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Building Bridges in Medical Science 2021 Conference Proceedings

The Building Bridges in Medical Science 2021 Conference was held virtually on March 6th, 2021. Abstracts were judged by panel consisting of representatives from both the BBMS Organising Committee and the Cambridge Medicine Journal. A selection of abstracts are included in this set of conference proceedings, published by the Cambridge Medicine Journal.

Contents

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Title:
A Computational Model of Cancer Metabolism for Personalised Medicine

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Abstract:
Cancer cells must rewrite their ‘‘internal code’’ to satisfy the demand for growth and proliferation. Such changes are driven by a combination of genetic (e.g., genes’ mutations) and non-genetic factors (e.g., tumour microenvironment) that result in an alteration of cellular metabolism.
For this reason, understanding the metabolic and genomic changes of a cancer cell can provide useful insight on cancer progression and survival outcomes.

In our work, we present a computational framework that uses patient-specific data to investigate cancer metabolism and provide personalised survival predictions and cancer development outcomes. The proposed model integrates patient-specific multi-omics data (i.e., genomic, metabolomic and clinical data) into a metabolic model of cancer to produce a list of metabolic reactions affecting cancer progression.
Quantitative and predictive analysis, through survival analysis and machine learning techniques, is then performed on the list of selected reactions.

Since our model performs an analysis of patient-specific data, the outcome of our pipeline provides a personalised prediction of survival outcome and cancer development based on a subset of identified multi-omics features (genomic, metabolomic and clinical data).

In particular, our work aims to develop a computational pipeline for clinicians that relates the omic profile of each patient to their survival probability, based on a combination of machine learning and metabolic modelling techniques. The model provides patient-specific predictions on cancer development and survival outcomes towards the development of personalised medicine.

Computational Modelling of Breast Cancer for Personalised Medicine

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Problem: Understanding Cancer Progression

Cancer cells must rewrite their "internal code" in order to satisfy the demand for growth and proliferation. Such changes result in an alteration of **cellular metabolism** and they are driven by a combination of genetic factors (e.g., genes' mutations) and non-genetic factors (e.g., tumour microenvironment).
For this reason, understanding the **metabolic and genomic changes** of a cancer cell can provide useful insight on cancer progression and survival outcomes.

Proposed Solution: Computational Model of Cancer

We present a **computational framework** that uses patient-specific data to investigate **breast cancer metabolism** and provide **personalised survival predictions** and **cancer development outcomes**.
The pipeline of the proposed model constists of four main steps:

(a) **Multi-omic data** (i.e., genomic, metabolomic and clinical data) are collected from publicly available cancer repositories, such as The Cancer Genome Atlas and cBioPortal (Figure 1(a));

(b) The collected data are integrated into a **metabolic model of breast cancer** to produce a list of metabolic reactions affecting cancer progression (Figure 1(b));

(c) Quantitative and predictive analysis, through **survival analysis and machine learning** techniques, is then performed on the list of selected reactions (Figure 1(c));

(d) Since our model performs an analysis of patient-specific data, the outcome of our pipeline provides a **personalised prediction** of survival outcome and cancer development based on a subset of identified multi-omics features (genomic, metabolomic and clinical data (Figure 1(d)).

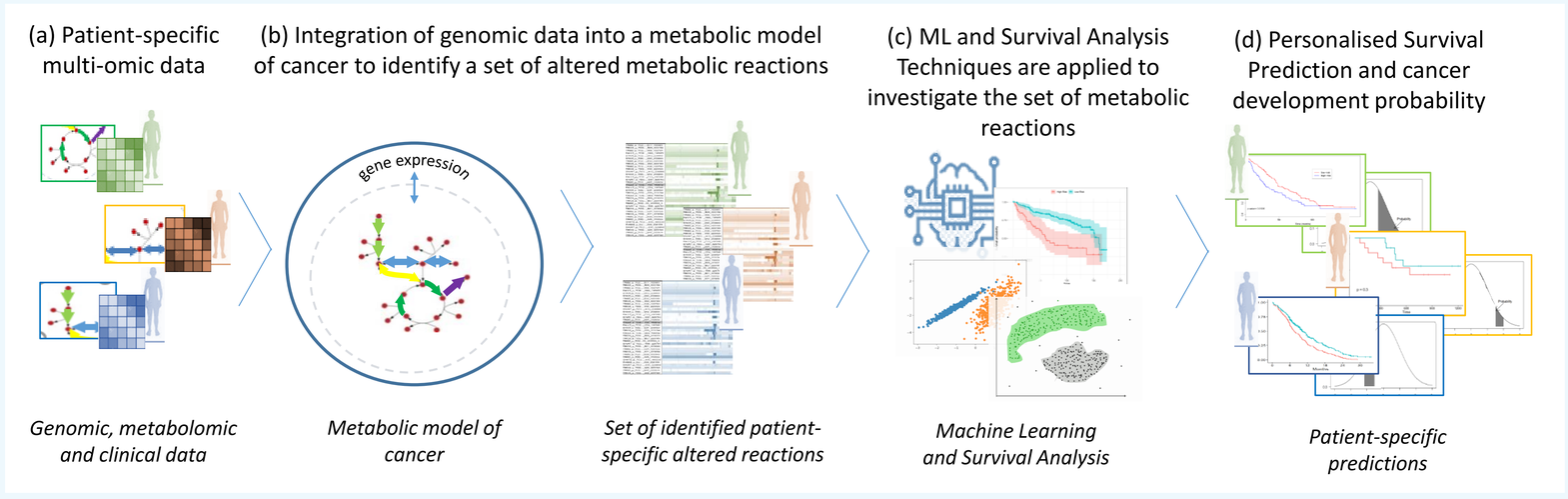

Figure 1. Pipeline of the proposed methodology for turning a metabolic model of cancer cell into a patient-specific tool for survival prediction and cancer development probability.

Results: Predicting Survival Outcomes

Patients are stratified in high/low-risk groups based on their prognostic index, a numeric value that is used to determine the status of the cancer. The predictive model of breast cancer can be used to produce two main outcomes:

- **Selection of cancer-related metabolic reactions**. 5 reactions resulted higher in the high-risk patients than in the low-risk patients. All the five reactions are involved in the fatty acids synthesis, which is strictly related to cancer (Figure 2(a)).
- **Survival Probability Prediction** The correlation between the selected fluxes and survival outcomes is used to build the predictive model (Figure 2(b)).

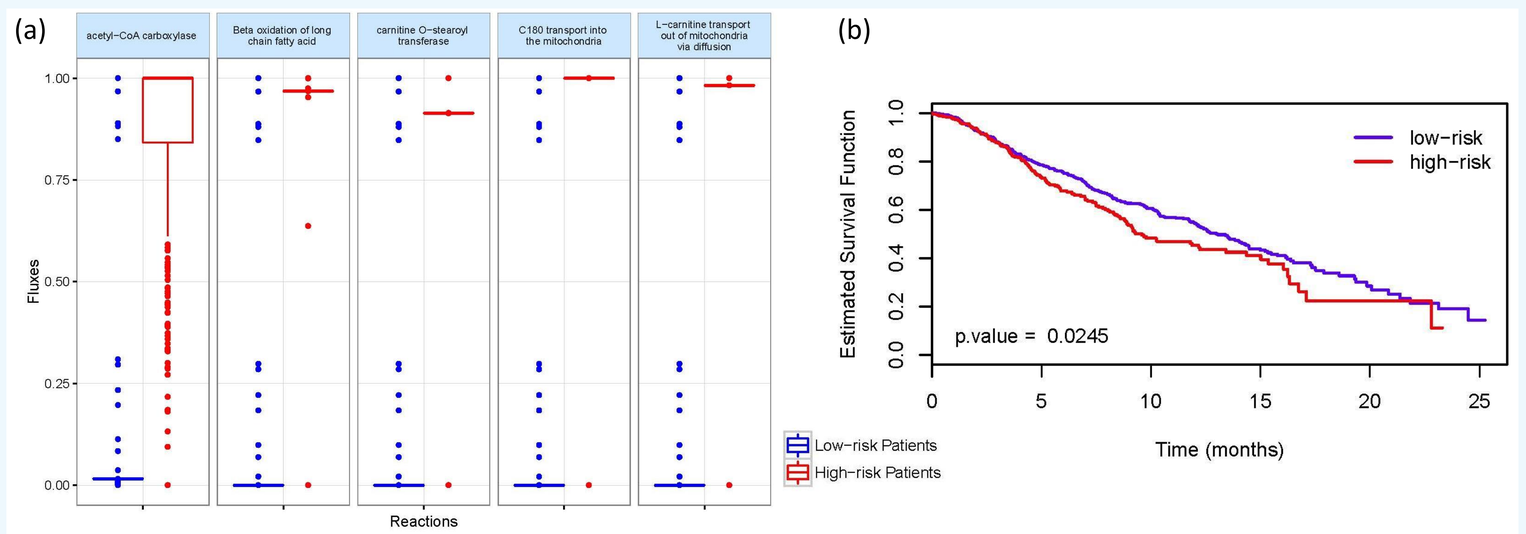

Figure 2. (a) Top-5 differentially active reactions in high-risk and low-risk patients.(b) Kaplan-Meier validation plot. We used the discovery Metabric set to train our model and to obtain a threshold t for stratifying the patients in high/low-risk groups based on their prognostic index. Such threshold was then used to predict the risk group of an independent dataset (validation Metabric set), never "seen" in the training phase. Figure (b) shows the obtained KM curve.

Methodology

1. **A computational model of cancer metabolism** is developed to investigate the reactions taking place in the cancer cell.
2. **Flux Balance Analysis** is then applied to identify the reactions affecting cancer progression.
3. **Machine Learning and Statistical Techniques** are run to uncover the relation between the selected reactions and patients survival.
4. **Survival Analysis** is finally applied to classify the patients into high-risk and low-risk groups, based on their omic information.

Conclusions

- We present a **patient-specific metabolic model model of breast cancer** to predict survival outcomes.
- **Machine Learning** techniques are used to investigate and analyse the **metabolic reactions** affecting breast cancer development.
- **Multi-omics data** were used to develop the model, providing a better predictions on cancer development and survival outcomes towards the development of **personalised medicine**.

Personalised test to predict the probability of developing breast cancer

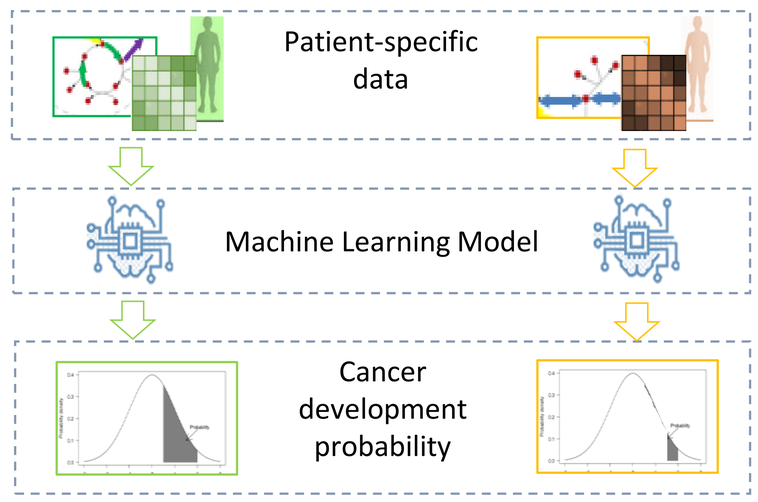

Figure 3. Main outcome of the proposed model. Starting from patient-specific data, our model uses machine learning techniques to predict the probability of developing breast cancer and provides patient-specific survival outcomes.

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