Accelerated drug development and precision pharmacotherapy using DeepPumas

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Scientific Modeling

- Encodes scientific understanding
- Data-efficient
- Transparent and interpretable
- Dosage optimization, etc.

Machine Learning

- Automatic model discovery
- Finding unintuitive relationships
- Handling complex data
- Lacks scientific understanding
- Requires big data
- Inscrutable

Scientific Machine Learning

- Labor intensive
- Misses unintuitive relationships
- Hard to utilize complex data
DeepPumas – simple and effective utilization of both knowledge and data

**Data**
- Clinical Tests
- Medical Images
- Omics
- Monitoring Devices
- Wearables

**Models**
- Known Molecular Interactions
- Known Cell Interactions
- Known Drug Properties
- Known Prognostic Factors

Good Predictions
Identifying oncology patient risk factors
Questions for our data

- What is driving tumor dynamics?
- What effect does the drug have?
- How does tumor size affect survival?

Training $N = 200$

Loosely mimicking Non-Small-Cell Lung Cancer
What is a neural network (NN)?

Information processing mechanism
Loosely based on neurons

Universal approximator!
- Approximate any function
- Functional form determined by parameters
- Link parameter fitting to patient outcome

Mathematically: Just a function!
NNs are useable anywhere where you’d use a function!

Use data to automatically discover relationships
Neural-embedded tumor size model

How do they grow? How does that differ between patients?

Parameters

\[ \xi = \text{NN (covariates)} \]
\[ CL = tvCL \]
\[ V_c = tvV_c \cdot e^{\eta V_c + \xi_1} \]
\[ TS_0 = tvTS_0 \cdot e^{\eta TS_0 + \xi_2} \]

\( \eta \sim \text{MvNormal (I (3))} \)
\( \eta TS_0 \sim \text{Normal (0, } \omega TS_0 \text{)} \)
\( \eta V_c \sim \text{Normal (0, } \omega V_c \text{)} \)

Could be

Dynamics

\[ Central' = -\frac{CL}{V_c} \cdot Central \]

Observational noise

\[ TS \sim \text{Normal (} TS_r + TS_u, \sigma \text{)} \]

Elucidation of relationship between tumor size and survival in non-small-cell lung cancer patients can aid early decision making in clinical drug development.

Y Wang, C Sung, C Dartois, R Ramchandani, B P Booth, E Rock, J Gobburu
Projecting technical success of oncology trials

Predicting tumor size from baseline (t=0) data
Estimating overall survival

Modeling overall survival over time…?

$\lambda = \text{Hazard}$

$\Lambda = \text{Cumulative Hazard}$

$\frac{d\Lambda}{dt} = \lambda(t)$

$\Lambda(0) = 0$

Exponential (for reference)

$\lambda(t) = c$

Weibull (for reference)

$\lambda(t) = \lambda_0 \cdot K \cdot (\lambda_0 \cdot t)^{K-1}$

Neural

$\lambda(t) = \text{NN}(t)$

- Quick
- Universal
- Fine with only survival data

- Risk overfitting
- No mechanism
- No counterfactual
Estimating tumor size dependent survival

\[
\frac{d\Lambda}{dt} = \lambda(TS)
\]

where

\[
\lambda(TS) = NN(TS)
\]

\[\lambda = \text{Hazard}\]

\[\Lambda = \text{Cumulative Hazard}\]
Predicting Expected Patient Survival

Overall Survival

Dose: 2.0mg

Dose: 3.0mg

Dose: 3.0mg

Dose: 3.0mg

Dose: 2.0mg
Refining individual predictions

Updating estimates as data comes in
Patient-level dosing guidance

Baseline predictions of individual survival for different dosing regimens

- Dose: None
- Dose: 1.0mg
- Dose: 3.0mg

Tumor size (cm)

Survival probability

Months

Dose
DeepPumas
Actual
DeepPumas model identified:
- Tumor dynamics
- Drug effect
- Covariate effects
- Tumor size – survival relationship

DeepPumas model enabled:
- Predicting outcomes
- Continually improving predictions
- Quantification of survival effects of treatment options

Could be used with other biomarkers, covariates, and time-to-event observations.
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Augmenting healthcare intelligence with predictive analytics that turn data into life-saving decisions