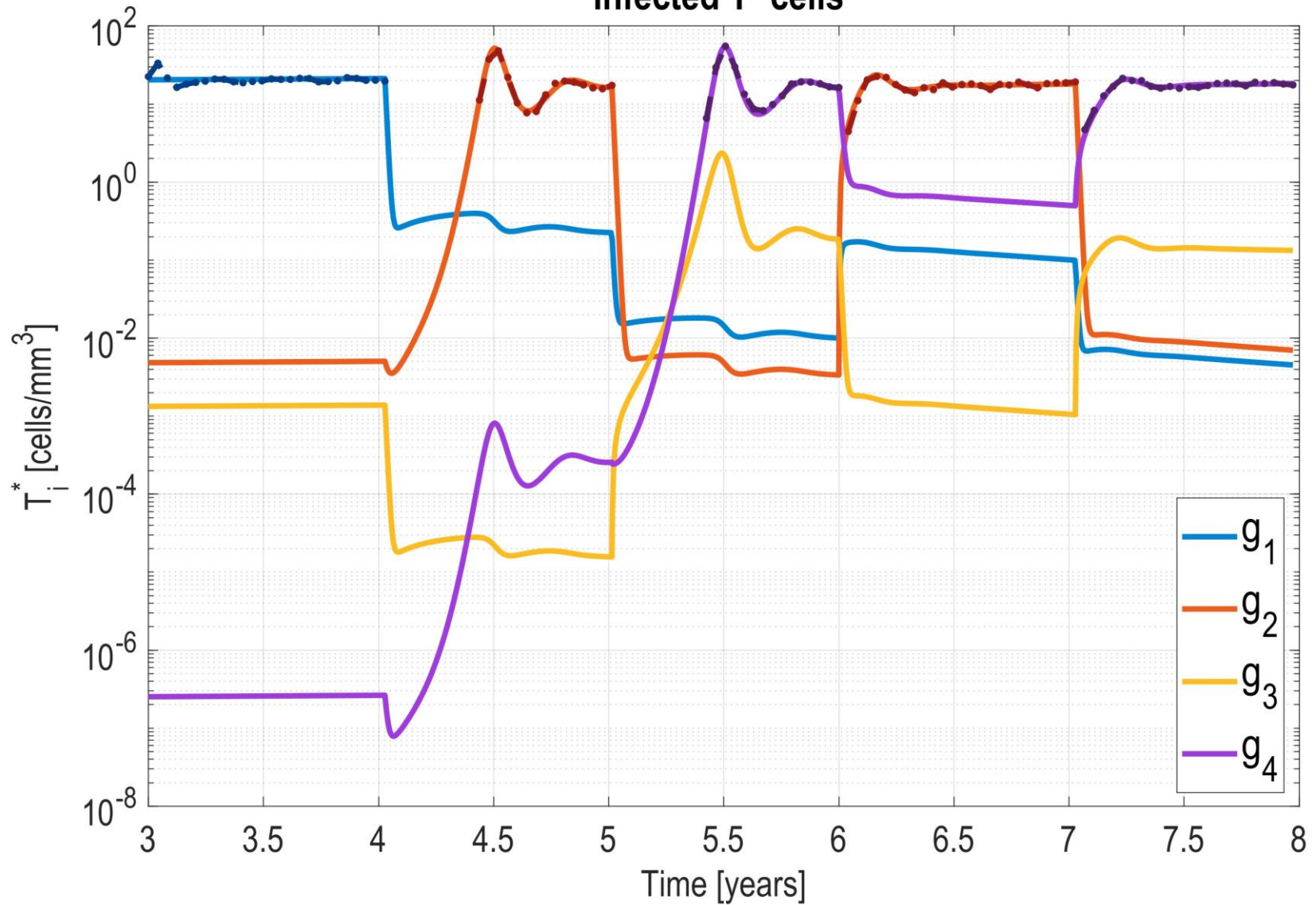


Figure 9. State estimation of Infected T cells.

Numerical Results

Infected M^* cells

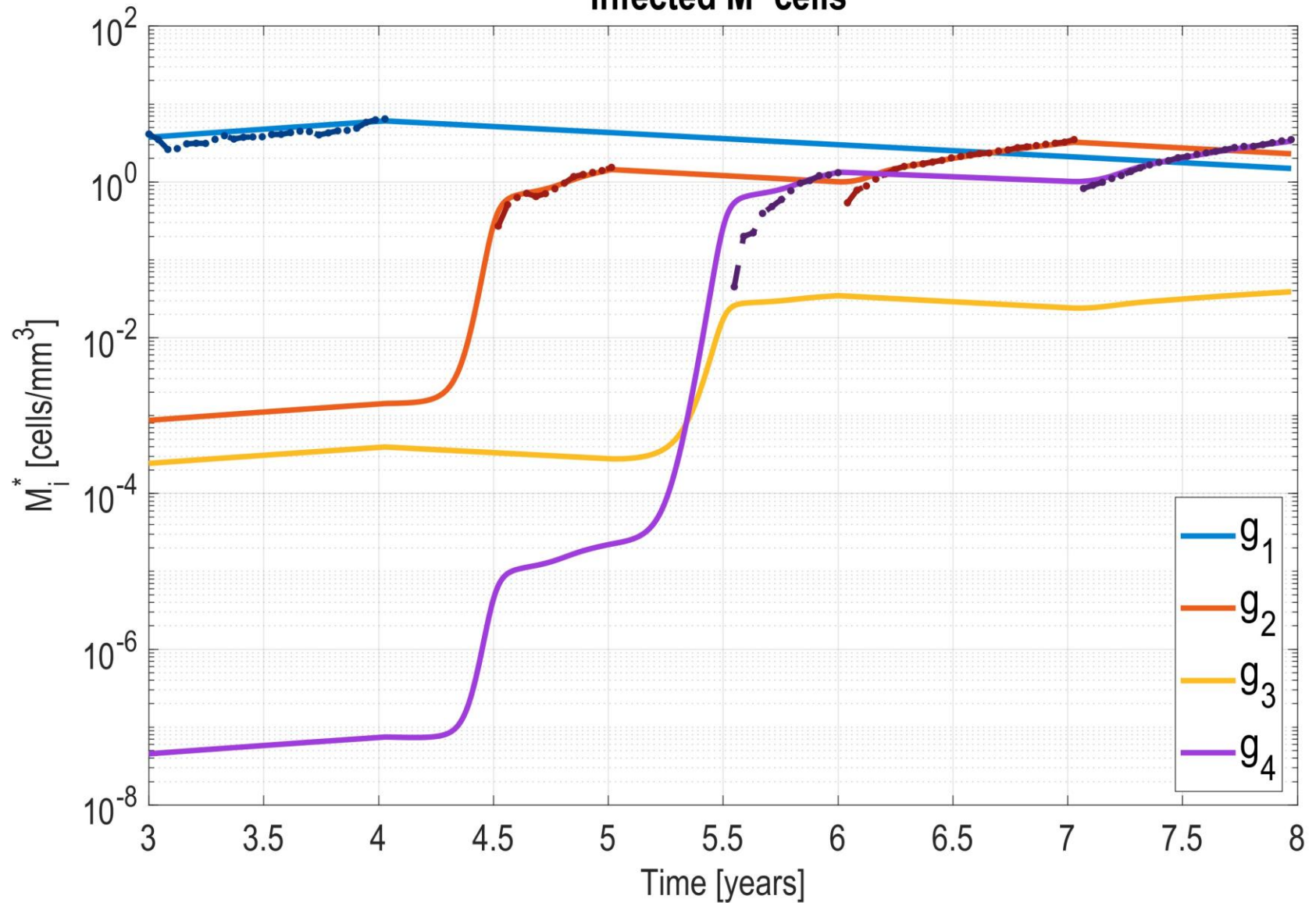


Figure 10. State estimation of Infected Macrophages.

Conclusions

- Digital Twins in medicine needs a paradigm shift from batch-based algorithms to real-time parameter updating.
- Real-time parameter updating is possible, but there are still several open problems, particularly in the medical field.
- Our iterative parameter updating algorithm ensure accurate predictions for the HIV infection, while tracking key biological parameters.
- Macrophages are weakly observable from the available measurements.



Systems Medicine of Infectious Diseases

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<https://www.systemsmedicine.de>



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Codes&GitHub Data Source Alumni Gallery

Machine Learning for Multiscale Analysis of Biomedical Data

Symptoms



COVID-19



Our research group seeks new avenues for holistic understanding against infections at the meeting point of mathematics, machine learning, and infection biology. By integrating multi-scale experimental data, modeling, and the power of computational simulations we aim to:

COVID-19 Research

Tweets by @systmedicine

Esteban A. Hernandez-Vargas Retweeted
Jesus Alvarez
@jgac79
Replying to @systmedicine



Contact us at:

esteban@systemsmedicine.de

Thanks for attending, questions ?

jserenom@uidaho.edu

About Me



Postdoctoral Research Fellow

I am a Postdoctoral Research Fellow at the [University of Idaho](#), Department of Mathematics and Statistical Science, in the [SMID Lab](#) under the supervision of Prof. Esteban Hernandez-Vargas. Previously, I obtained my Ph.D. in Mathematical Engineering from the [Universidad Nacional del Litoral](#), Argentina, where I worked on the design of predictive controllers for hybrid systems with applications to socio-biomedical processes, under the supervision of Prof. Alejandro H. Gonzalez.

I am currently seeking postdoctoral appointments for the next academic year, starting around August 2026. Please feel free to get in touch if you are interested in my research!

- **Name:** Juan Esteban Sereno Mesa
- **Title:** Postdoctoral Research Fellow
- **E-mail:** jserenom@uidaho.edu
- **Institution:** University of Idaho
- **Google Scholar:** [Click here](#)
- **ORCID:** [0000-0002-8498-1277](#)
- **Location:** Moscow, Idaho, USA
- **Nationality:** Colombian

juansereno.github.io

References

- [1] Wright, L., & Davidson, S. (2020). How to tell the difference between a model and a digital twin. AMSES, 7, 1-13.
- [2] Hernandez-Vargas, E. A., & Middleton, R. H. (2013). Modeling the three stages in HIV infection. Journal of theoretical biology, 320, 33-40.
- [3] Rodríguez, A., et al. An adaptive observer for operation monitoring of anaerobic digestion wastewater treatment. J. Chem. Eng. 269 (2015): 186-193.
- [4] Hernandez-Vargas, E. A. (2019). Modeling and control of infectious diseases in the host: with MATLAB and R. Academic Press.