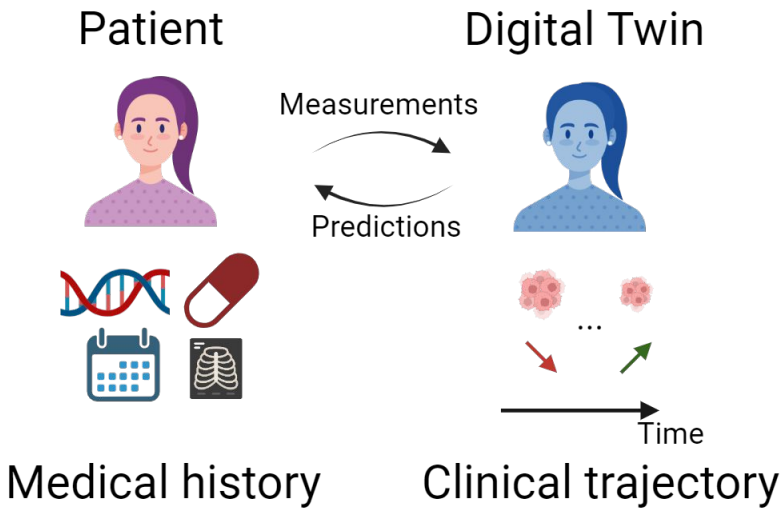
Towards Digital Twins for Clinical Trials

PRISME Forum
Spring 2024 Technical Meeting

Dr. Fabian Schmich
Senior Principal Scientist, Capability Lead AI/ML
Roche Pharma Research and Early Development

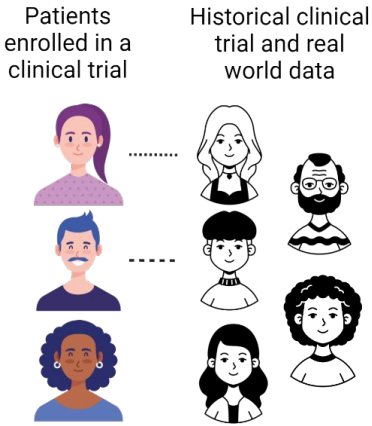
May 21st, 2024 | Saclay, France

What are Digital Twins in the Context of Clinical Trials?



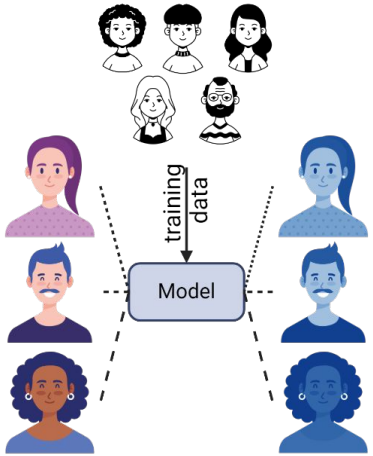
- *Virtual representation* of a patient resembling their *longitudinal characteristics* such as dynamics of blood biomarkers or disease progression
- *Bidirectional connection* between the patient and their DT → patient information informs the state of the DT and the DT's prediction facilitate medical decision making for the patient

Digital Twins Differ vs. Other Approaches



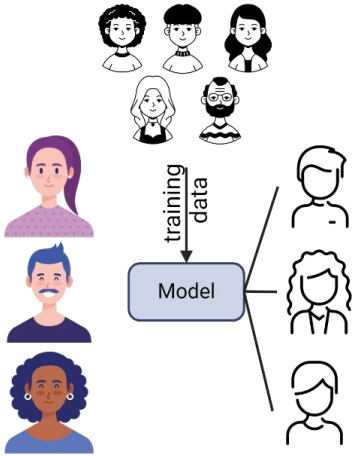
External control arm

- Matching of patients from available data sources to those enrolled in the trial
- Mature and FDA approved methodology



Digital twin

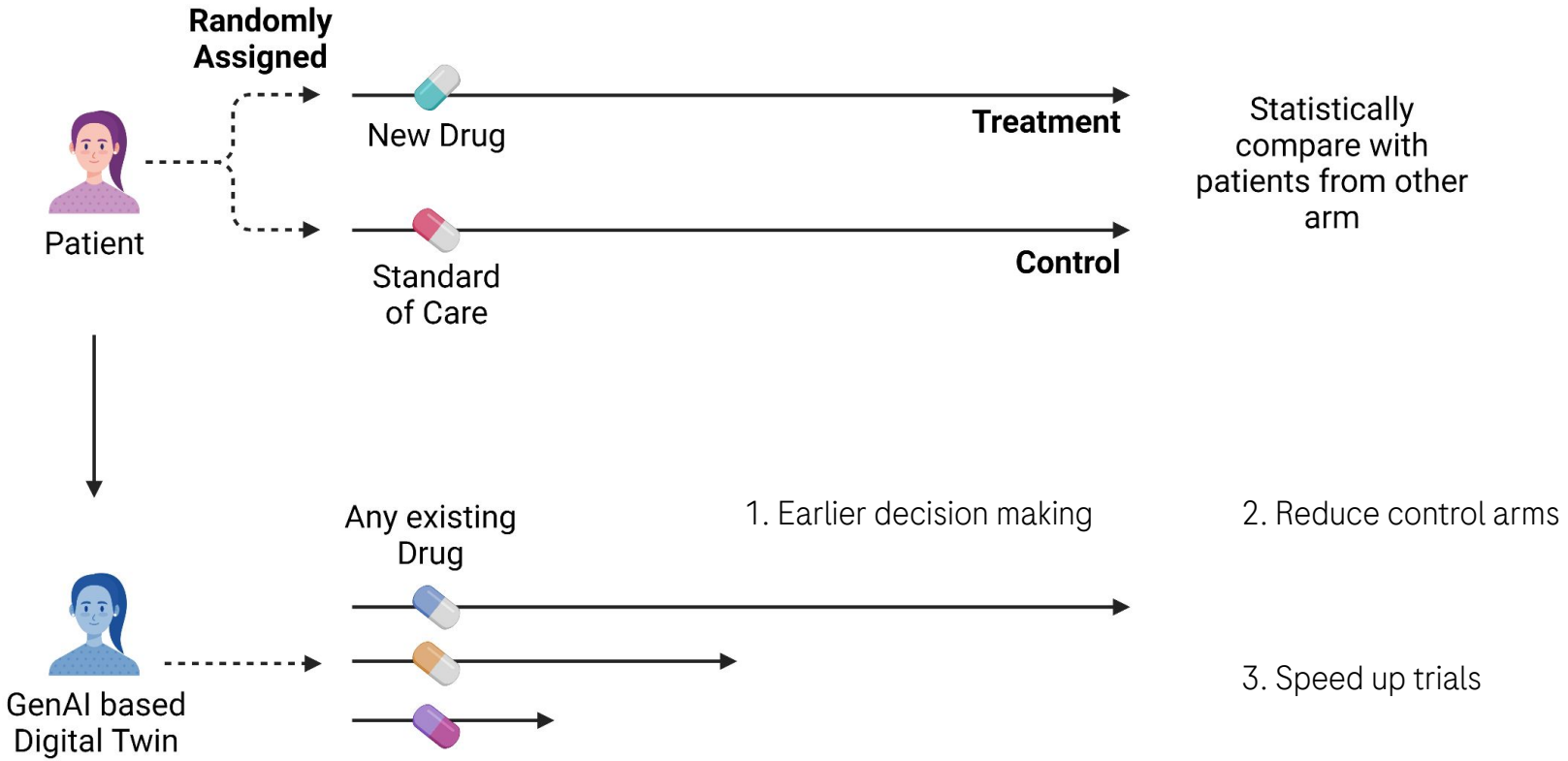
- Use available data to fit a model that predicts counterfactual trajectories
- Unknown performance and not FDA approved



***In silico* clinical trial**

- Use available data to fit a model that generates synthetic patient trajectories
- Mechanistic models can be considered and qualified by FDA

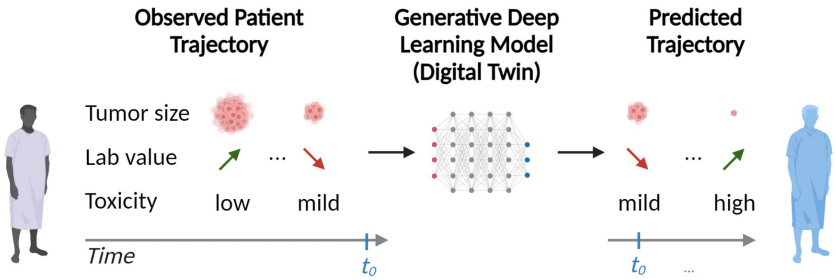
Clinical Trials & Digital Twins



Two Focus Applications for Digital Twins in Clinical Trials

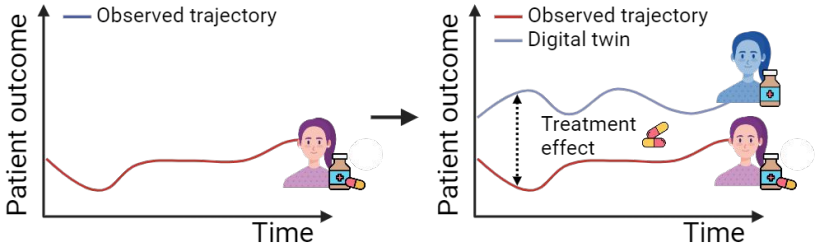
Patient Trajectory Prediction

- Predict future states of patient, given their current medical history
- Multivariate, irregularly sampled time series setting with high missingness
- Forecast patient trajectories for earlier decision making

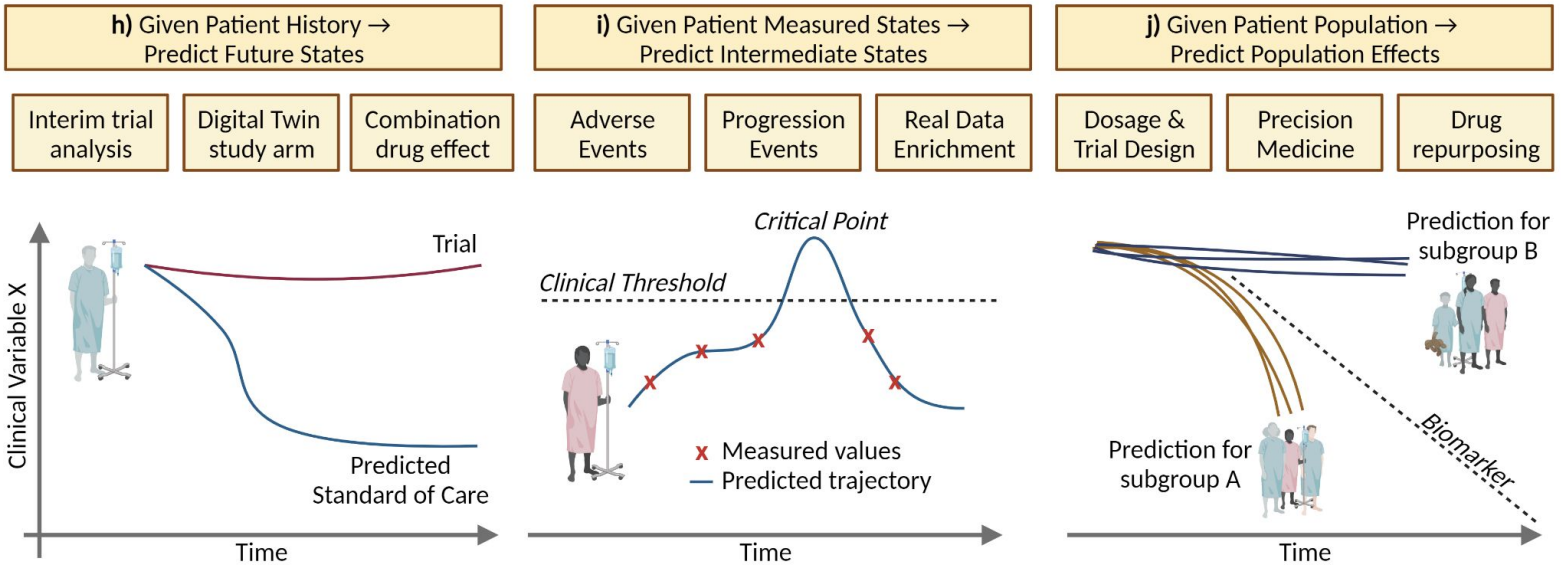


Combination Therapy Deconvolution

- Setting: Combinatorial trial with established + novel therapeutic modality
- For a patient with an observed combination therapy trajectory, deconvolute effect of novel modality

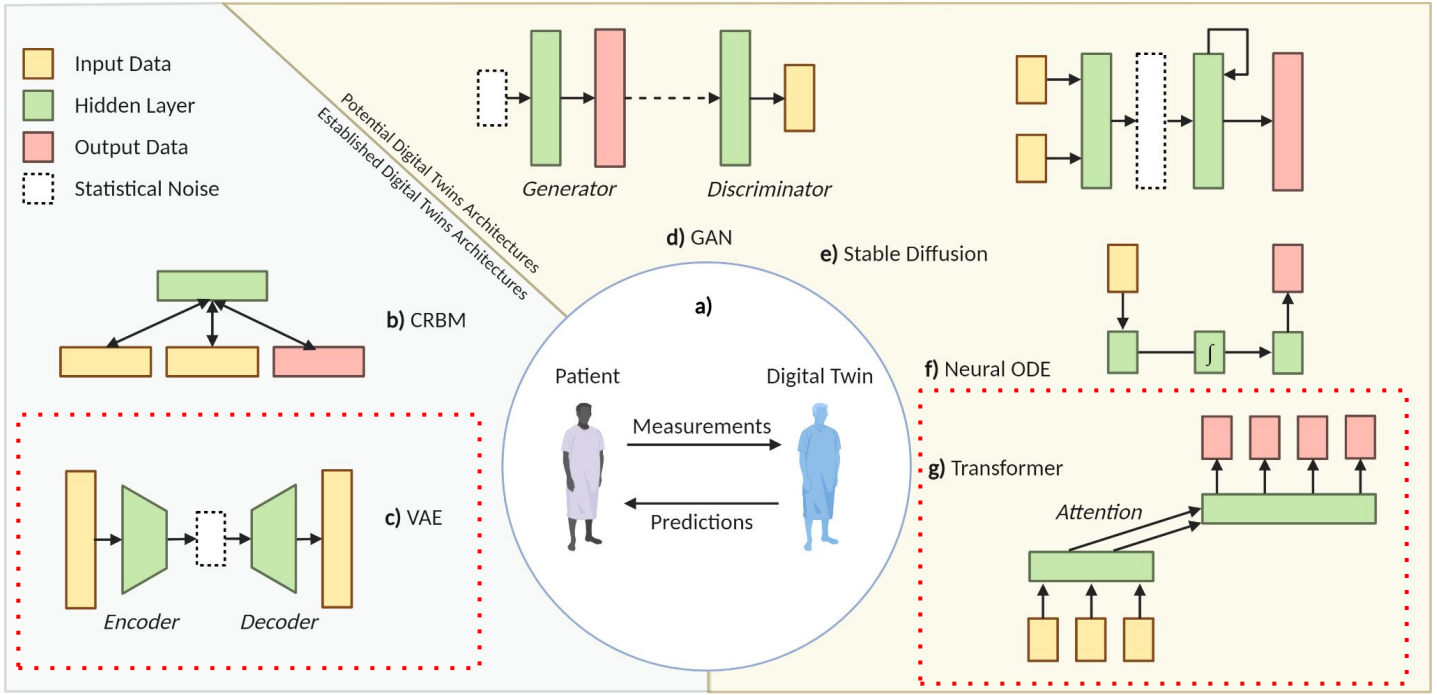


Additional Use Cases for Digital Twins in Clinical Trials



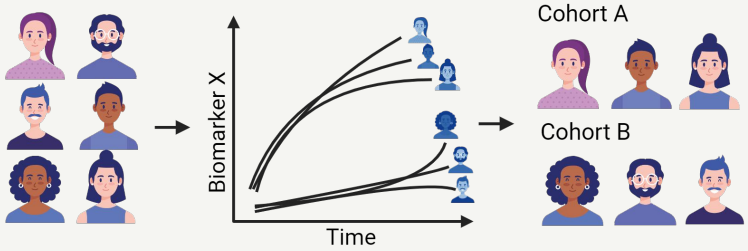
Bordukova and Makarov et al., https://doi.org/10.1080/17460441.2023.2273839

Established and Potential Model Architectures for Digital Twins

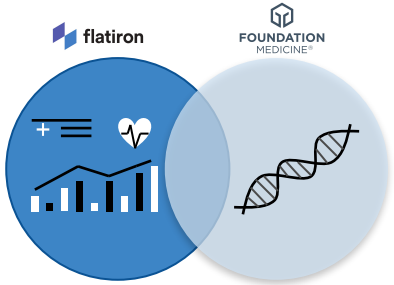


Bordukova and Makarov et al., https://doi.org/10.1080/17460441.2023.2273839

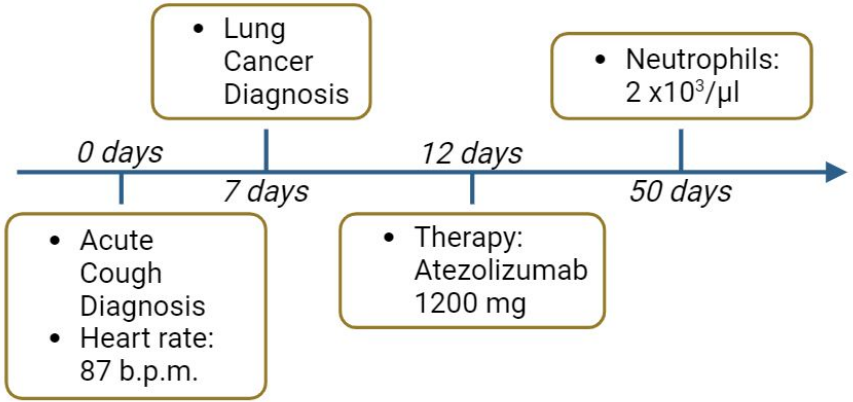
Patient Trajectory Forecasting with LLMs



Real World Data (RWD) from Flatiron & FMI



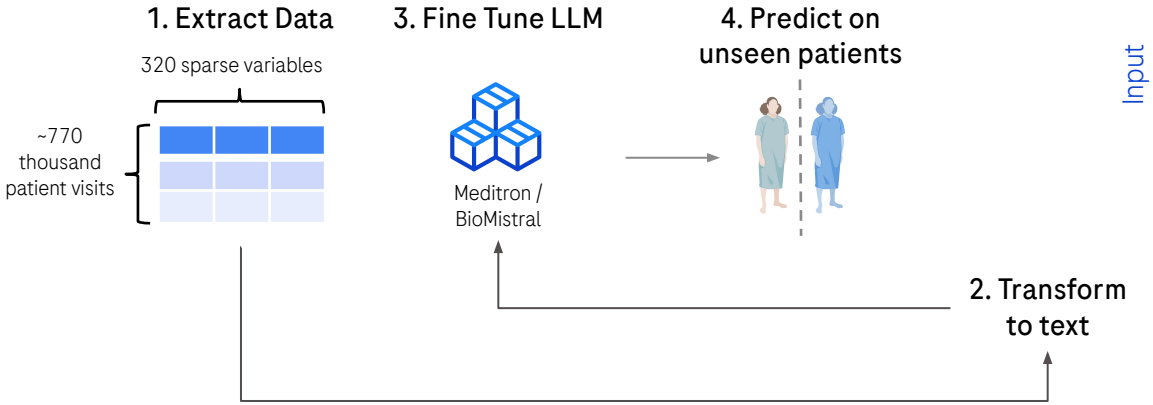
- Electronic Health Records from US oncology clinics
- ~16.5k NSCLC patients
- Trajectories usually going multiple years



Why we use (among other models) Large Language Models for Digital Twins

1. (Non-random) Missingness is a key issue in biomedical data - natural language handles this implicitly
2. EHR RWD dat data is noisy and incomplete - natural language allows flexibility to reduce amount of preprocessing needed + flexibility even after training (e.g. zero shot or in-context learning)
3. Many important variables are often rare, e.g. genes - LLMs can handle these gracefully
4. Recent papers have applied LLMs in other areas for forecasting
5. Could be used as a platform to perform many tasks, e.g. for medical practitioners to converse with model

How we use Large Language Models for Digital Twins



Input

```
{ Patient history: {
   0 days later: {
            neutrophils: 4.2,
            leukocytes: 15,
            ...
   }, 1 days later: { ..
   ...
  Baseline data: {
   birth year: 1958 - 01 - 01, ...
   },
  Output variables: [progression, neutrophils, ...],
  Output future day: [7, 14, ...],
  Prompt:  Please output for the previously noted down days...
}
```

Output

```
{ "7 days later": {
   "progression": "Not documented",
   "neutrophils": "1.2",
   ...}}
```

Preliminary Results for Patient Trajectory Forecasting with LLMs

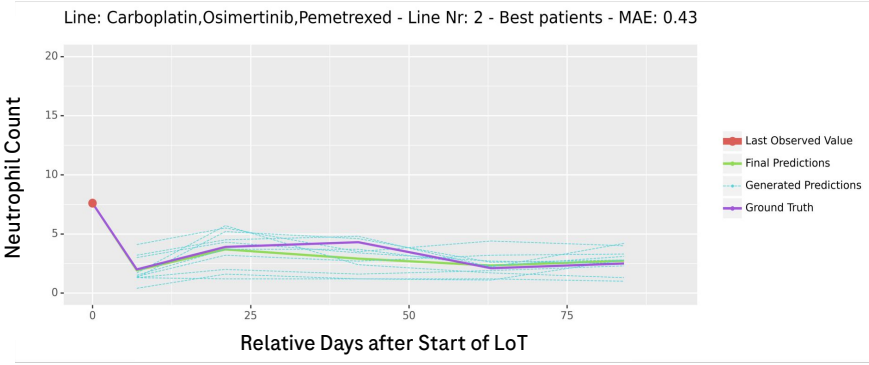
Task

Predict 6 key *Non Small Cell Lung Cancer* variables over 91 days after the start of a new line of therapy

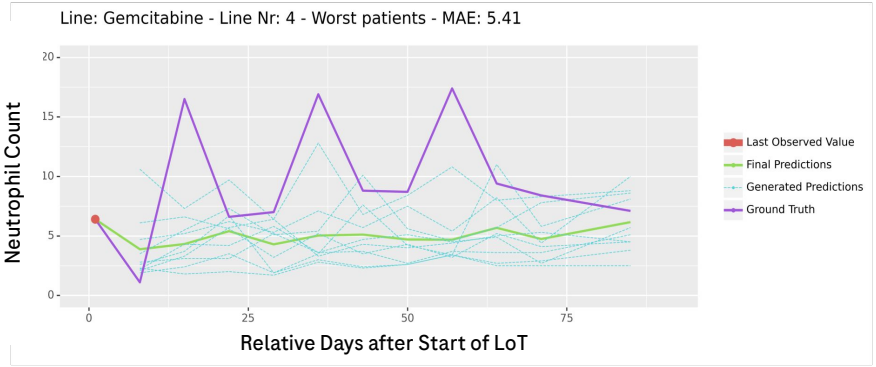
Summary

- Better or equal to state of the art baselines in 8/10 metrics
- Within 3.2% of performance for all others

Low Error Prediction



High Error Prediction

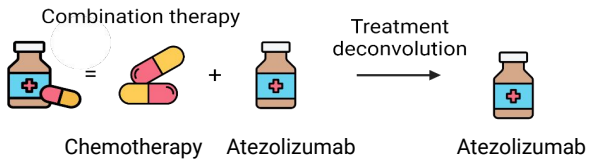


Treatment Deconvolution with cVAEs

Randomized Clinical Trial (RCT) Dataset and Deconvolution Approach

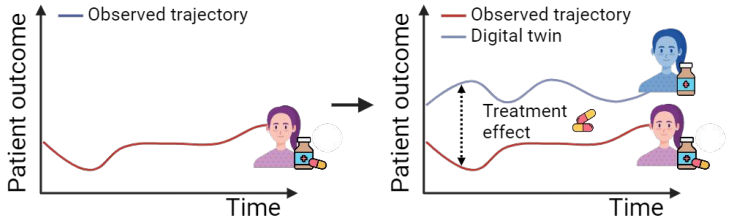
Historical RCT Data

- Roche internal collection of curated and harmonized historical CIT trial data
- Multimodal: clinical, genomics, transcriptomics, histopathology
- Total: 36 studies and 19 430 patients, >17 indication and > 31 treatments
- NSCLC: 9 studies with 6592 patients (Atezo mono and combo)

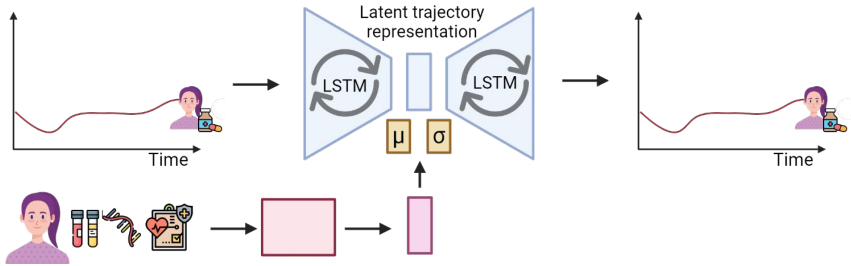


Combination Therapy Deconvolution

- Goal: Deconvolution towards Atezolizumab, i.e. predict patient trajectories under Atezo-only treatment
- Create a reference to estimate effect contribution of the experimental drug

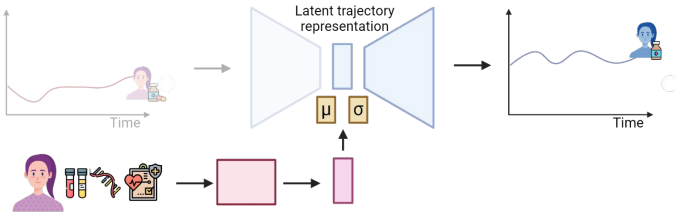


LSTM-Based Conditional Variational Autoencoders (cVAEs)



- **Autoencoder** - unsupervised feature extraction from patient trajectories, low-dimensional trajectory embedding
- **Variational** - generation of new trajectories through sampling from the latent distribution
- **Conditional** - sampling of patient-specific trajectories
- **LSTM** - accounting for longitudinal component

Predict a counterfactual trajectory using baseline data



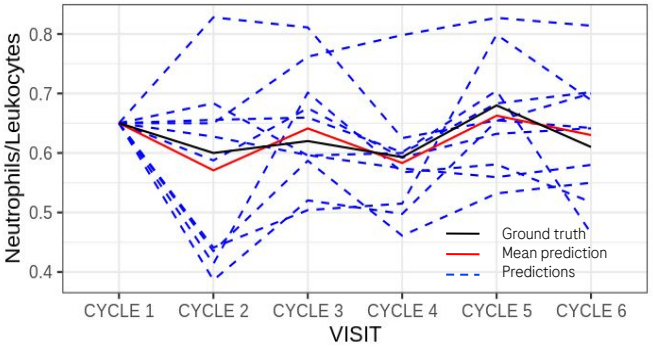
Condition includes treatment, patient demographics data and integrates **omics data**

- Fully data-driven

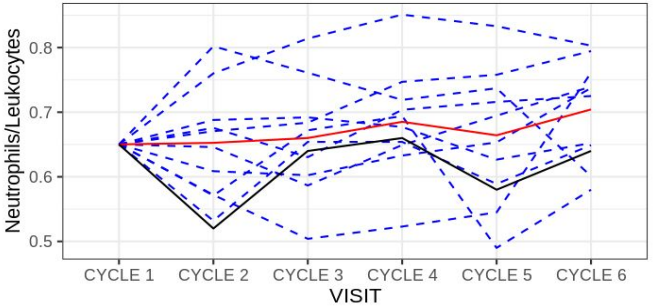
Preliminary results: Patient Trajectory Forecasting with cVAEs

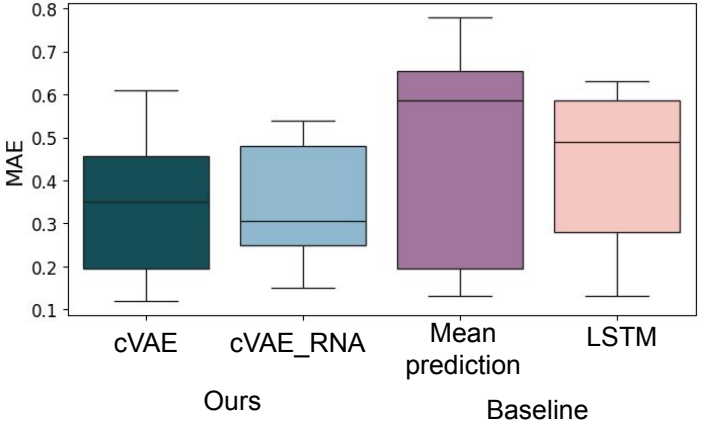
- Predict 17 clinical lab values for 5 time points

Low error prediction example



High error prediction example





- Better performance than baselines
- Integration of RNA-Seq data improves performance

Take-Home Messages

- Digital Twins are virtual representations of patients resembling their longitudinal characteristics
- Digital Twins have a broad potential in the context of clinical trials, e.g. for forecasting patient trajectories or counterfactual predictions
- We are pioneering a the field of *clinic-in-the-loop,* leveraging generative AI to train models from historical RCT and RWD data to augment clinical trials
- Preliminary results show that LLM-based and cVAE-based models exhibit promising performance

Acknowledgements: The Digital Twins Project

An academic collaboration in the Munich AI ecosystem

MUDS | MUNICH SCHOOL FOR DATA SCIENCE
HELMHOLTZ | TUM | LMU

Nikita Makarov

Maria Bordukova

Fabian Schmich

Raul Rodriguez -Esteban

HELMHOLTZ MUNICH

Michael Menden

C. López

C. Marr

T. Peng

F. Theis

Doing now what patients need next