Mathematically mapping the network of cells in the tumor microenvironment

Mike van Santvoort[1,2,5], Óscar Lapuente-Santana[2], Francesca Finotello[3,4], Pim van der Hoorn[1,5] and Federica Eduati[2,5]

✉ m.v.santvoort@tue.nl   o.lapuente.santana@tue.nl   w.l.f.v.d.hoorn@tue.nl   f.eduati@tue.nl

[1] Department of Mathematics and Computer Science, Eindhoven University of Technology, The Netherlands
[2] Department of Biomedical Engineering, Eindhoven University of Technology, The Netherlands
[3] Institute of Molecular Biology, University of Innsbruck, Austria
[4] Digital Science Center (DiSC), University of Innsbruck, Austria
[5] Institute for Complex Molecular Systems, Eindhoven University of Technology, The Netherlands

Tumors as communication networks

- The interaction of all cells/proteins inside the TME determine how a tumor develops (Figure 1).
- Reconstructing the cell-cell interaction network informs on TME functioning and potential therapeutic intervention (e.g. immunotherapy[1]).
- Single-cell RNA sequencing (scRNA-seq) can characterize elements in the TME, but has limited clinical applications.[2]
- Building cell-cell interaction networks from increasingly available bulk RNA sequencing (RNA-seq) can allow characterization at the individual patient level.[3]

Aim:
1. Create a model (called **RaCInG**) to reconstruct cell-cell interaction networks in the TME using bulk RNA-seq data.
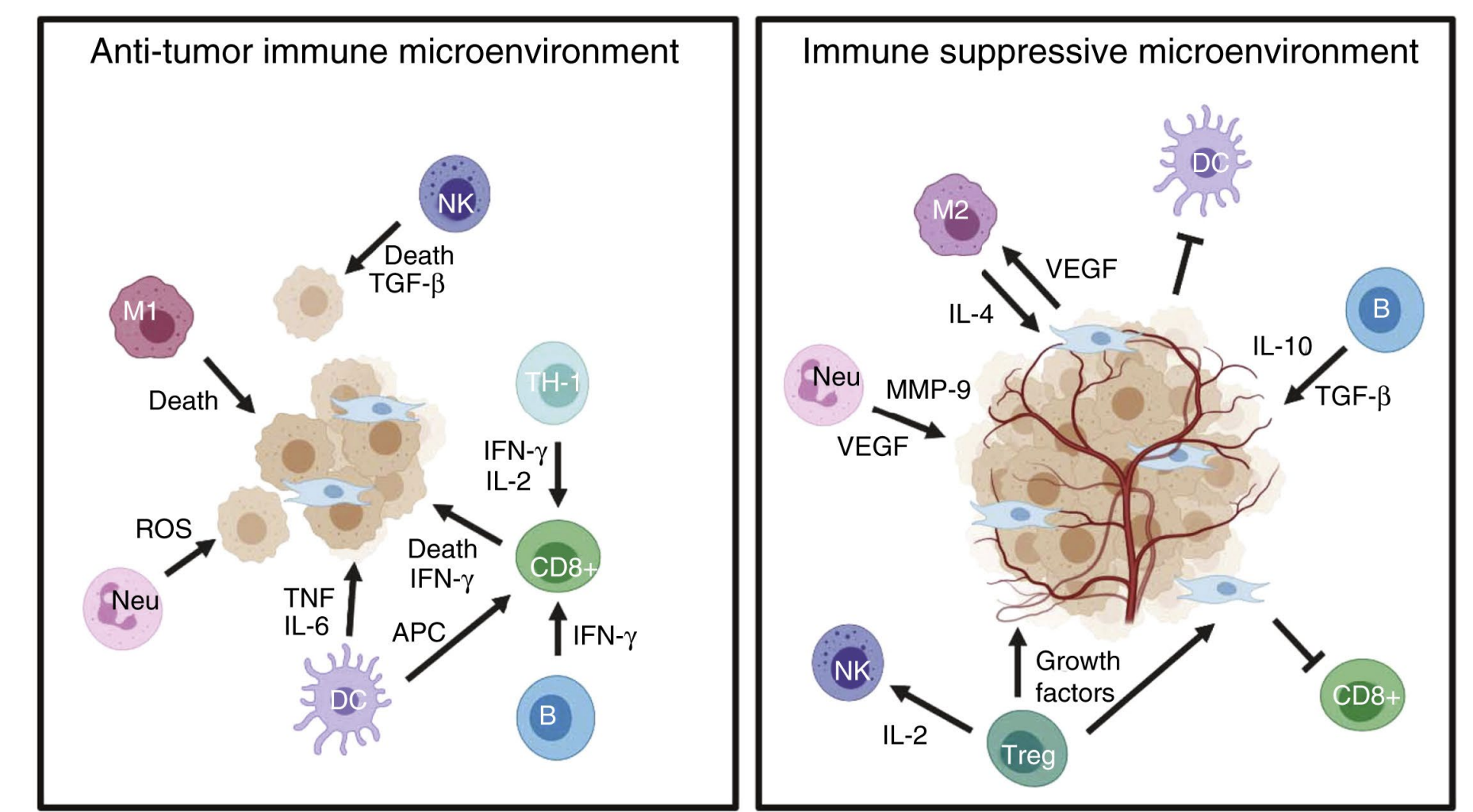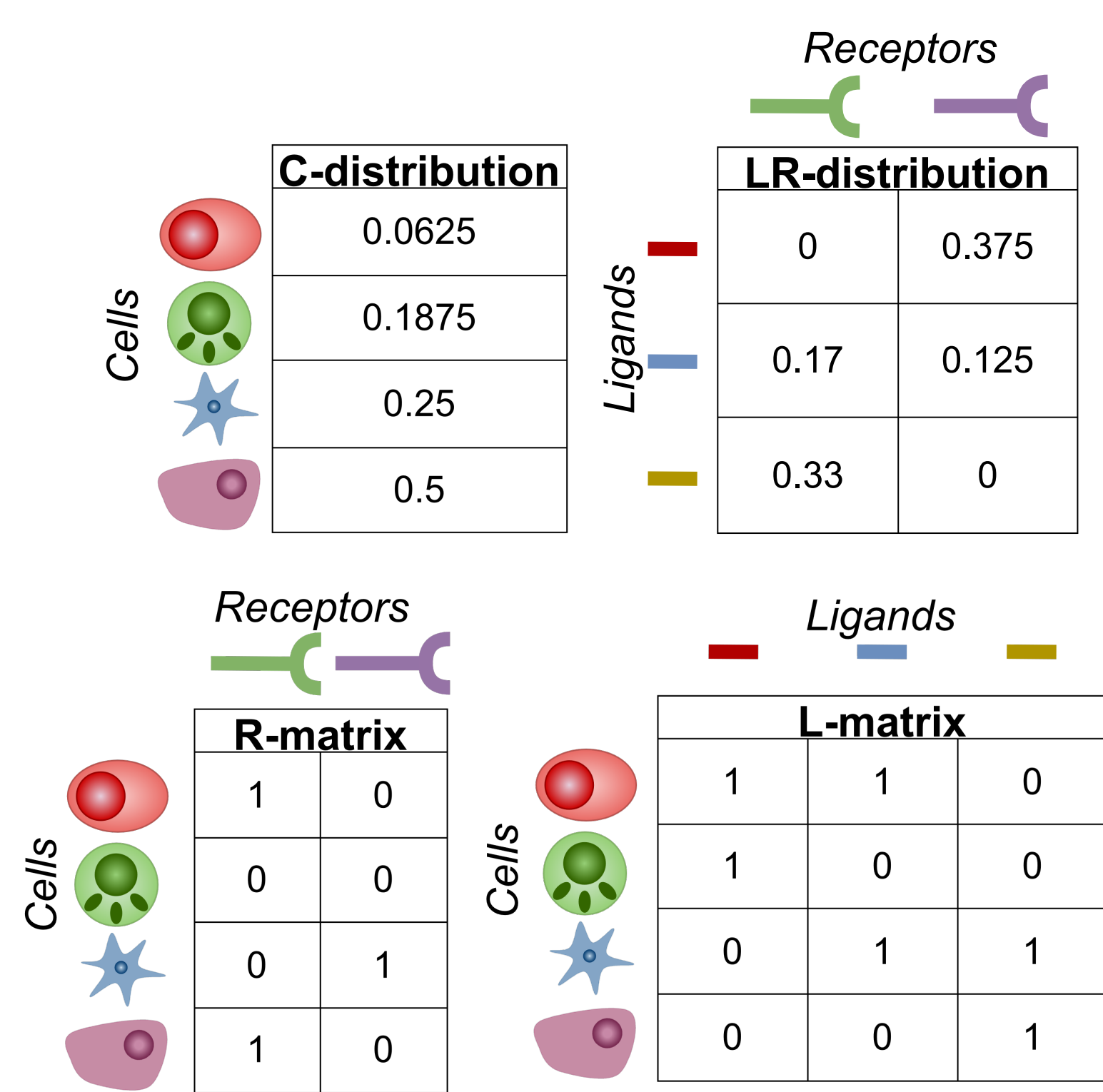2. Use the model to quantify important features of a patient's TME.

Figure 1: All facets of the TME contribute to cancer malignancy.[4]

Building patient-specific cell-cell networks using random graphs
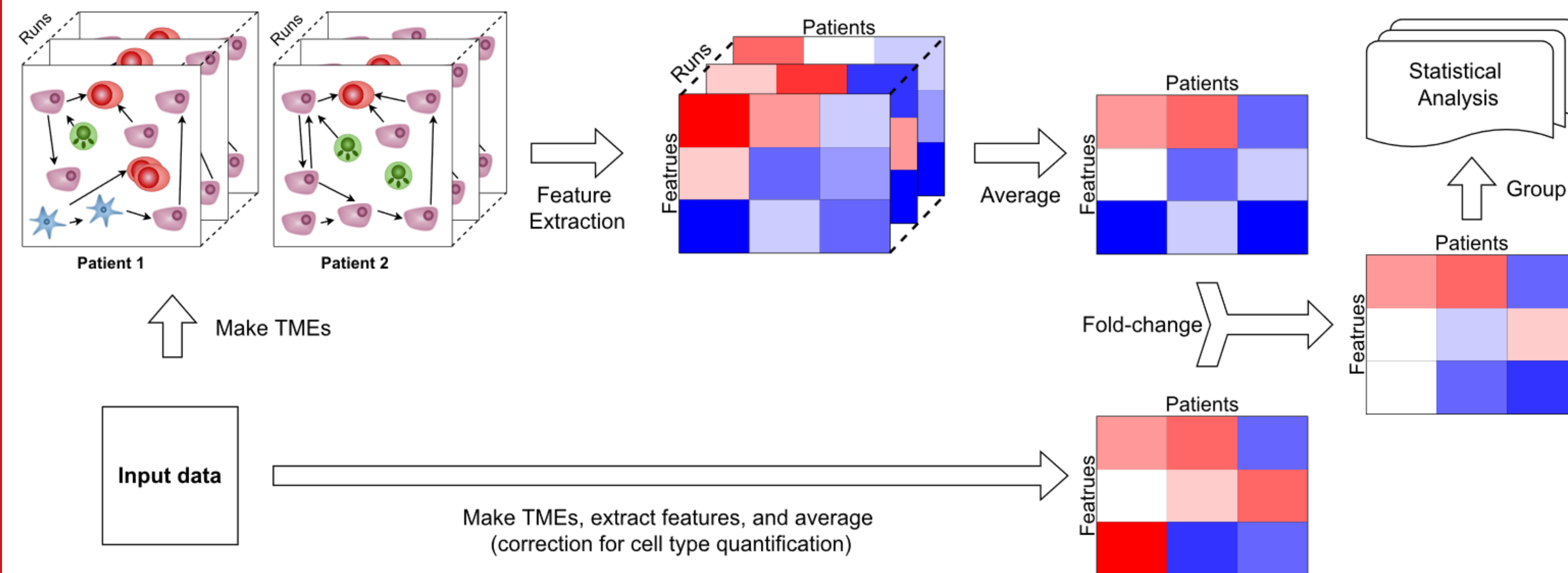
Patient-specific characterization

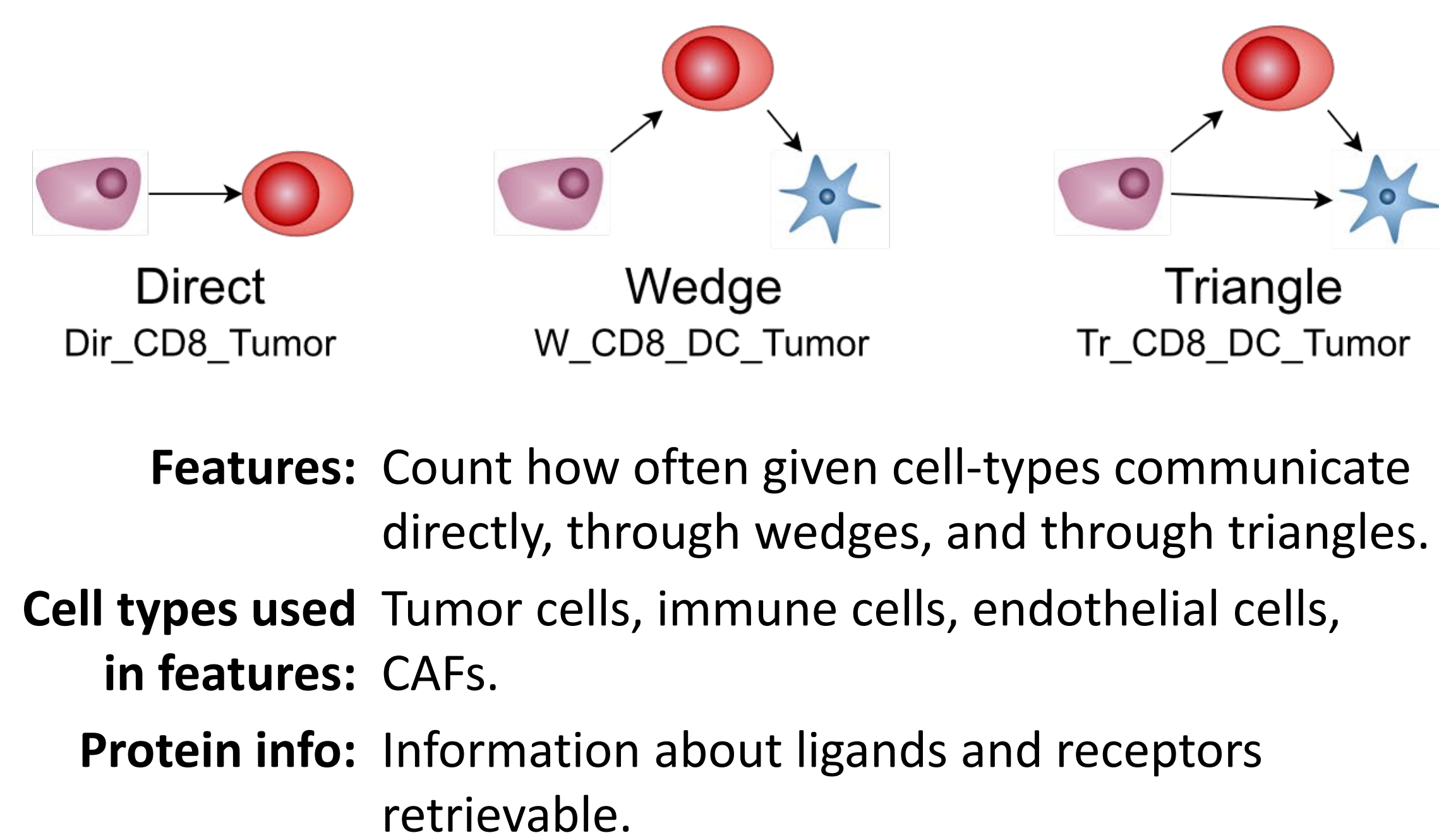Cell-type and ligand-receptor pair quantifications using **bulk RNA-seq**.

Cell-ligand and cell-receptor compatibility matrices based on **cell-type specific gene expression data**.

Extracting features from the TME

Extracted features

Direct
Dir_CD8_Tumor

Wedge
W_CD8_DC_Tumor

Triangle
Tr_CD8_DC_Tumor

Features: Count how often given cell-types communicate directly, through wedges, and through triangles.

Cell types used in features: Tumor cells, immune cells, endothelial cells, CAFs.

Protein info: Information about ligands and receptors retrievable.

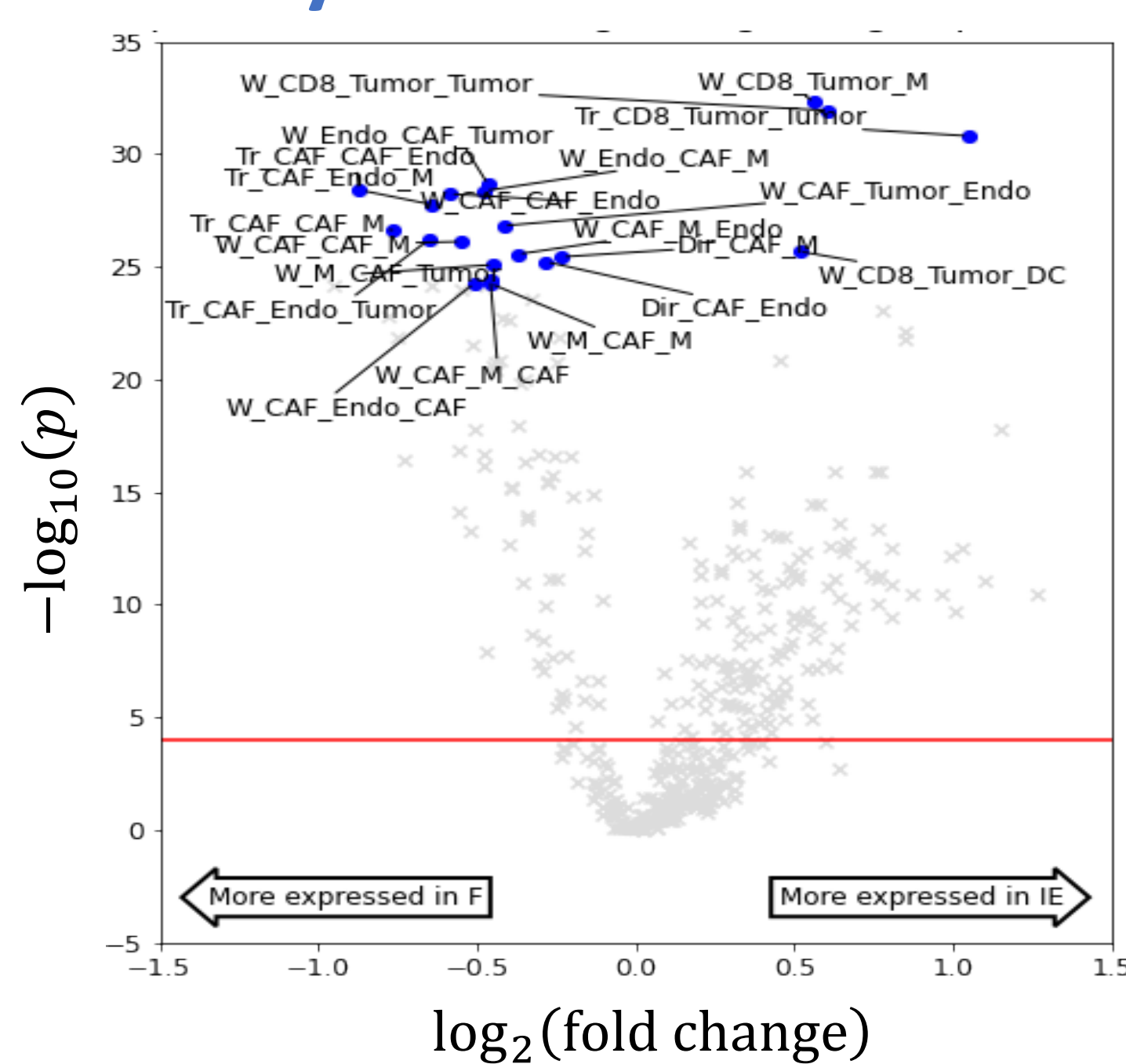## Case study: TME and immune subtypes in skin cutaneous melanoma (SKCM)

Figure 2: Comparison of immune enriched (IE) and fibrotic (F) patients[5] from TCGA[6] SKCM dataset. Top 20 features with lowest p-value (Wilcoxon rank sum test) are highlighted.
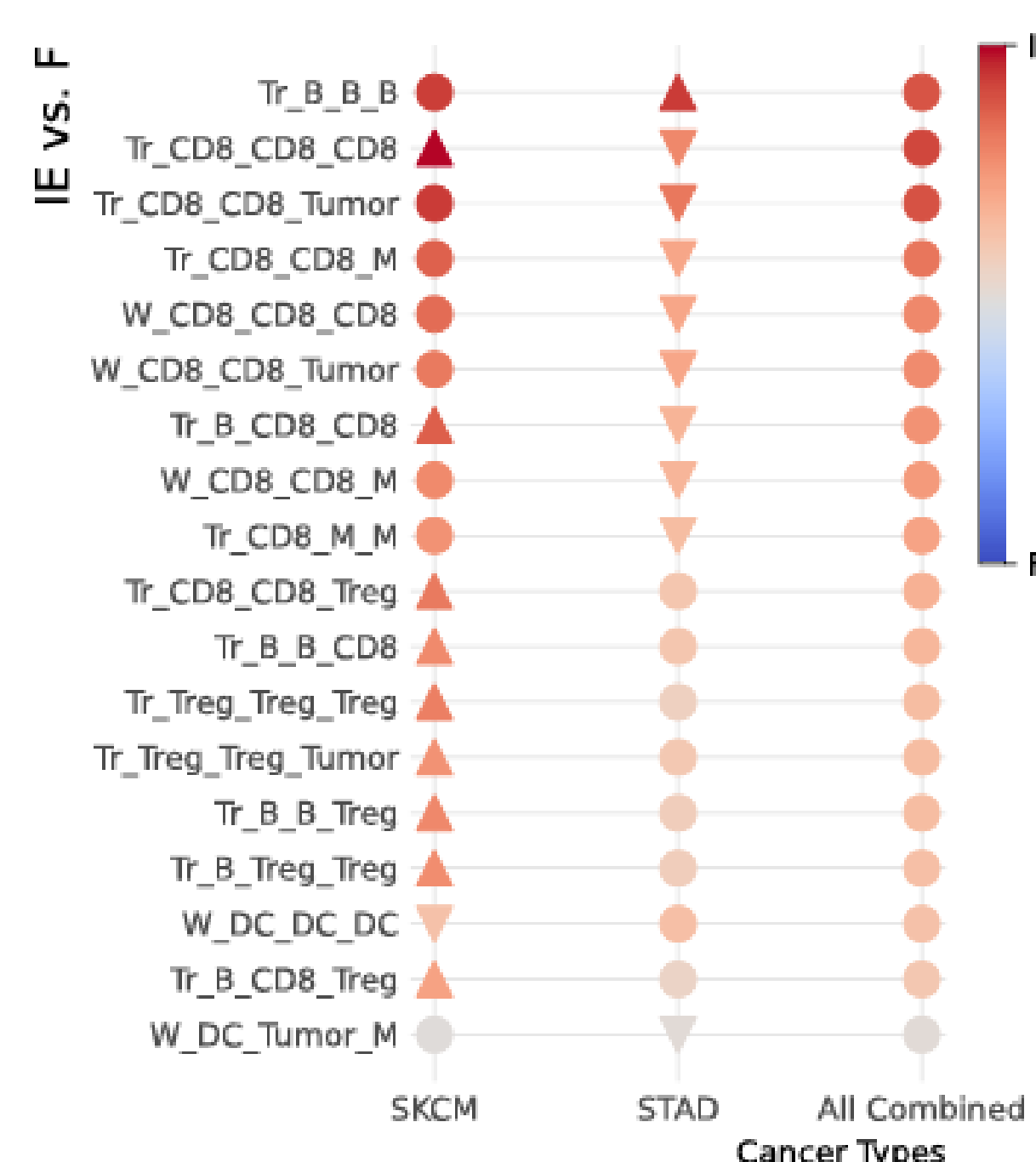

Figure 3: Features comparing SKCM and STAD with other TCGA cancer types. Feature is chosen when its deviates the most from the same feature in pan-cancer analysis.

Observations:
- More CD8+ T-cell and Treg-cell communication with tumor cells in IE group.[5]
- More CAF communication with tumor and endothelial cells in the F group.[7]
- Macrophage regulation by CAFs and endothelial cells in F group.[8]

Conclusion:
- TME reconstruction with RaCInG can **highlight detailed properties** that contribute to patient grouping.
- These features **go beyond** what can be directly inferred from **(bulk) transcriptomics and cellular deconvolution**.
- **Methodology blocks can be adjusted** to fit research needs.

Case study: Network communication and response to immunotherapy in melanoma

Observations:
- Increased CD8+ T-cell activity in responders due to blockage of PD-L1: self-activation and greater cytotoxicity.[9]
- More macrophage communication with tumors in the non-responder group: new mechanisms of immune evasion exploited.[10]

Conclusion:
- TME reconstruction with RaCInG can reveal TME features **explaining/predicting patient response to ICB therapy**.
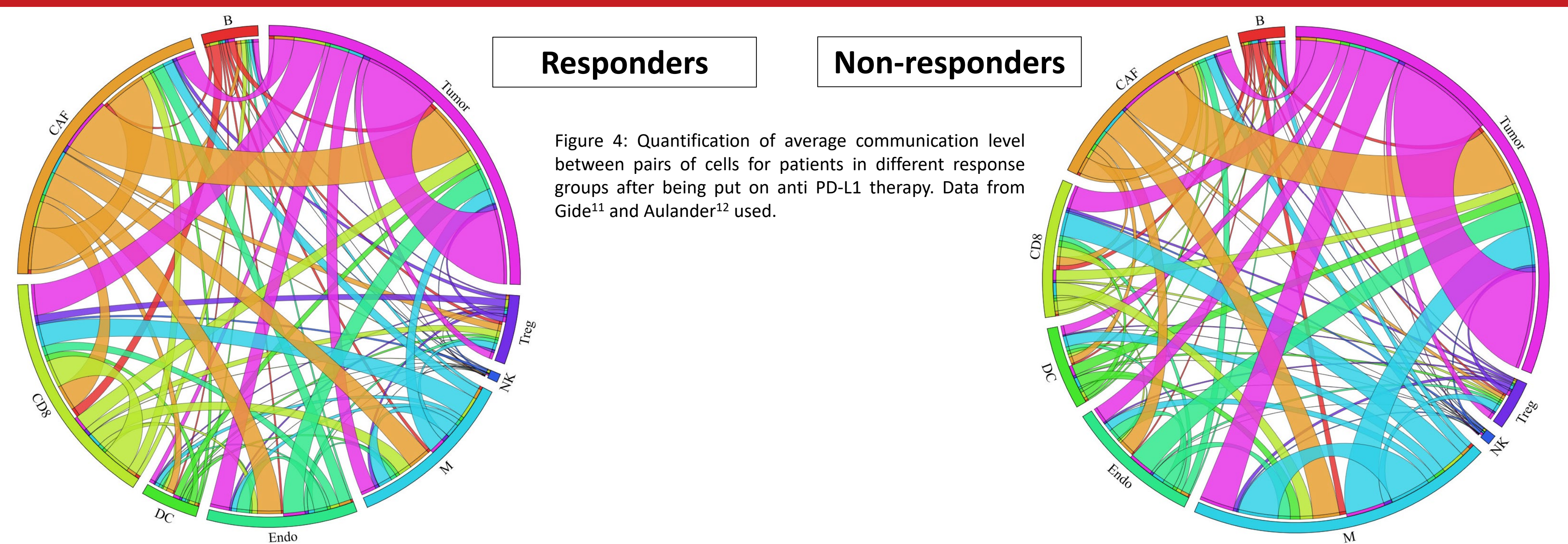
Figure 4: Quantification of average communication level between pairs of cells for patients in different response groups after being put on anti PD-L1 therapy. Data from Gide[11] and Aulander[12] used.

References

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