

Predictive modelling for personalized breast cancer treatment

SysBioCancer 2021, Institut Curie

Michal Kloc

Bentires-Alj Lab, University Hospital Basel, Switzerland, September 27, 2021



Outline

Projects:

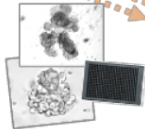
1. Drug sensitivity prediction for efficient screening
 - a. Drug screening platform, pipeline
 - b. PaccMann: open source model of cancer drug sensitivity by IBM
2. Optimizing a mathematical model of cancer therapy using differentiable programming
 - a. Cancer therapy as dynamical system
 - b. Optimal control problem

1 .Personalized treatment

PDO imaged-based drug screening platform - overview

PDO = patient-derived organoid

University Hospital Basel



- Processing BC tissues
- Breast cancer PDO cultures: Establishment, Expansion and Characterization

- Single cell + organoid quantification
- Evaluation + analysis

Basic +
Translational
Scientists



Liquid handler



Yokogawa CQ1

Tissue
culture

Ex vivo
PDO drug
screen

Microscopy

Image +
clinical data
analyses

Microscopy + Screening Scientists

- Automated confocal microscopy
- Maintenance
- Data transfer

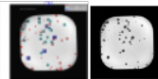


Temporary Storage
PC/server



SciCore server
Image processing + storage

Image + Data Scientist

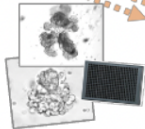


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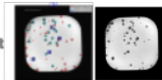


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The amount of
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→
not all drugs can be tested

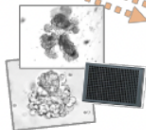
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predictive model: input \rightarrow transcriptomic profile of the tumor
output \rightarrow drug efficacy

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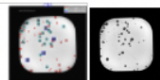


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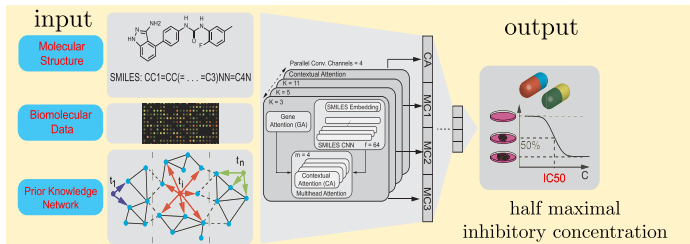
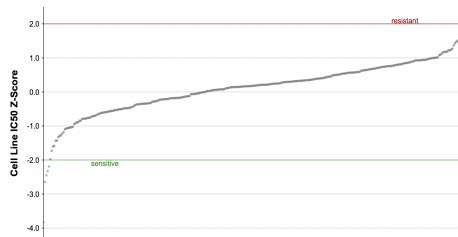
1. PaccMann: predictive model by IBM

- trained on GDSC data
Genomics of Drug Sensitivity in Cancer

Drugs (ranked by cell line sensitivity)

| Drug | Targets | Z score |
|-----------|--------------------|----------|
| LCL161 | XIAP, cIAP1, cIAP2 | -3.83214 |
| MCT4_1422 | MCT4 | -2.64526 |
| FMK | RSK | -2.45049 |
| LGK974 | PORCN | -2.32604 |
| Wnt-C59 | PORCN | -2.1921 |

Relative sensitivity of MDA-MB-231



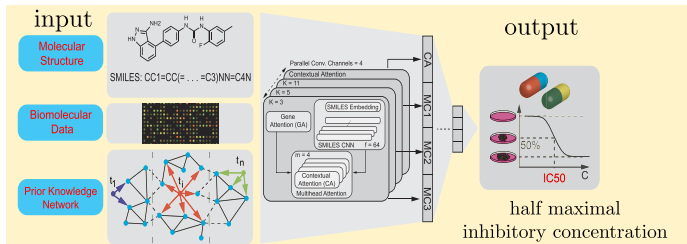
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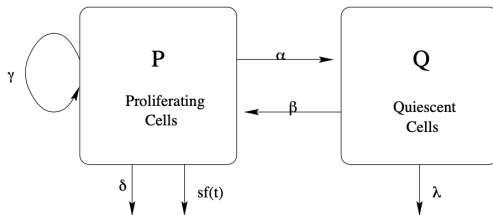


- Can 2D cell lines be a good training set for predictions for patients' samples?
- Perhaps a different source of the training data (TSGA database)?

2. Optimizing a model of cancer therapy

Cancer therapy as dynamical system
Model of bone marrow under chemotherapy

$$\begin{bmatrix} \frac{dP}{dt} \\ \frac{dQ}{dt} \end{bmatrix} = \begin{bmatrix} \gamma - \alpha - \delta - sf(t) & \beta \\ \alpha & -\beta - \lambda \end{bmatrix} \begin{bmatrix} P \\ Q \end{bmatrix}$$

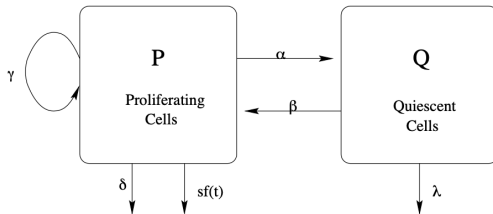


- P : proliferating bone marrow cell mass, Q : quiescent bone marrow cell mass
- γ : growth rate of cycling cells
- α : transition rate from proliferating to resting
- β : transition rate from resting to proliferating
- δ : natural cell decay, λ : quiescent cell loss
- $0 \leq f(t) \leq 1$: time-dependent dosage of the chemotherapeutic treatment with amplitude s

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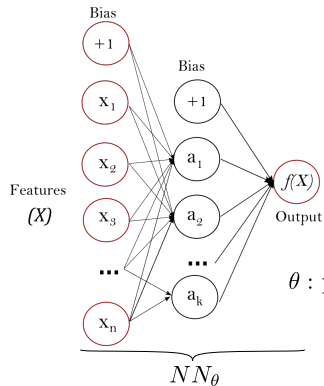
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Optimal control problem:
Maximize the dose while maintaining
bone marrow cell mass

2. Optimizing a model of cancer therapy

Let's employ the workhorse of machine learning:

automatic differentiation

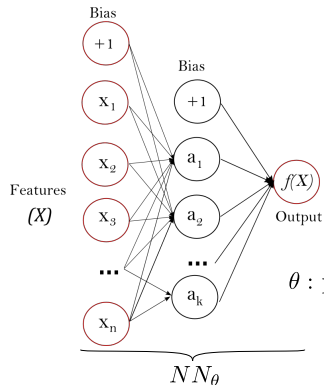


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θ : parameters of the network

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Implement the task in a form of loss function \mathcal{L} that needs to be minimized

$$\mathcal{L} = \sum_{i=1}^N \frac{c_1}{2} (1 - f(t_i)) - c_2 (P(t_i) + Q(t_i))$$

maximize the dose

maximize the overall cell number

using AD compute gradients $\frac{\partial \mathcal{L}}{\partial \theta_i}$

Update parameters θ in direction given by the gradient

$$\theta_i \rightarrow \theta_i - \eta \frac{\partial \mathcal{L}}{\partial \theta_i}$$

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Not only the NNs but whole segments of the code (like ODE solver for example) are fully differentiable \Rightarrow can get gradients with AD

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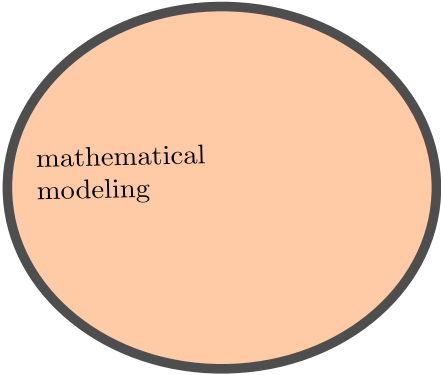
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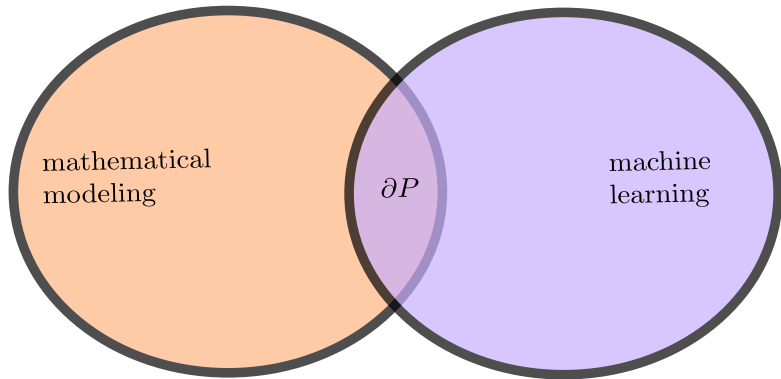


mathematical
modeling

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References

- PaccMann (IBM)

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Panetta, J. C., and Fister, K. R. (2000). *Optimal control applied to cell-cycle-specific cancer chemotherapy*. *SIAM Journal on Applied Mathematics*, 60 (3), 1059-1072.

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Thanks for your attention.