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

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Abstract

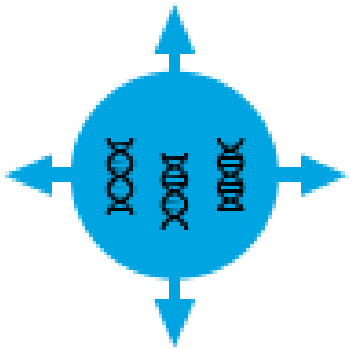
I. Problem: **Predict response to immunotherapy** with targeted gene panels.

II. 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)**.

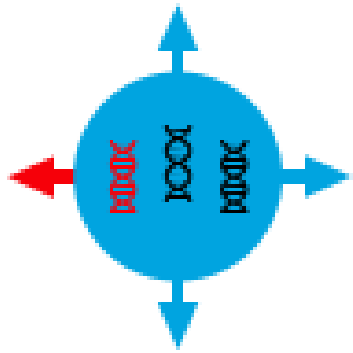
Outline

Cancer is a disease of the genome

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



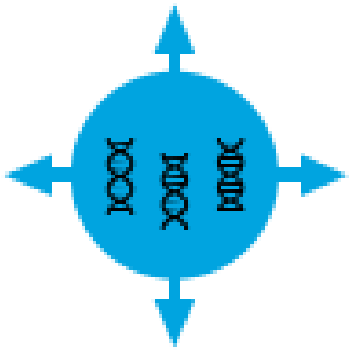
(a) Non-cancer cell: Normal DNA.



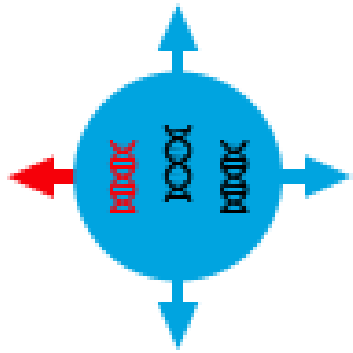
(b) Cancer cell: Mutated DNA.

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:

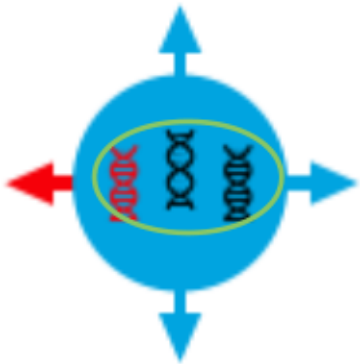
I. Calculated from DNA sequencing only (compatible with liquid biopsy [5]).
II. Relevant across cancer types.

Disadvantages:

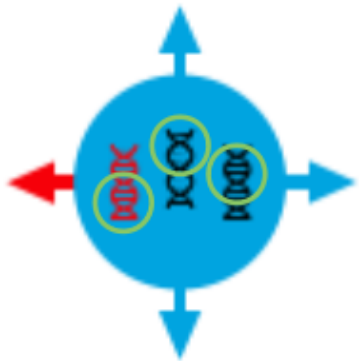
I. Requires Whole-Exome Sequencing (WES) to measure directly.
II. Fails to incorporate other features of the immune environment.

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 ith 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 and **variant-gene interactions**:

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

where

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

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].

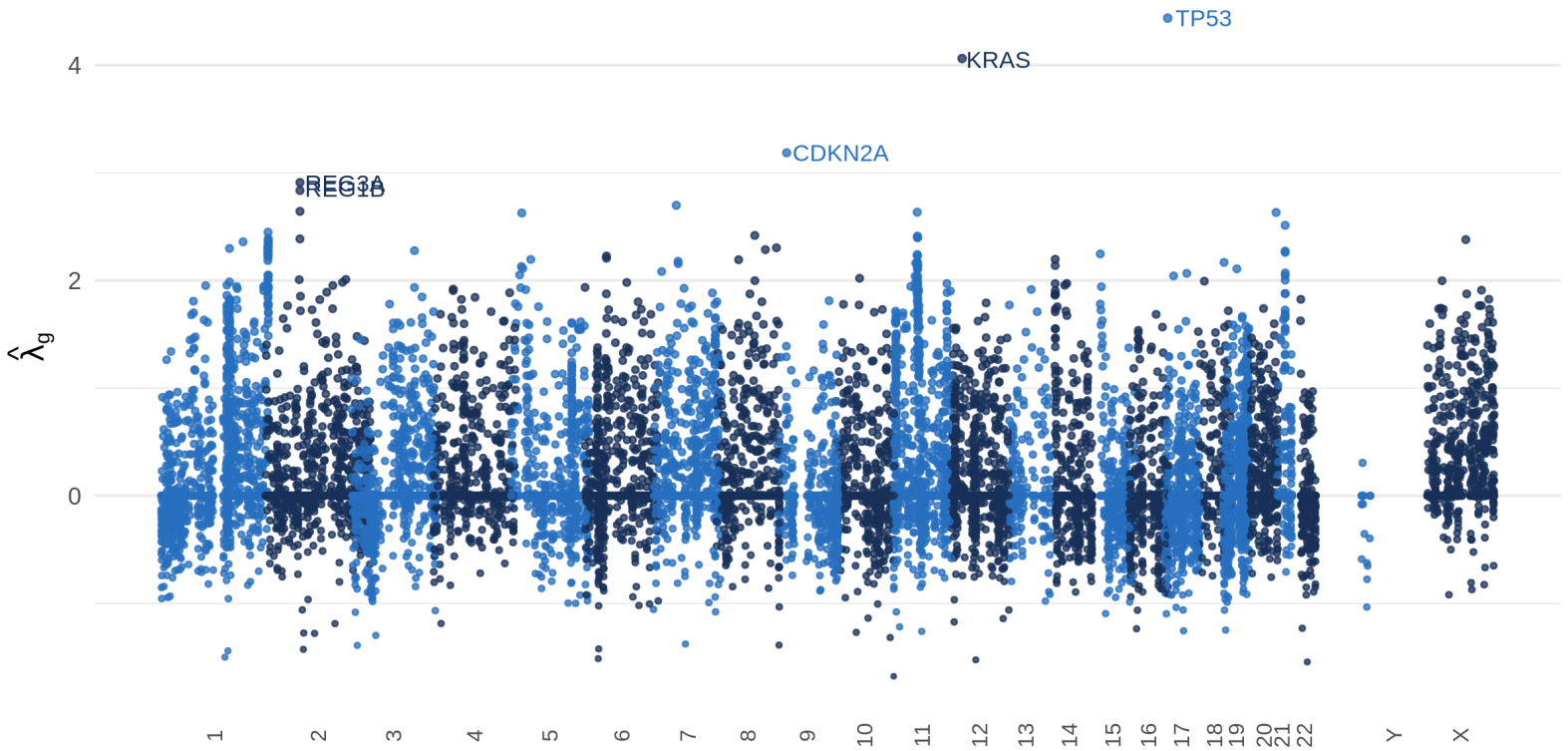


Figure: Generative model parameters. [7]

NSCLC: Poisson-based generative model fit

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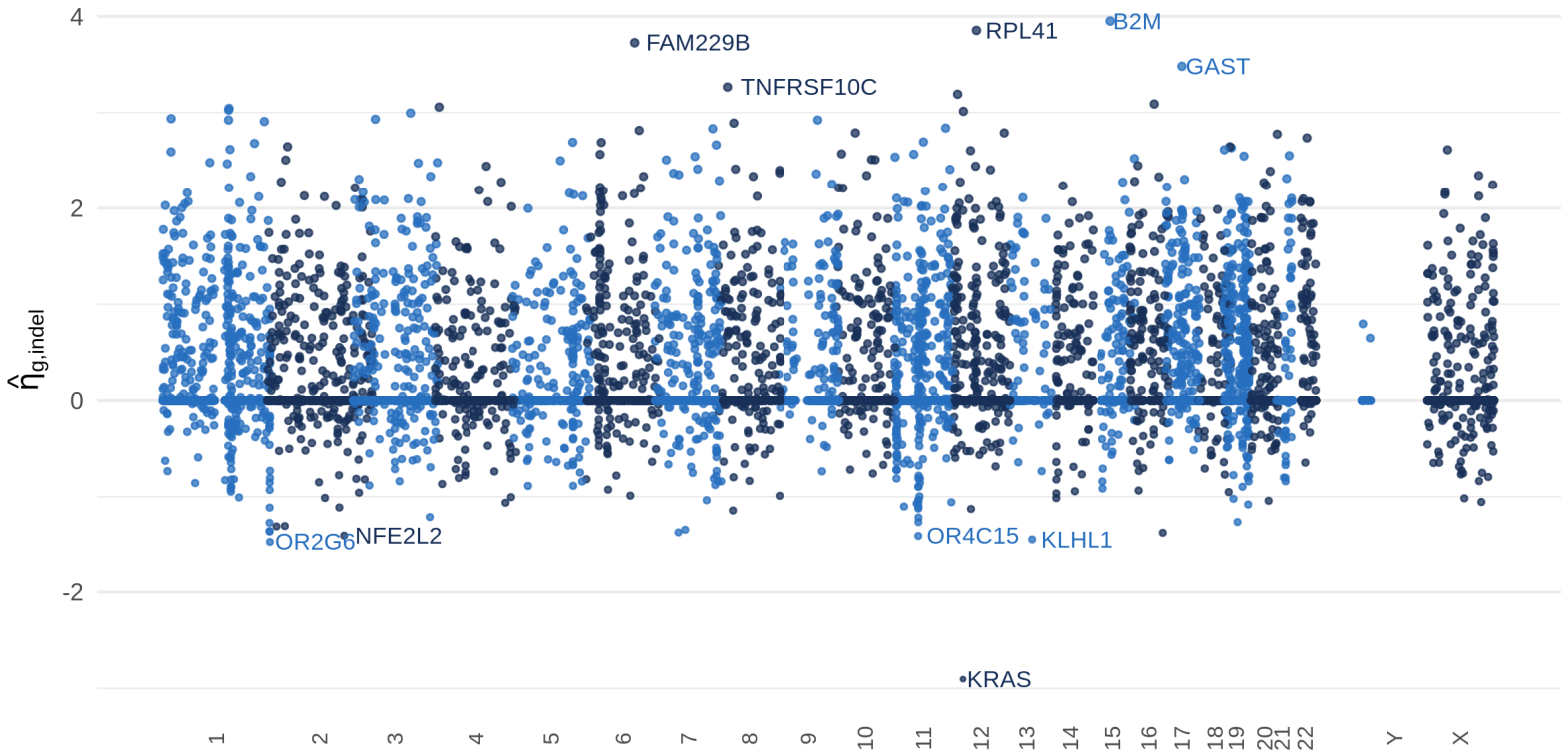

Figure: Generative model parameters (indel-specific) [7].

Proposed estimator

Aims:

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

Our estimator:

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

How we fit our estimator:

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

where λ 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

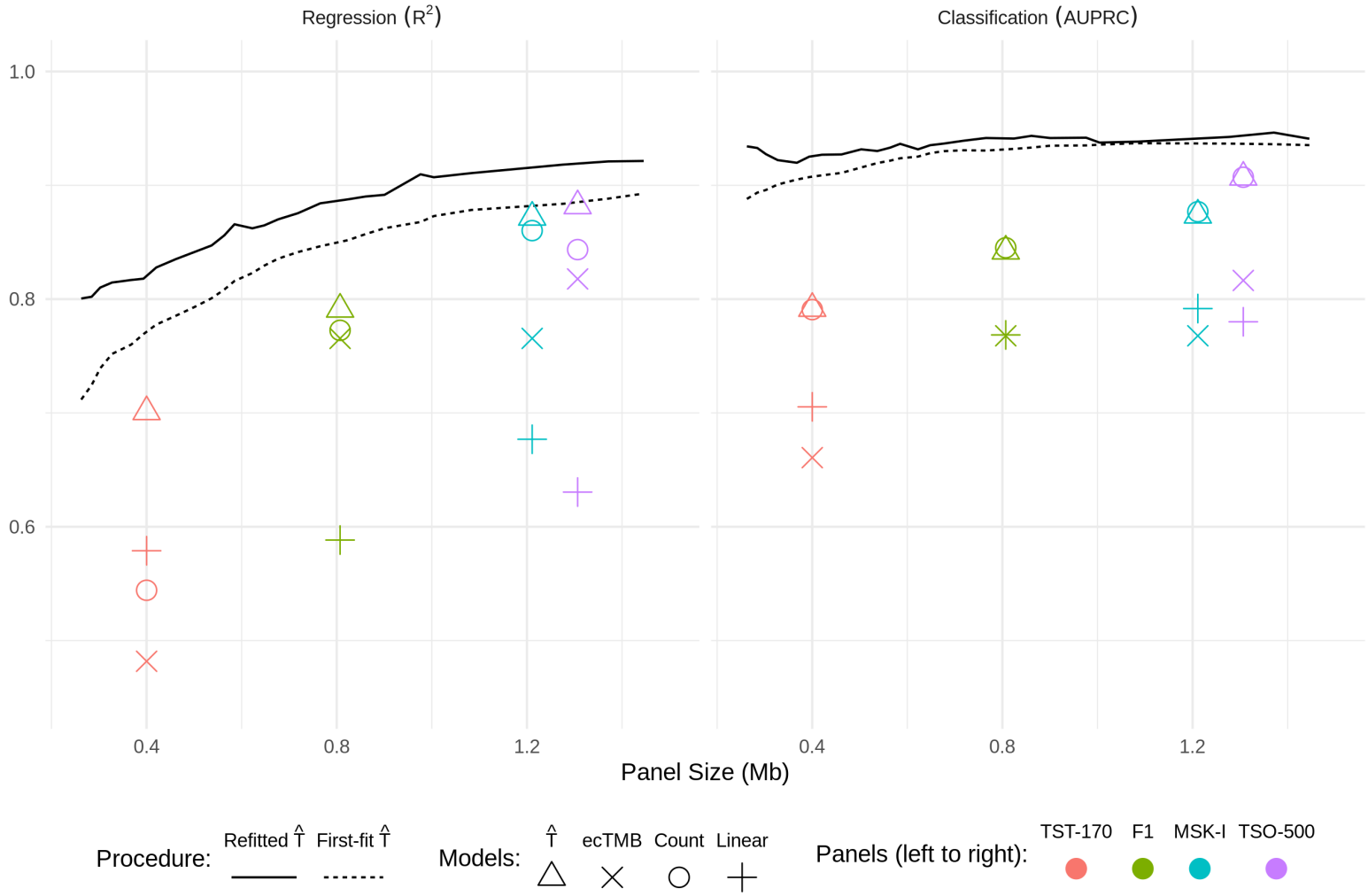

Figure: Predictive model performance: comparison with commercial panels and other predictive methods [7, 8].

Bonus material

Our method is flexible enough that we can:

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

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

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[7] Jacob R. Bradley and Timothy I. Cannings. Data-driven design of targeted gene panels for estimating immunotherapy biomarkers, January 2021. https://github.com/cobrbra/TargetedPanelEstimation_Paper.

[8] Lijing Yao, Yao Fu, Marghoob Mohiyuddin, and Hugo Y. K. Lam. ecTMB: a robust method to estimate and classify tumor mutational burden. *Scientific Reports*, 10(1):1–10, March 2020. Number: 1 Publisher: Nature Publishing Group.