

Data-driven design of targeted gene panels for estimating immunotherapy biomarkers

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Abstract

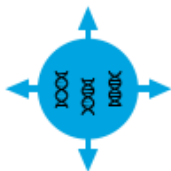
- ❶ Problem: **Predict response to immunotherapy** with targeted gene panels.
- ❷ Our approach: First fit a **generative model** of exome-wide mutation, then use this to construct efficient **predictive models** of biomarkers such as **Tumour Mutation Burden (TMB)**.

Outline

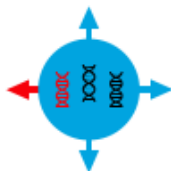
- 1 Biological/Clinical Background
 - Cancer and immunotherapy
 - Exome-wide biomarkers
 - Targeted gene panels
- 2 Generative/predictive modelling framework
 - Generative model
 - Predictive model
- 3 Application to non-small cell lung cancer

Cancer is a disease of the genome

Cancer arises when DNA in cells changes (mutates) [1].



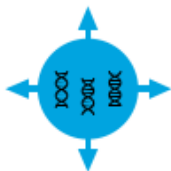
(a) Non-cancer cell: Normal DNA.



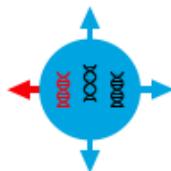
(b) Cancer cell: Mutated DNA.

Immunotherapy enables the immune system

Immunotherapy 'releases the brakes' on the immune system in order for it to attack tumours [2].



(a) Low-damage cell: **unrecognisable** to immune system.



(b) High-damage cell: **recognisable** to the immune system.

However, the immune system can only attack tumours that it recognises!

Tumour mutation burden stratifies patients for immunotherapy response

As a simple proxy for likelihood of immune response, we can use **tumour mutation burden**: the total count of non-synonymous mutations throughout the tumour exome [3, 4].

Advantages:

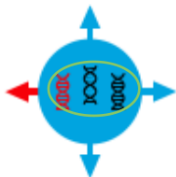
- ❶ Calculated from DNA sequencing only (compatible with liquid biopsy [5]).
- ❷ Relevant across cancer types.

Disadvantages:

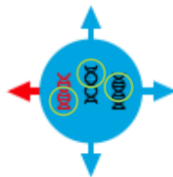
- ❶ Requires Whole-Exome Sequencing (WES) to measure directly.
- ❷ Fails to incorporate other features of the immune environment.

Targeted panels make genomic biomarkers viable

Rather than the entire exome/genome, targeted gene panels sequence a **subset** of genes.



(a) Whole-exome sequencing: **all genes** sequenced.



(b) Targeted panel sequencing: **subset** of genes sequenced.

Problem Statement

Aims:

- ① Select a discrete set of genes to form a panel (of pre-specified cost).
- ② Estimate TMB from panel sequencing data.

Mutations and biomarkers: some notation

We'll use i , g , and s to refer to:

- 1 A sample i (ranging from $i = 1$ to $i = N$),
- 2 A gene g (belonging to some index set G),
- 3 A variant type s (for example synonymous/non-synonymous).

Finally, we write:

- 4 M_{igs} , to refer to a mutation count of a particular sample, gene, and mutation type.

We then can define the TMB of the i th sample via:

$$T_i = \sum_{\substack{g \in G \\ s: \text{non-synonymous}}} M_{igs}.$$

Our generative model

A generative model of mutation attempts to capture the **underlying distribution** of variants across the entire exome/genome.

Our model incorporates **sample-specific** effects, **gene-specific** effects, **variant-specific** effects, **variant-gene interactions** and **gene length**:

$$M_{igs} \sim \text{Poisson}(\phi_{igs}) \quad (1)$$

where

$$\log(\phi_{igs}) = \mu_i + \lambda_g + \nu_s + \eta_{gs} + \ell_g \quad (2)$$

NSCLC: Poisson-based generative model fit

We fit our generative model with a WES non-small cell lung cancer dataset from Campbell et al. (2016) [6].

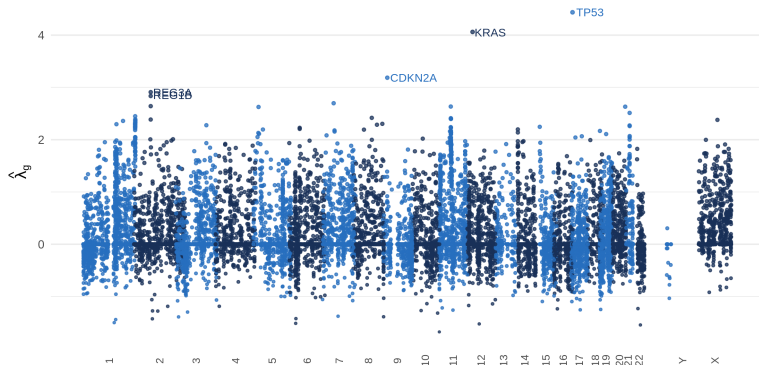


Figure: Generative model parameters. [7]

Proposed estimator

Aims (reminder):

- 1 Select a discrete set of genes to form a panel (of pre-specified cost).
- 2 Estimate TMB from panel sequencing data.

Our estimator:

$$\hat{T}_i(w) = \sum_{g,s} w_{gs} M_{igs} \quad (3)$$

How we fit our estimator:

$$\hat{w} := \arg \min_w \left\{ \mathbb{E}[(\hat{T}_i(w) - T_i)^2] + \kappa |w| \right\}, \quad (4)$$

where κ is a penalty specifying panel cost, and the expectation \mathbb{E} is over the distribution learned by our generative model.

NSCLC: Comparison panels and estimation methods

We compare our methodology with four commercial gene panels, and with three other means of predicting TMB. These panels are:

- 1 The **TST-170** gene panel.
- 2 The **Foundation One** gene panel.
- 3 The **MSK-IMPACT** gene panel.
- 4 The **TSO-500** gene panel.

and these methods are:

- 1 ecTMB (\times) [8].
- 2 Simple counting (\circ).
- 3 Linear regression ($+$).

NSCLC: Estimation performance

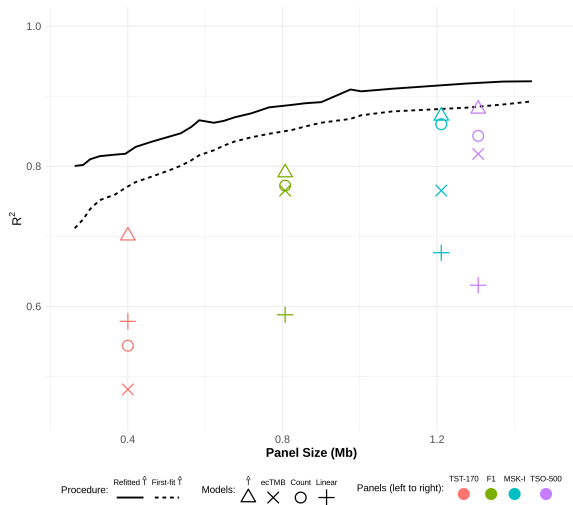


Figure: Predictive model performance: comparison with commercial panels and other predictive methods [7, 8].

Bonus material

Our method is flexible enough that we can:

- ➊ Predict other exome-wide biomarkers, such as Tumour Indel Burden (TIB).
- ➋ Augment existing gene panels to improve their predictive performance.

For more information check out our (draft) paper [7]!

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