Leveraging Neural Networks to Model Pharmacology: The Example of CAR-T Therapies

Martina Tarozzi, PhD , Federico Magnani

6th Physical Sensing and Processing Summer school

Department of Physics and Astronomy , Alma Mater Studiorum - Università di Bologna

11/07/2024

Overview of CAR-T Cell Therapies

What are CAR-T Cells?

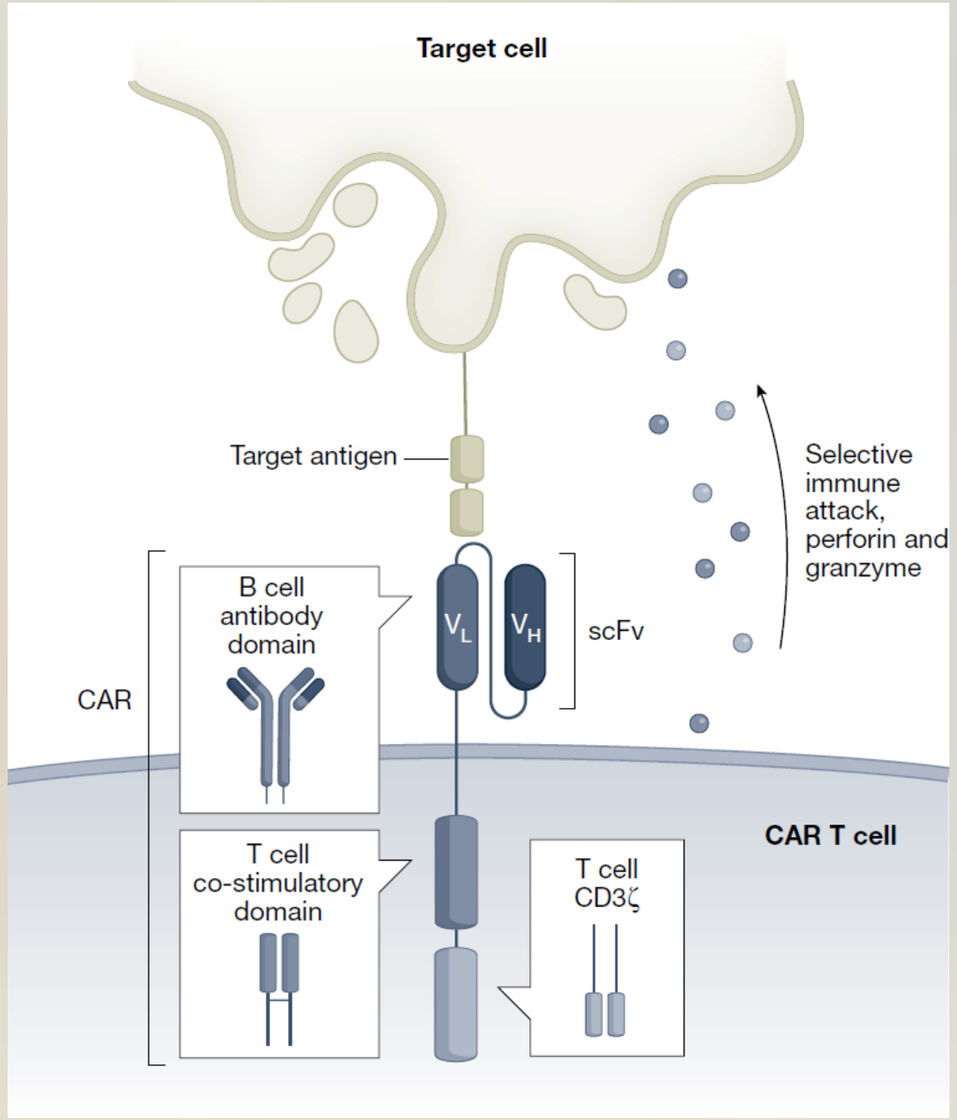
CAR-T cells are genetically modified T cells that express a Chimeric Antigen Receptor (CAR) on their surface. This receptor allows the T cells to recognize specific proteins on the surface of cancer cells, enabling a directed immune response.

Structure of a CAR-T cell

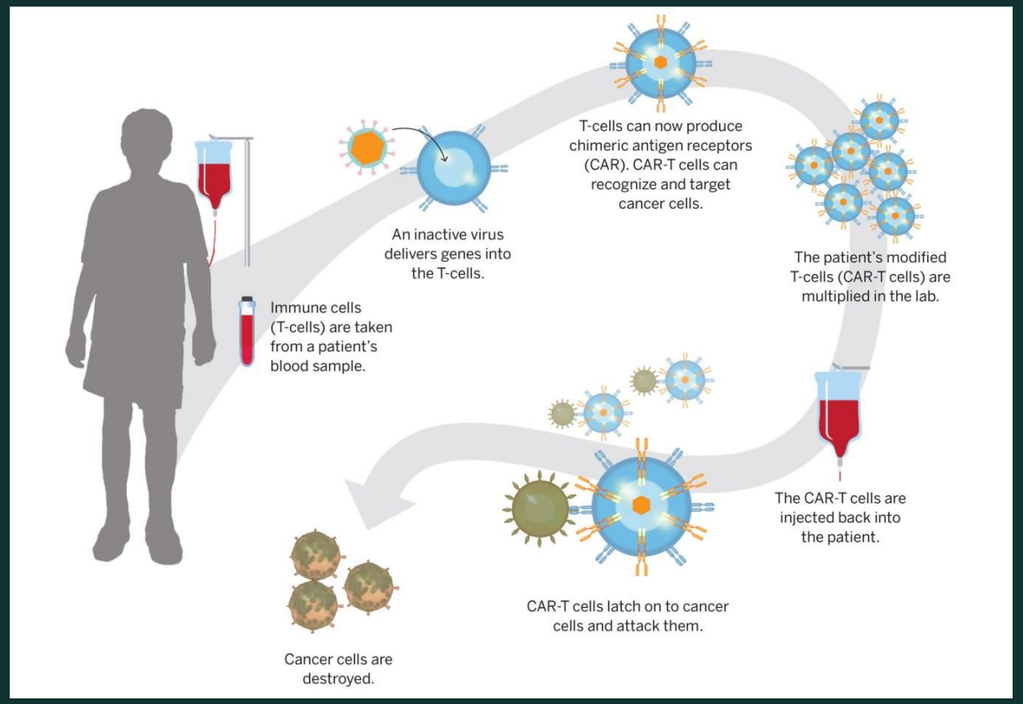
CAR-T cell are made of an antigen-binding domain, a spacer region connecting the antigen-binding domain to the transmembrane domain, which anchors the CAR in the T cell membrane. Inside the cell, there are the Intracellular signaling domains, responsible for activating the T cell once the CAR has bound to its target antigen.

Applications

Six CAR-T therapies have been approved by the FDA to treat certain blood cancers (e.g. ALL, CLL, MM, DLBCL, FL among other) targeting either CD19 or B Cell Maturation Antigen (BCMA). Ongoing research tries to expand these therapies to solid tumors, autoimmune and infectious diseases.



CAR-T therapy foundations



1 T-cell Collection and Modification

The patient's T cells are collected through a process called leukapheresis. These T cells are then genetically modified in a lab to express a Chimeric Antigen Receptor (CAR) that targets CD19, a protein found on the surface of diseased and healthy B cells.

2 Lymphodepleting Chemotherapy:

Before the modified T cells are reintroduced into the patient, the patient undergoes lymphodepleting chemotherapy. This process helps to create a more favorable environment for the CAR T cells by reducing the number of other immune cells that could compete with the CAR T cells. Each patient's immune system and response to CAR-T therapy can vary widely, making it difficult to develop universal predictive models.

3 Optimization of Therapy

The patient's T cells are activated ex vivo, and then the CAR construct is introduced into the T cells, typically by random integration with a viral vector. CAR T cells are grown on the scale of days in bioreactors and then delivered back to patients for infusion.

4 CAR-T cell Infusion

The modified T cells, now called CAR T cells, are infused back into the patient in a single dose (usually). These cells can bind to CD19 on B cells, leading to the activation of the T cells and the destruction of the CD19-expressing cells

Principles of Pharmacology

Pharmacokinetic (PK)

WHAT THE BODY DOES TO THE DRUG

PK describes how the body affects a specific substance after administration. It refers to the movement of a drug into, through, and out of the body—the time course of its absorption, bioavailability, distribution, metabolism, and excretion.

Pharmacodynamics (PD)

WHAT THE DRUG DOES TO THE BODY

PD is the study of the biochemical, physiologic, and molecular effects of drugs on the body. It involves receptor binding (including receptor sensitivity), post-receptor effects, and chemical interactions

Exposure-response (ER) [aka PKPD]

It characterizes the relationship between drug exposure metrics and response. The understanding of this relationship by considering key processes that qualitatively and quantitatively impact processes along the causal pathway can help define optimal dose, frequency of administration, dose adjustments for special populations.

Pharmacology of CAR-T cell therapies

1

Biodistribution

Following infusion, CAR-T cells rapidly disappear from circulation, and blood concentration will drop by orders of magnitude within a few days due to T cell infiltrations into tissue from circulation and activation once in contact with the antigen.

2

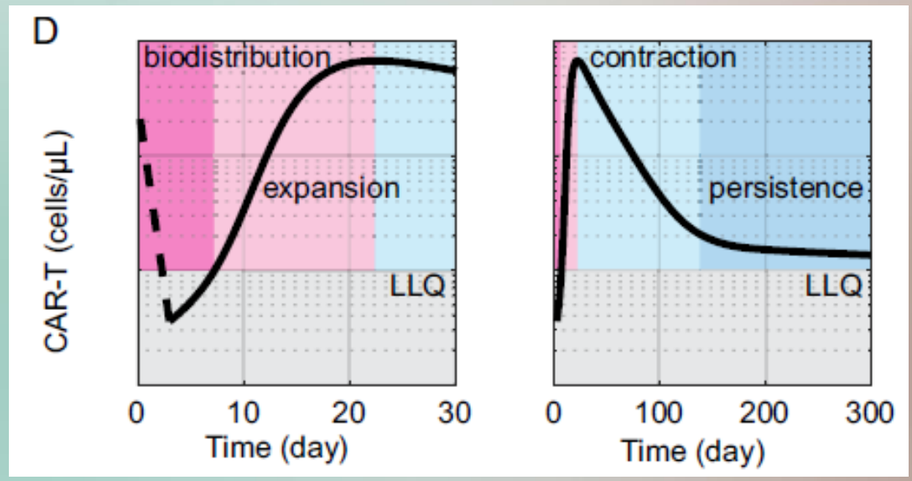
Expansion

CAR-T expansion capacity is correlated with the response to therapy. When therapy is successful, activated CAR-T cells start proliferating and expand (even a single clone can be enough) and start fighting and killing all cells expressing their target antigen.

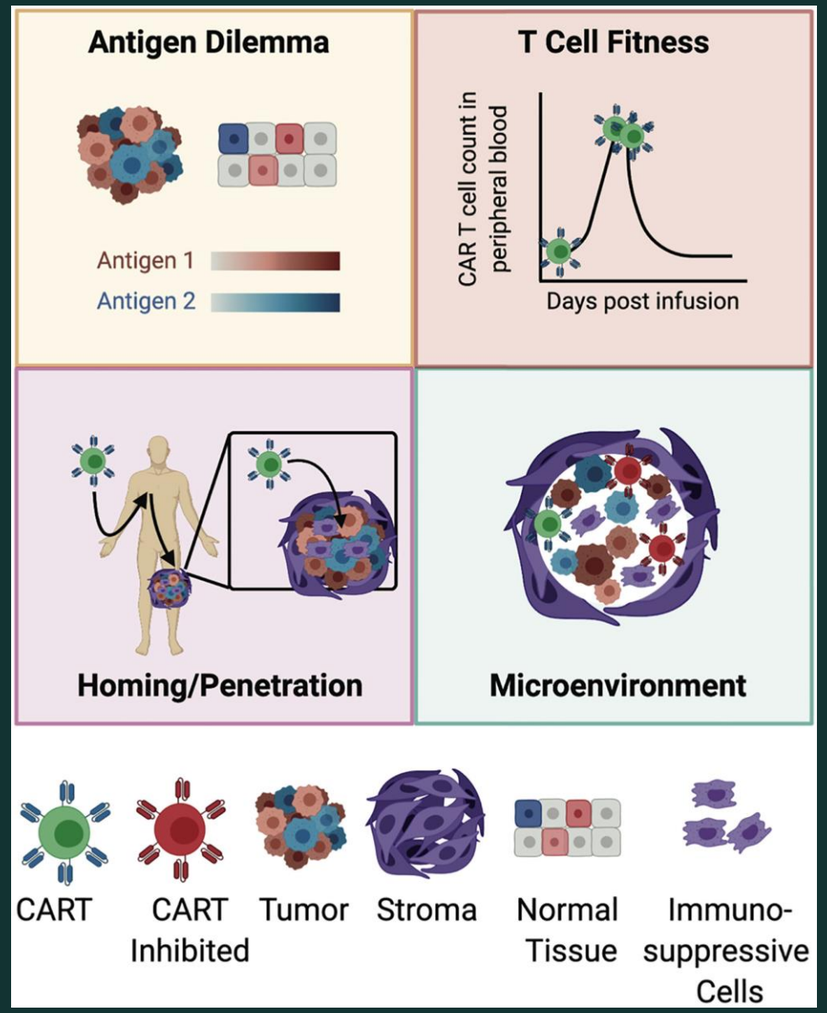
3

Contraction and persistence

After reaching Cmax, circulating cell numbers begin to rapidly contract. As antigen is cleared, active effector T cells either die or convert to long-term memory T cells, when therapy is successful. Activated CAR-T cell suffer from exhaustion, which also causes a contraction in T cells concentration, but it is associated with negative outcome of the therapies as T cell stop fighting cancer cells and die.



Challenges in Modeling CAR-T Therapies



1 Complex Biological Interactions

CAR-T therapy involves an intricate interplay between genetically modified T cells, tumor cells, and the patient's immune system. Accurately modeling these dynamic interactions is a significant challenge.

2 Patient Variability

Each patient's immune system and response to CAR-T therapy can vary widely, making it difficult to develop universal predictive models. Accounting for individual patient characteristics is crucial.

3 Adverse Effects

CAR-T therapies can sometimes cause severe side effects, such as cytokine release syndrome and neurotoxicity. Predicting and mitigating these adverse events is a key challenge.

4 Optimization of Therapy

Determining the optimal CAR design, T-cell manufacturing process, and dosing regimen is an ongoing challenge that requires advanced modeling and simulation capabilities.

Data Inputs for CAR-T Neural Network Models

Patient Clinical Data

Demographic data, medical history, and other patient-specific information are crucial inputs for neural network models to account for individual variability.

Tumor specific Properties

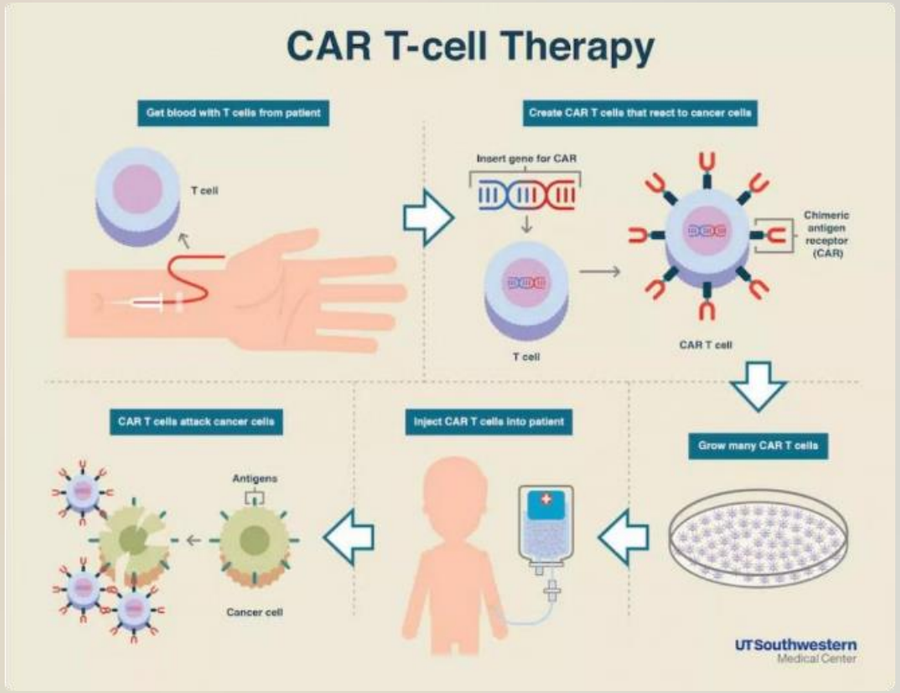
Information about the patient's cancer, including the genetic profile, pre-infusion transcriptomics, cancer type, stage and other tumor-specific data, can be used as input for neural networks to understand the disease context and predict treatment responses.

CAR-T Cell Properties

metrics relating pre-infusion product characteristics, such as receptor design, signaling domains, activation process, T cell subpopulation phenotyping, cytokine-release assays, transcriptome profiles and other biophysical characteristics, are essential for modeling their behavior.

Biomarker Data

Measuring relevant biomarkers, such as cytokine levels, immune cell counts, and other clinical indicators, provides valuable insights for neural network models to assess therapy effectiveness and adverse events.



Training and Validating CAR-T Neural Network Models

Data Collection

Gathering curated, multi-layered, high-quality datasets from clinical trials, real-world patient records, and in experimental studies is crucial for training robust neural network models for CAR-T therapies.

Model Architecture

Designing the appropriate neural network architecture, is essential to capture the complex dynamics of CAR-T therapy effectively.

Model Validation

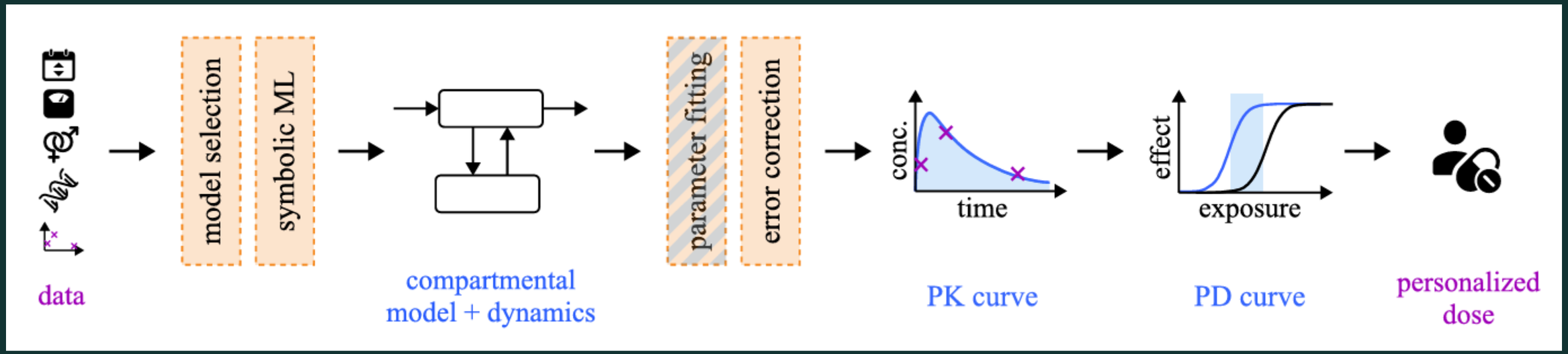
Rigorous validation, using techniques like cross-validation and holdout testing, ensures the neural network models generalize well and can accurately predict CAR-T therapy outcomes for new patients.

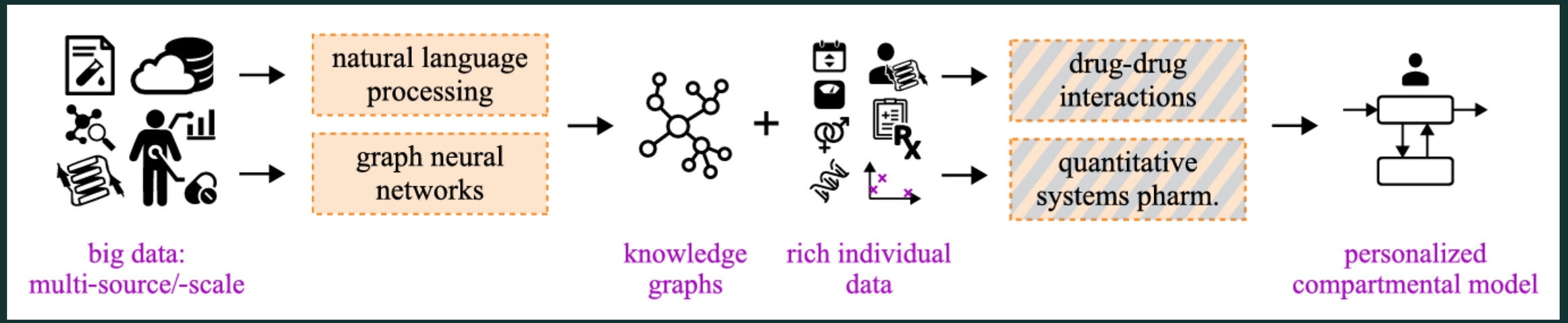
Iterative Optimization

Continuously refining the neural network models by incorporating new data and adjusting hyperparameters is key to improving their predictive performance and clinical utility over time.

Room for experimentation

Artificial Neural Networks can be applied to any of the numerous subtasks of the complex pharmacological pipeline. Even considering just the mathematical modeling part, there is a lot of room for experimentation. We focus on the link between ANNs and dynamical systems.





The CARRGO model

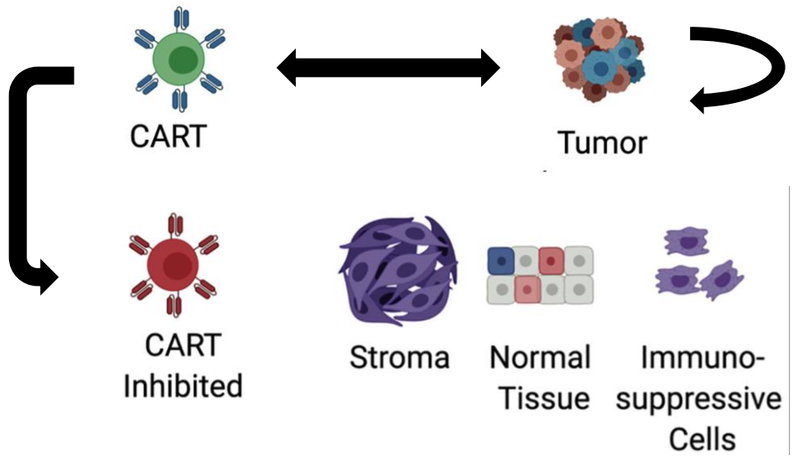
Chimeric Antigen Receptor t-cell treatment Response in GliOma

Tumor

$$\frac{dX}{dt} = \rho X(1 - \frac{X}{K}) - k_1 XY$$

CART

$$\frac{dY}{dt} = k_2 XY - \theta Y$$



In-Vitro

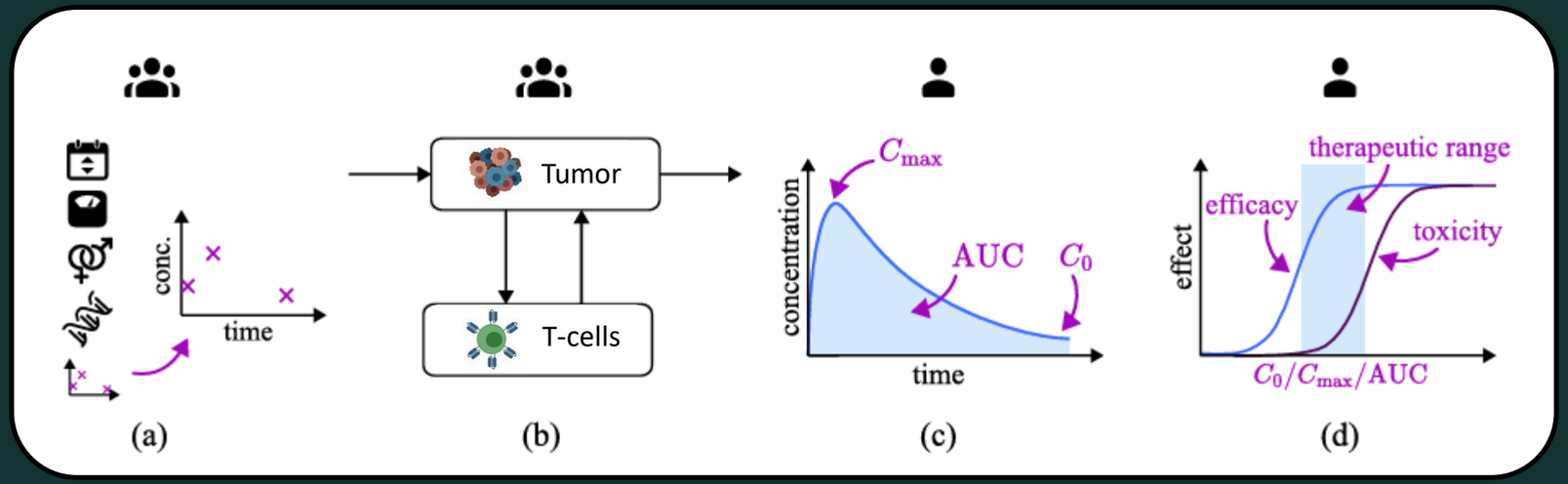
- Closed system
- Well-mixed system
- Tumor growth limited by space and nutrients
- Fixed interactivity of the two populations

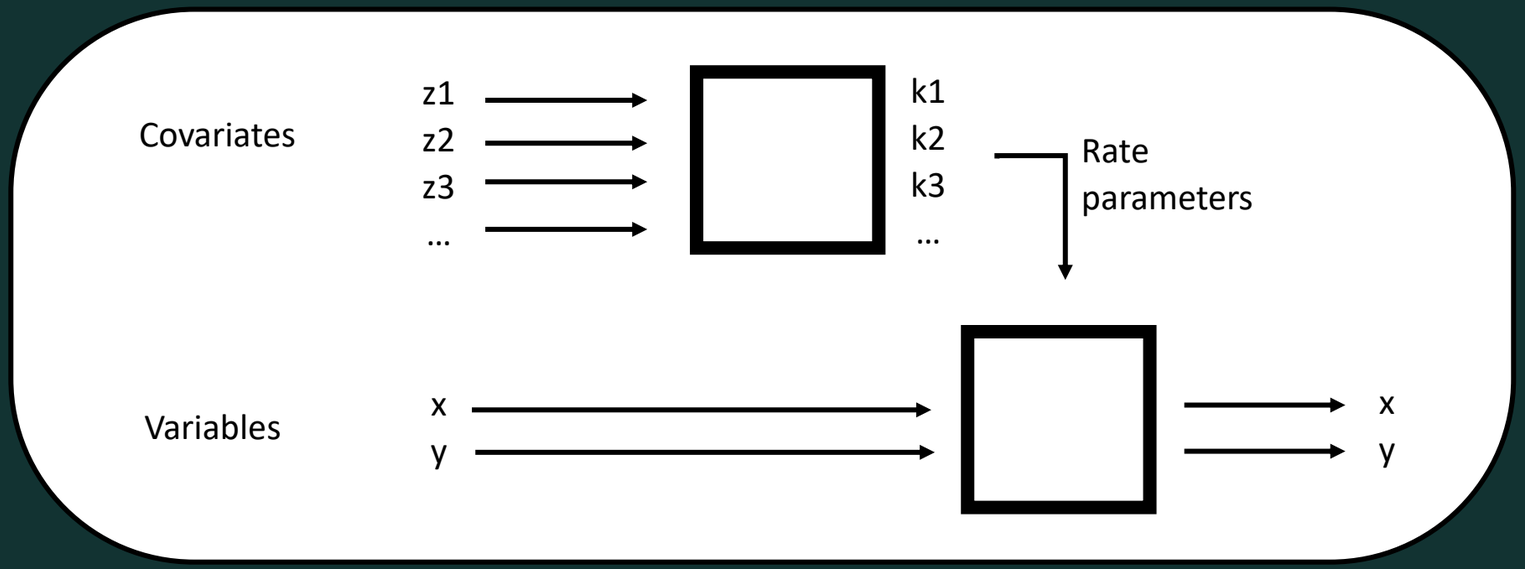
In-Vivo

- Tumor Microenvironment, made up also of cytokines, stromal cells, others immune cells
- Reachability issues of the tumor site, heterogeneous spatial distribution
- Tumor growth specific to tissue and tumor's characteristics
- Antigens could be expressed at different levels

- Patient variability
- Personalization
- Adverse Effects
- Sparse data

Quantitative Systems Pharmacology (QSP)





- White Box dynamics
- Statistical parameter estimation

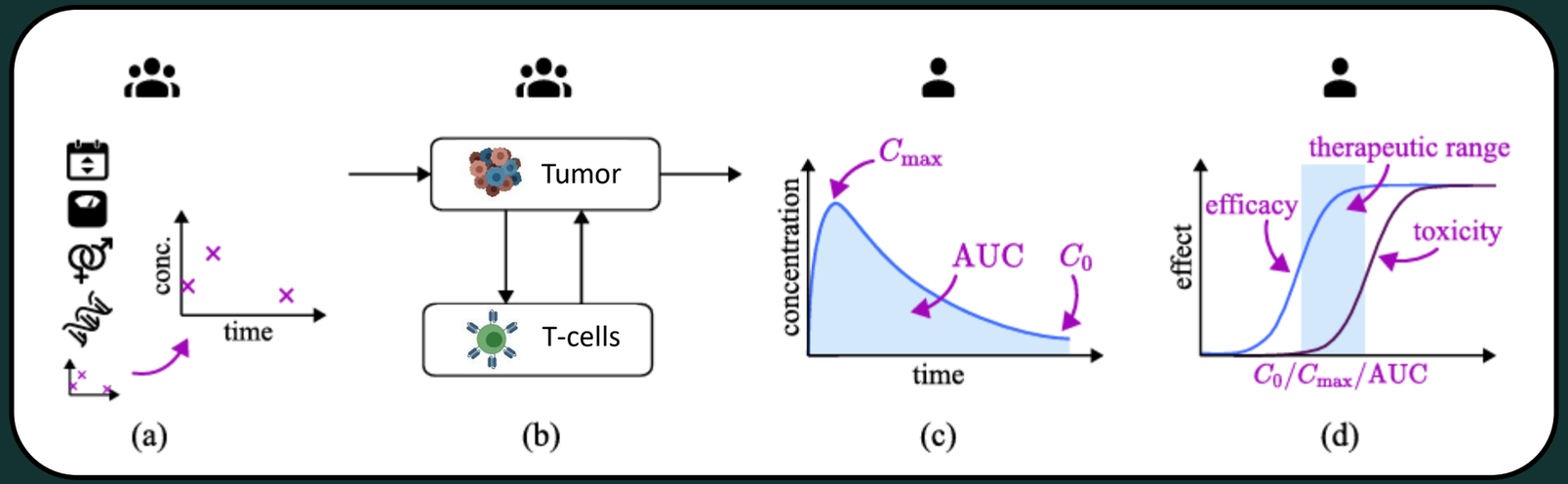
- Interpretability

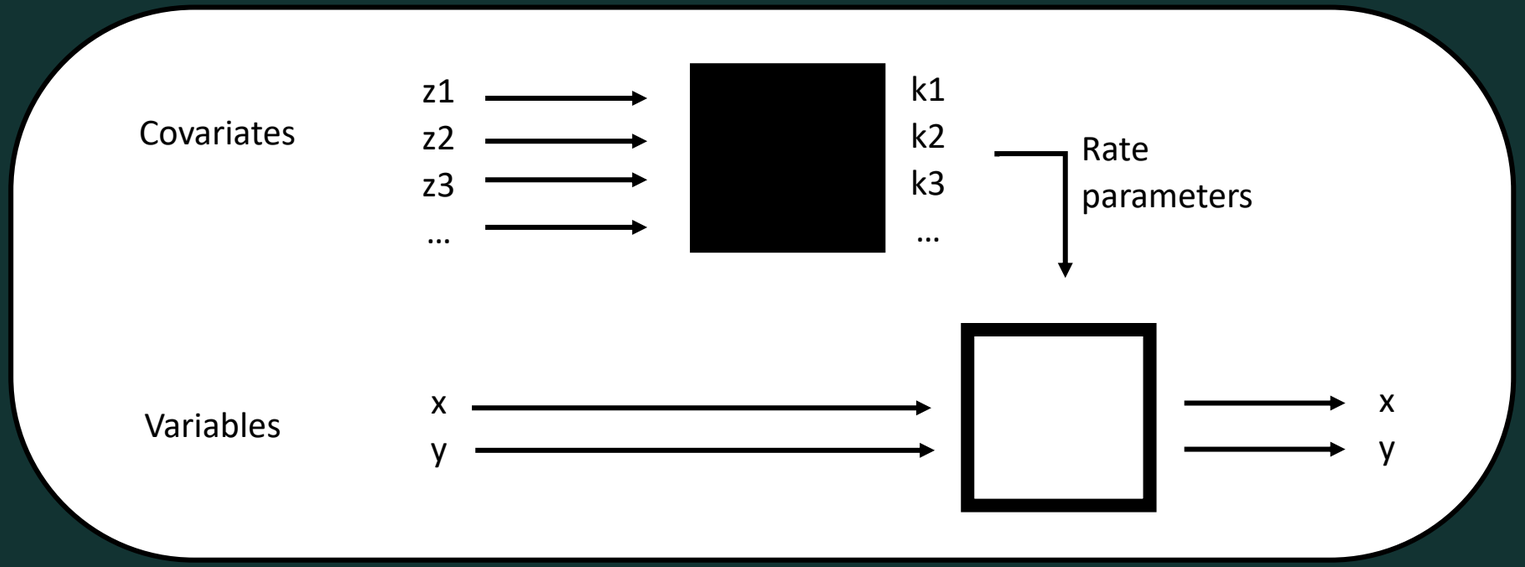
- Partial knowledge of the system
  - Complex biological interactions
  - Adverse Effects

- Sparse data

- Patient variability
- Personalization
- Heterogeneous, multi-scale data integration

Quantitative Systems Pharmacology (QSP) & ML





- White Box dynamics
- Machine Learning for parameter estimation

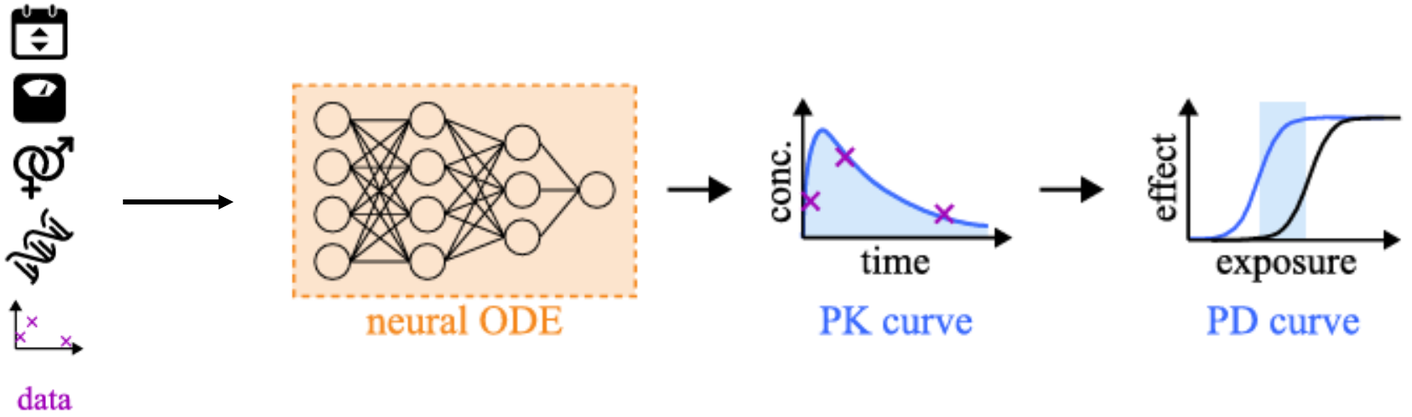
- Interpretability

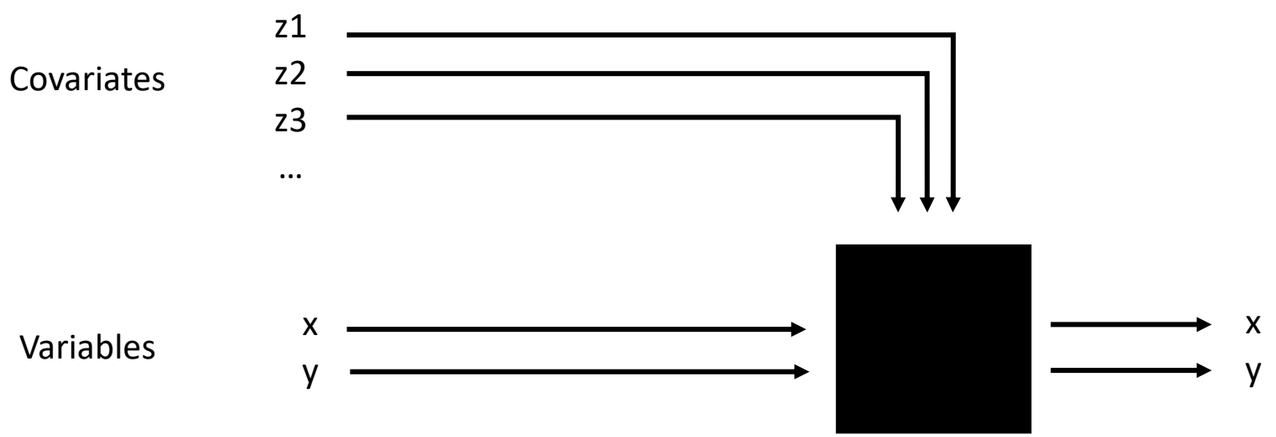
- Partial knowledge of the system
  - Complex biological interactions
  - Adverse Effects

- Sparse data

- Patient variability
- Personalization
- Heterogeneous, multi-scale data integration

Neural ODEs





- Black Box dynamics
- Black Box parameter estimation

- Interpretability

- Partial knowledge of the system
  - Complex biological interactions
  - Adverse Effects

- Sparse data

- Patient variability
- Personalization
- Heterogeneous, multi-scale data integration

Neural Differential Equations

$$y_{k+1} = y_k + f_\theta(y_k)$$

Residual Neural Network (**ResNet**): the Neural Network models the **residual** between input and output, i.e. the **increment**. This can be applied **iteratively** (**Recurrent Neural Network**, **RNN**), generating a discrete evolution.

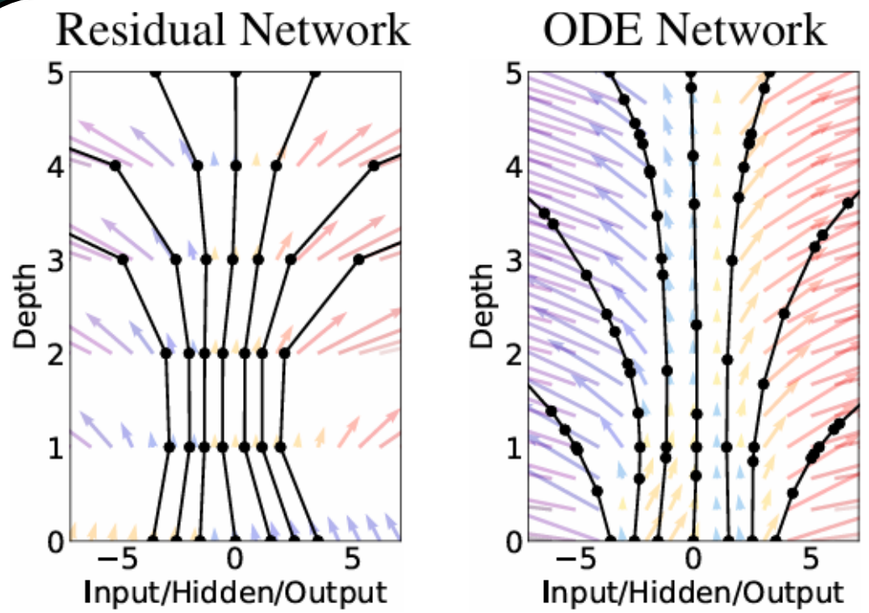
$$\frac{dy}{dt}(t) = f_\theta(y(t), t)$$

Neural Differential Equations (**NDEs**) employ a Neural Network to model the continuous **evolution** of a dynamical system.

$$y(t_{k+1}) \simeq y(t_k) + \Delta t f_\theta(y(t_k))$$

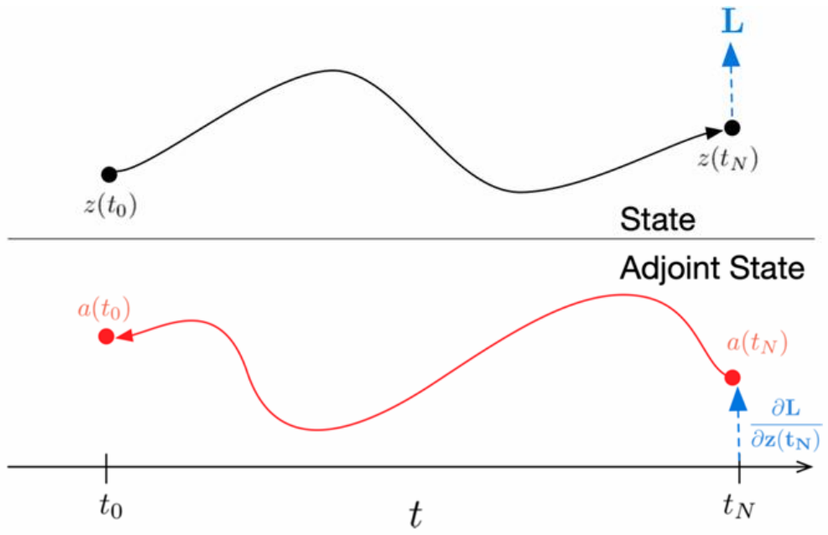
Neural ODEs are the **continuous limit of residual networks**. Equivalent to a ResNet with infinitely many layers, each making an infinitesimal change, they are also called **continuous-depth** neural networks.

Neural Differential Equations



Prediction of ResNets is made by passing the input through all the sequential layers and using the output for updating the input.

Prediction from NDEs is obtained by **integrating** them from time 0 to time T, with the **input given as initial conditions.**

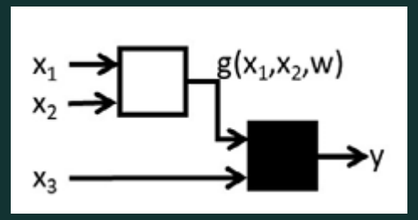


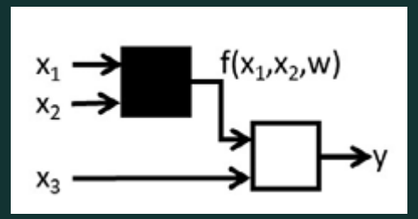
Adjoint sensitivities: the system is trained through the **gradient of the Loss with respect to the parameters of the evolution** (aka of the neural network). Such gradients are found by **integrating the tangent space backward in time** from time T to time 0 and then using it as a change of basis for the gradient of the Loss.

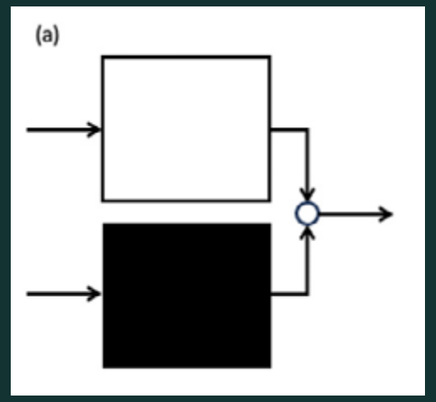
Hybrid Modeling & Inductive bias

How to tackle data sparsity

- Inductive bias: incorporation of fundamental knowledge into Machine Learning models (in particular, neural networks), as a regularization mechanism: reduced risk of overfitting, reduced amount of data needed, enhanced interpretability
- Hybrid modeling: augmentation of mechanistic models with black-box components: enhanced flexibility, automatic integration of covariates





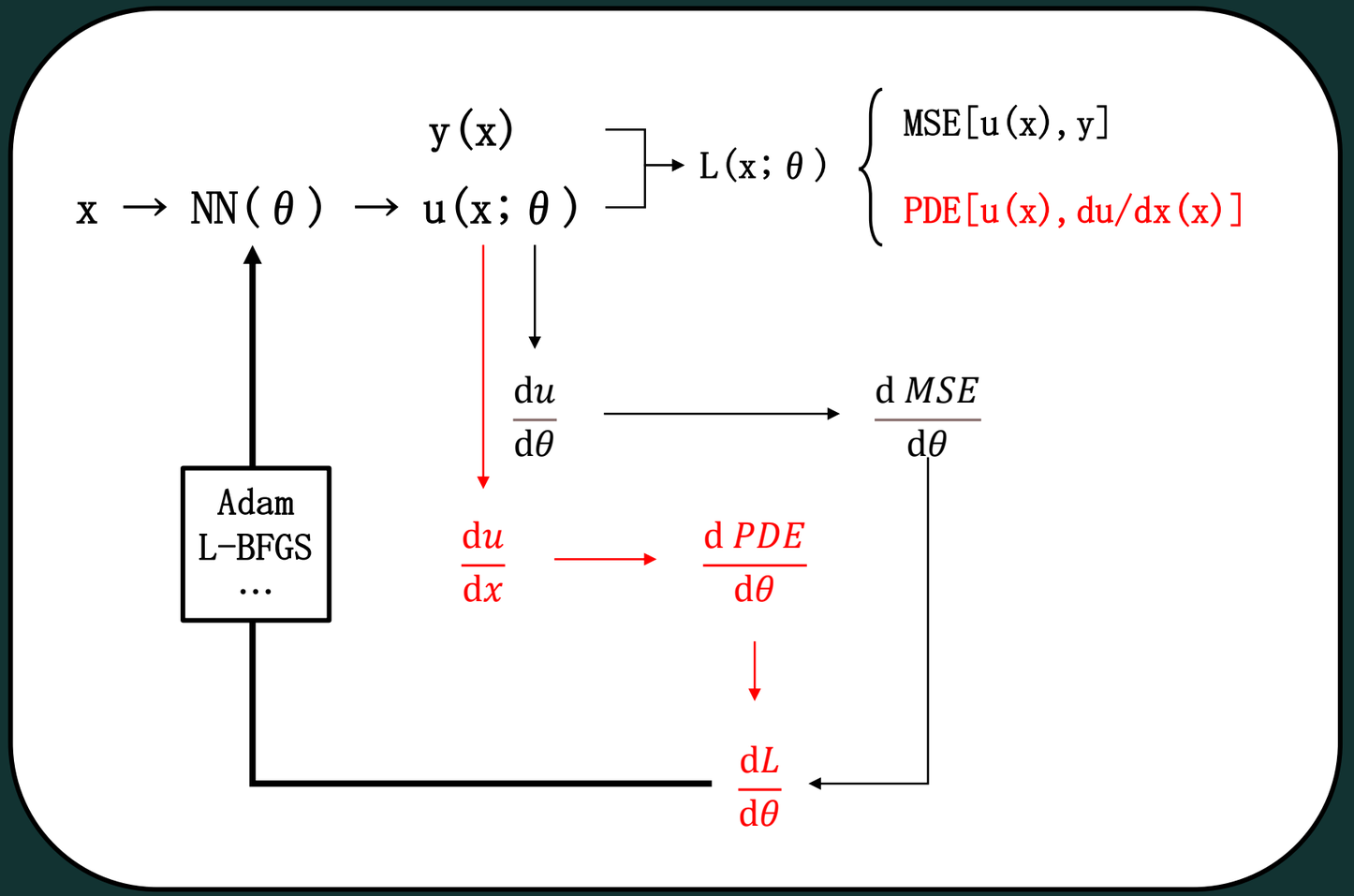


- Hybrid serial model
  - Feature engineering
  - Parameter estimation
  - Multi-branch networks
  - Boundary conditions
    ex. possible ranges of outputs

- Hybrid parallel model
  - Universal Differential Equations
  - Mechanism correction
  - System identification
  - Global vs local parameters

- Smaller and less parametrized modules
  - Interpretability
  - Sparse data
- Partial knowledge of the system
  - Complex biological interactions
  - Adverse Effects
- Patient variability
- Personalization
- Heterogeneous, multi-scale data integration
- Training procedure

Physics-Informed Neural Networks



- Model the **solution**, not the evolution
- Can constrain anything that can be expressed as a PDE
- Meshless method
  - Noisy data
  - Ill-posed problems
- Forward problem
- Inverse problem
  - Parameter estimation
- Sparse data
- Partial knowledge of the system

Conclusions

1

Neural Networks Empower CAR-T Modeling

Neural networks offer a powerful tool for modeling the complex, nonlinear relationships inherent in CAR-T therapies, enabling more accurate predictions of treatment outcomes and adverse events.

2

Personalized Insights for Optimized Care

By incorporating patient-specific data, neural network models can provide personalized insights to guide treatment decisions and improve outcomes for individual patients undergoing CAR-T therapies.

3

The hybrid framework is the only framework

Both the complete causal understanding of the system and the implementation of fully automatic algorithms are unreasonable options. The accumulation of sparse theoretical insights and empirical approaches is the only possibility, and the expertise of the mathematical modeler passes through her ability in their integration.

Thanks for your attention!