Asymmetric Shapley values to quantify the importance of genes in clinico-genomic applications

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Workshop: Methods for Explainable Machine Learning in Health Care

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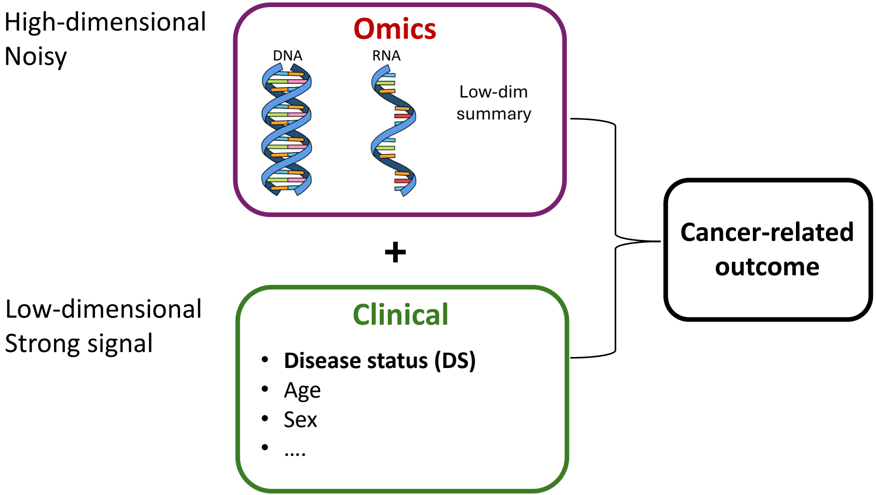
Amsterdam UMC
University Medical Centers

How important are omics variables for predicting cancer?



Leave covariates out to quantify the importance of the genes

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Table 1: C-index estimated on test data

Model	**C-index**
Clinical only (Cox PH)	0.72
Clinical + Omics (Ridge)	0.73

We assume that the genes (G) drive disease status (DS)

G: Gene expression, Clustering

DS: Disease state = I, II, III, IV

C: age, gender, tumor site

Y: Relapse-free survival; N = 845

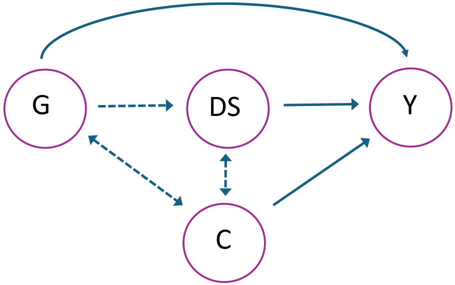

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Table 2: Global Shapley (SAGE): average performance

	G	DS	C	**Total**
C-index	0.22	0.3	0.2	0.72

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Table 3: Local Shapley: average prediction

	ϕ_{G}	ϕ_{DS}	ϕ_{C}	$\widehat{\mathbf{Y}}_{\mathrm{pred}}$
Patient 1	1.1	2.3	0.3	3.7
Patient 2	-2.8	0.3	0.5	-2.0
⋮	⋮	⋮	⋮	⋮

Shapley values as a generalization of partial dependence

- **Partial dependence (PD):** effect of a feature x_j, averaged over all others

$$\mathrm{PD}(x_j) = \mathbb{E}_{X_{-j}}[\hat{f}(x_j, X_{-j})]$$

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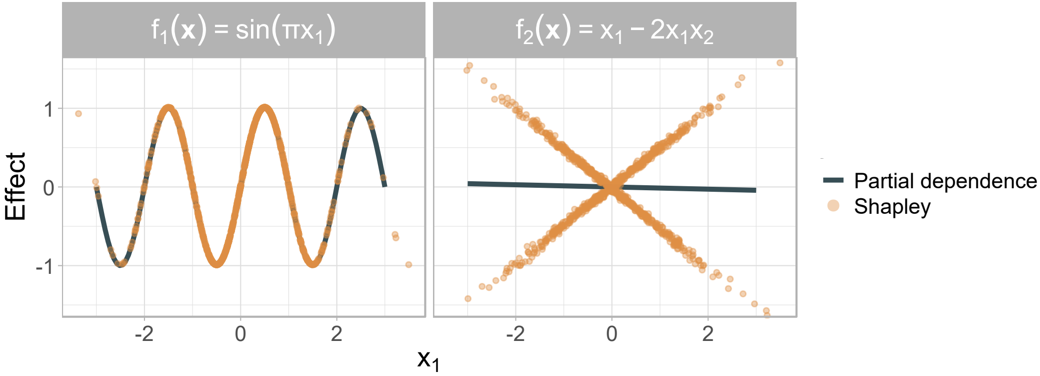
$$\textbf{Example (genes G):} \quad \mathcal{S} \in \Big\{ \{\emptyset\}, \{\mathrm{DS}\}, \{\mathrm{C}\}, \{\mathrm{DS}, \mathrm{C}\} \Big\}$$

Shapley values find the interaction whereas PD does not



Asymmetric Shapley values ignore subsets that do not respect the (causal) ordering

For variable G with variables $\{\mathrm{G}, \mathrm{DS}, \mathrm{C}\}$:

- $\{\emptyset\}$
- $\{\mathrm{DS}\}$
- $\{\mathrm{C}\}$
- $\{\mathrm{DS}, \mathrm{C}\}$

For variable C with variables $\{\mathrm{G}, \mathrm{DS}, \mathrm{C}\}$:

- $\{\emptyset\}$
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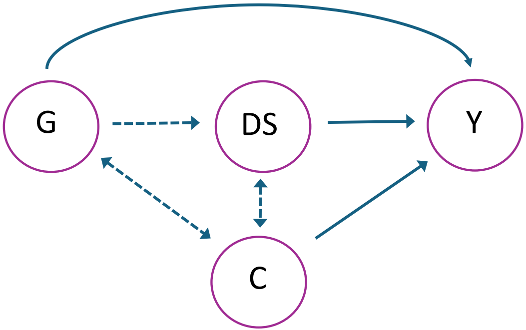

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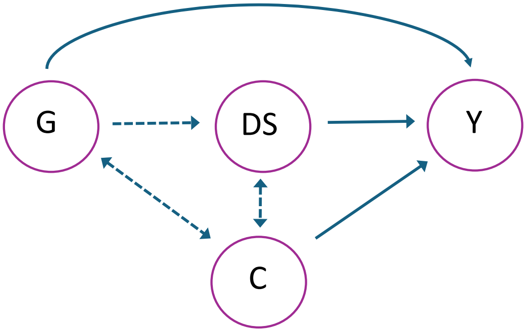
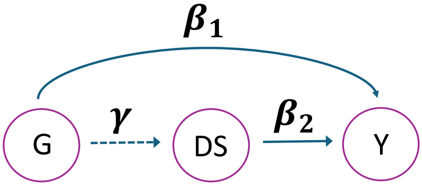


Intuition 1: Analytical expressions for a 2D toy example



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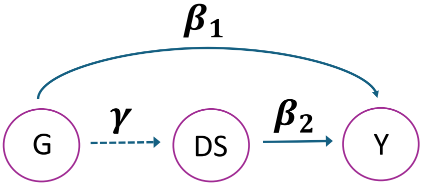

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Table 4: Asymmetric and symmetric Shapley values (and independent Shapley values).

Variable	Asymmetric	Symmetric	Independent
G	$\mathrm{G}\,(\beta_1 + \beta_2 \gamma)$	$\beta_1 \mathrm{G} + \frac{\gamma}{2}(\beta_2 \mathrm{G} - \beta_1 \mathrm{DS})$	$\beta_1 \mathrm{G}$

Intuition 2: Including a confounder and a nonlinearity

$$C_0,\ S_0,\ U_0,\ \sim \mathcal{N}(0,1)$$

$$\mathrm{G} \sim \mathcal{N}(0,1)$$

$$\mathrm{DS} = S_0 + \beta_1 G + U_0,$$

$$\mathrm{C}_1 = C_0 + U_0$$

$$\hat{f} = \beta_2 \mathrm{C}_1 + \beta_3 \mathrm{G} + \beta_4 \mathrm{DS}^2$$

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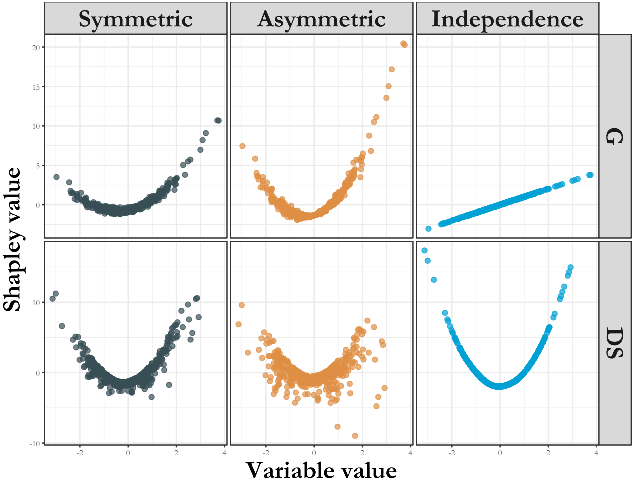

Computing Shapley values for the data set described earlier

Recalling the set-up

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Experiment

- Fit a `blockForest` model using a train test split and estimate the Shapley values (both asymmetric and symmetric)
- Consider global and local feature importance

Global importance: SAGE nicely decomposes the C-index

	Symmetric	Asymmetric
intercept	0.500	0.500
Genes (G)	0.130	0.173
Profile	*0.076*	*0.082*
CMS	*0.028*	*0.043*
Disease state (DS)	0.091	0.062
Gender (C_1)	0.010	0.008
Age (C_2)	0.021	0.010
Tumor site (C_3)	0.002	0.00
Total	**0.754**	**0.754**

Table 5: SAGE decomposition of the C-index of a `blockForest` model for the symmetric and asymmetric version.

Local importance: Interplay between different variables

	ϕ_{G}	ϕ_{DS}	ϕ_{Gender}	ϕ_{Age}	ϕ_{Site}
Patient 1	1.1	2.3	0.3	0.01	0.02
Patient 2	-2.8	0.3	0.5	-0.02	-0.3
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
Patient N	0.1	-1.0	0.08	0.0	-0.1

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Conditional on the model, we can ask many (inference) questions:

- Does the importance of DS differ between left and right tumor site
- Does the importance of Gender differ across DS categories
- *et cetera* ... (p-hacking)

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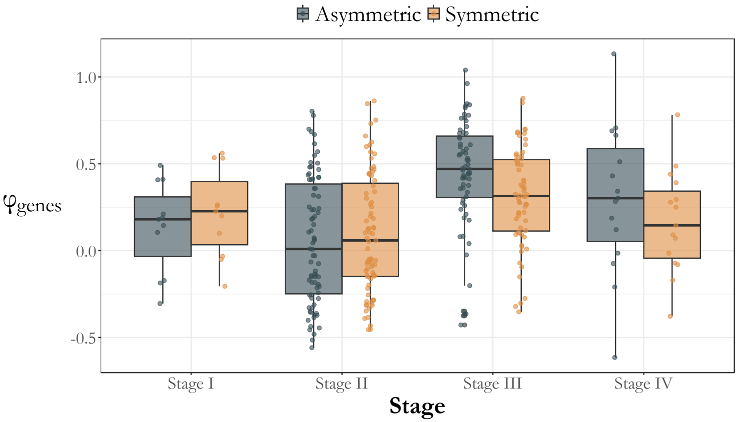
We are interested in the interplay between genes and disease status

The importance of genes differs more substantially across tumor stages in the asymmetric setting



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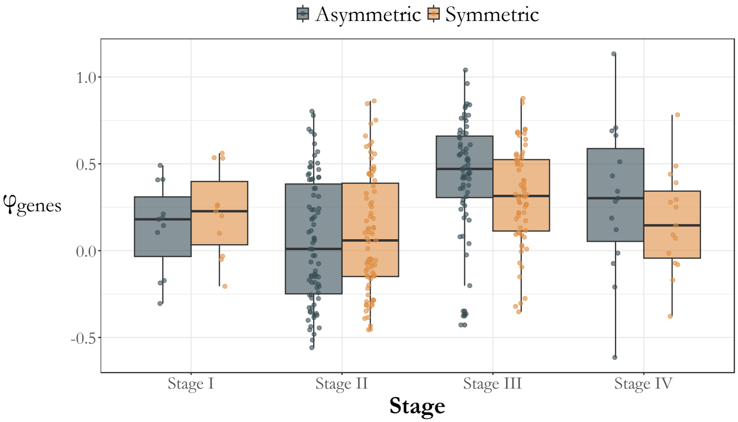

Kruskal-Wallis test:

$$p_{\text{symmetric}} = 1.4 \times 10^{-3}$$
$$p_{\text{asymmetric}} = 4.3 \times 10^{-9}$$

A discussion and look ahead

- A (maybe not required) disclaimer: there is no general best way to quantify feature importance
- In this setting: asymmetric Shapley values are interesting as they put more weight on relevant aspects of the data generating mechanism
- Dependency modeling ($p\left(X_{-\mathcal{S}} \mid X_{\mathcal{S}}\right)$) is challenging and can be improved
- Asymmetric Shapley values are a good starting point to ask more meaningful biological and clinical questions
  - *Biological:* Grouping of genes
  - *Clinical:* For which patients omics variables are not relevant

Thank you

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References

[1] Scott M. Lundberg and Su-In Lee. "A unified approach to interpreting model predictions". In: *Proceedings of the 31st International Conference on Neural Information Processing Systems*. NIPS'17. Curran Associates Inc., 2017, pp. 4768–4777. ISBN: 9781510860964.

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Technical details: Asymmetric Shapley value estimation

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- **Weights** $w_{\mathcal{S}}$
  - Combinatorial redefinition for omitted subsets
  - Importance sampling for large p
- **Conditional dependencies**
  - Dimension reduction for high-dimensional G
  - Dependency estimation in reduced space