SUPPLEMENTARY MATERIAL
mixOmics: an R package for 'omics feature selection and multiple data integration

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S1 General definitions

S1.1 General notations

We assume each data set has been normalised using appropriate techniques specific for the type of ‘omics platform prior to the mixOmics analysis. Let X denote a data matrix of size N observations (rows) × P predictors (e.g. expression levels of P genes, in columns). The categorical outcome y is expressed as a dummy indicator matrix Y where each column represents one outcome category and each row indicates the class membership of each sample. Thus, Y is of size N observations (rows) × K categories outcome (columns). We denote for all $a \in \mathbb{R}^n$ its ℓ^1 norm $||a||_1 = \sum_1^p |a_j|$ and its ℓ^2 norm $||a||_2 = (\sum_1^p a_j^2)^{1/2}$. For any matrix we denote by $^\top$ its transpose. In the methods discussed in this article, the data X are internally centered and scaled, as proposed by default in PLS-based methods (Wold, 1975).

S1.2 Cross-validation

Cross-validation (CV) is a model validation technique used in statistical and machine learning to assess whether the results of the analysis can be generalised to an independent data set. It consists in dividing the data set into s subsets (or folds), fitting the model on $s-1$ subsets and evaluating the prediction performance on the left-out subset. This process is iterated until each subset is left out once; the prediction performance are then averaged. In our methods, we define the prediction performance as the overall misclassification error rate of the left-out samples.

We define *stratified CV* when there is approximately the same proportion of each class in each of the folds. Repeated cross-validation implies that the whole CV process is repeated a number of times `nrepeat` to reduce variability across the different subset partitions. In the case of Leave-One-Out CV (`validation = 'loo'`), each sample is left out once ($s = N$) and therefore `nrepeat` is set to 1.

For the P- integration with MINT, we use *Leave-One-Group-Out CV* as described in Section S5.2.

S1.3 Prediction distances

As mentioned in the main article, different prediction distances are proposed and implemented in the functions `predict`, `tune` and `perf` to assign to each predicted score of a test sample a final predicted class. Recall that for each class k of a test sample we obtain a predicted score:

- The maximum distance `"max.dist"` is the simplest method to predict the class of a test sample. For each new individual, the class with the largest predicted score is the predicted class.
- The centroid distance `"centroids.dist"` allocates the new sample the class that mimimises dist(t^h, G_k), where G_k, $k = 1, \ldots, K$ are the centroids of the classes calculated on the latent components of the model.
- The Mahalanobis distance `"mahalanobis.dist"` allocates the new sample the class defined as the centroid distance, but using the Mahalanobis metric in the calculation of the distance.

In practice, we choose the prediction distance that leads to the best performance of the model, as highlighted in `tune` and `perf`.

S2 Graphical outputs to visualise multivariate analysis results

mixOmics (Lê Cao et al., 2017) aims to provide insightful and user-friendly graphical outputs to interpret statistical and biological results, some of which (correlation circle plots, relevance networks and clustered image maps) were introduced in González et al. (2012). Via the use of R/S3 functions listed in S2, the function calls are identical for all multivariate methods implemented in the mixOmics package, as we illustrated in the Result section. We offer various visualisations, including sample plots and feature plots, which are based on the component scores and the loading vectors, respectively. Here we list the main important visualisation functions in mixOmics for which outputs are shown in Figure 1 of the manuscript.

S2.1 `plotIndiv` (Sample plot)

The plot represents samples by plotting the component scores. Such plot visualises similarities between samples in the small subspace spanned by the latent components. For the integrative methods (e.g. `DIABLO` and `MINT`), samples from separate data set are plotted on separate figures, allowing to assess the agreement between the data sets at the sample level. Confidence ellipse plots for each class can be displayed. To visualise the prediction areas of each class, users can overlay prediction results to sample plots via the `background` input parameter (see 'Prediction area visualisation' Section and Fig 2 in the main article). The method define surfaces around samples that belong to the same predicted class. These surfaces are then be used to shade the background of the sample plot. More details are provided in our help file `?background.predict`. This functionality is currently only implemented for supervised analyses of single 'omics analysis (`plsda, splsda`) with no more than 2 dimensions.

S2.2 `plotArrow` (Arrow representation)

The plot overlays the components scores from multiple datasets and draws arrows between scores associated to the same sample. For most supervised methods and two-'omics integration methods listed in Table 1, the start of the arrow represent the component score in the X data set and the tip of the arrow is the component score associated to the outcome, or the Y data set. For N-integration, the start of the arrow indicates the centroid between all 'omics data sets for a given sample and the tips of the arrows the location of that sample in each data set. In two-'omics and N-integration methods, short arrows indicate a strong agreement between the matching data sets, long arrows a disagreement between the matching data sets. For supervised analyses, short arrows indicate a good discrimination of the classes (see Figure 3 in main article).

S2.3 `plotVar` (Correlation circle plots)

Correlation circle plots display the correlation between variables (biological features) and latent components. Each variable coordinate is defined as the Pearson correlation between the original data and a latent component (see González et al. 2012 for a detailed description). Correlation circle plots are particularly useful to visualise the contribution of each variable to define each component (variable close to the large circle of radius 1), as well as the correlation structure between variables (clusters of variables). The cosine angle between any two points represent the correlation (negative, positive or null) between two variables.

S2.4 `cim` (Clustered Image Maps)

This heatmap plot visualises the distances between two types of variables (two-'omics integration), or between variables with respect to each sample (single 'omics supervised and P- integration). By default we use Euclidian distance and complete linkage method but other distances and methods can be chosen. For N-integration, the function `cimDiablo` represents the selected features from the different data sets.

S2.5 `network` (Relevance networks)

Relevance networks represent the correlation structure between variables of different types. A similarity matrix representing the association between pairs of variables across all components is calculated as the sum of the correlations between the original variables and the latent components across all dimensions of interest (see González et al. 2012 for more details). Those networks are bipartite and thus only a link between two variables of different types can be represented. The network can be saved in a .glm format using the `igraph` package, the function `write.graph` and extracting the output `$gR`, see details in our Sweave workflow for `DIABLO`.

S2.6 `plotLoadings` (Loading plots)

The plot represents the loading weights of each variable (selected) on each dimension of the multivariate model. Most important variables (according to the absolute value of their coefficients) are ordered from bottom to top. For supervised analyses, colours indicate the class for which the mean (or median) expression value is the highest or the lowest for each feature (`contrib = 'max'` or `'min'`). This graphical output enables to better understand the discriminative ability of the molecular signature, especially when interpreted in conjunction with the sample plot (see Fig. S1).

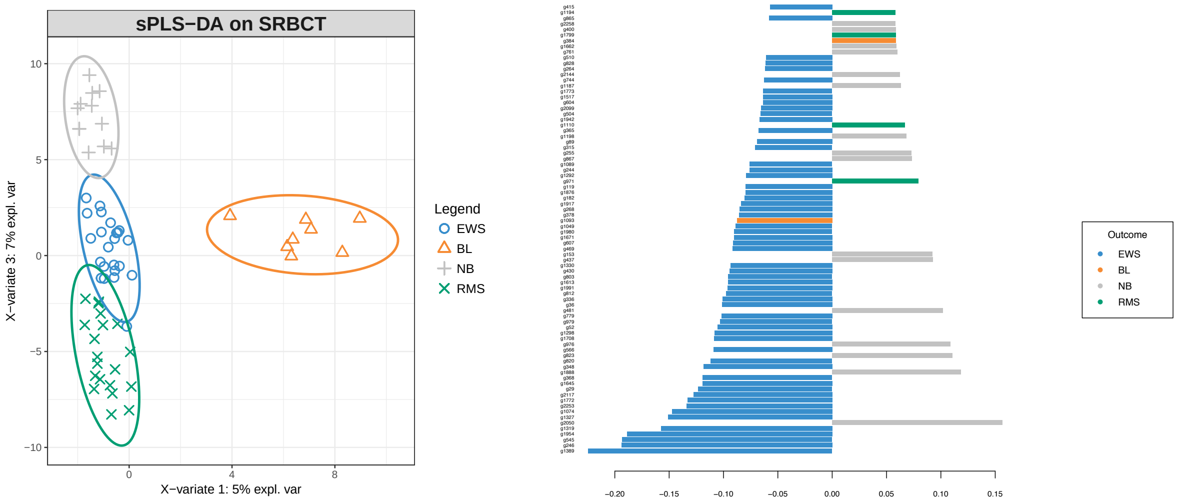


Figure S1: **Example of sample plot with `plotIndiv` and loading plot with `plotLoadings` with sPLS-DA**. The loading plot (right) represents the top 80 genes selected on the second component of the sPLS-DA model. Colors indicate the tumour subtype where the mean expression levels of the gene is maximal. More details in the 'Results' Section R and sweave code S3.4.

S2.7 Additional graphical outputs

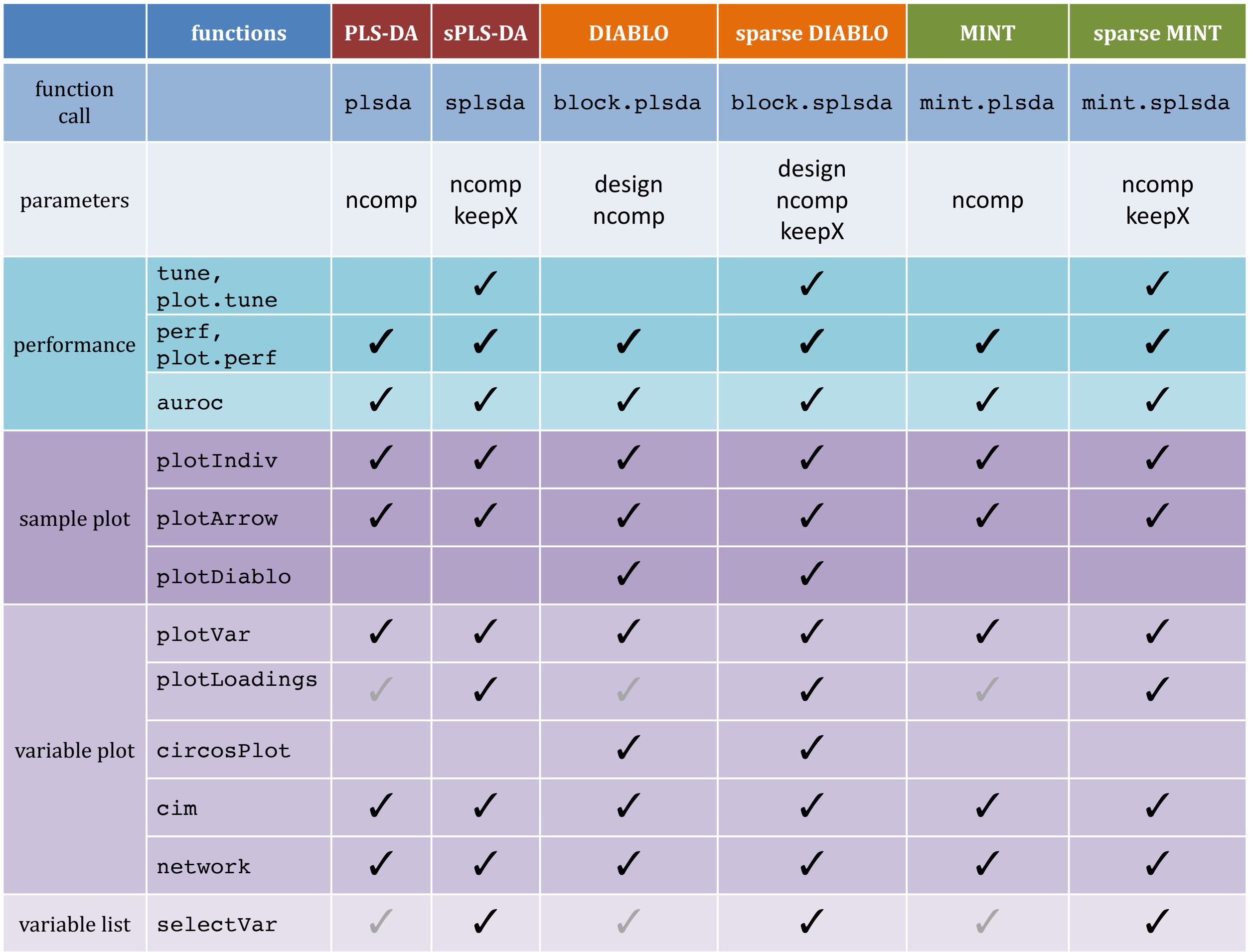
Both `plotIndiv` and `plotVar` offer usual plot arguments to display symbols, colours and legend, with graphic styles include `ggplot2` (by default), `graphics`, `lattice` and 3D plots.

Other graphical outputs are available in `mixOmics` to visualise the classification performance of the multivariate models using the generic function `plot`. The listing of the functions for each framework presented in our main article are summarised in Fig S2.

Finally, additional graphical outputs or variants for the frameworks `DIABLO` and `MINT` are described below (`plotDiablo, circosPlot`).

S3 Single 'omics supervised multivariate analysis with PLS-DA and sPLS-DA

Linear Discriminant Analysis (LDA) and Projection to Latent Structure (PLS, Wold 1966) are popular multivariate methods for supervised analyses. In `mixOmics` we mainly focus on PLS methods for their flexibility to solve a variety of analytical problems (Boulesteix and Strimmer, 2007). PLS regression (Wold, 1966) was originally developed for unsupervised analysis to integrate two data sets with continuous variables, measured on the same observations or samples. We briefly present the supervised version of PLS, called PLS-Discriminant Analysis (PLS-DA, Nguyen and Rocke 2002; Barker and Rayens 2003). PLS-DA is natural extension of PLS that substitutes one of the data set for a dummy indicator matrix Y. PLS-DA fits a classifier multivariate model that assigns samples into known classes, with the ultimate aim to predict the classes of external test samples where the outcome might be unknown.



	functions	PLS-DA	sPLS-DA	DIABLO	sparse DIABLO	MINT	sparse MINT
function call		plsda	splsda	block.plsda	block.splsda	mint.plsda	mint.splsda
parameters		ncomp	ncomp keepX	design ncomp	design ncomp keepX	ncomp	ncomp keepX
performance	tune, plot.tune		✓		✓		✓
	perf, plot.perf	✓	✓	✓	✓	✓	✓
	auroc	✓	✓	✓	✓	✓	✓
sample plot	plotIndiv	✓	✓	✓	✓	✓	✓
	plotArrow	✓	✓	✓	✓	✓	✓
	plotDiablo			✓	✓		
variable plot	plotVar	✓	✓	✓	✓	✓	✓
	plotLoadings	✓	✓	✓	✓	✓	✓
	circosPlot			✓	✓		
	cim	✓	✓	✓	✓	✓	✓
	network	✓	✓	✓	✓	✓	✓
variable list	selectVar	✓	✓	✓	✓	✓	✓

Figure S2: **Summary of the main `mixOmics` S3 functions for supervised multivariate analyses.**

S3.1 PLS - Discriminant Analysis

PLS-DA is an iterative method that constructs H successive artificial (latent) components $t_h = X_h a_h$ and $u_h = Y_h b_h$ for $h = 1, .., H$, where the h^{th} component t_h (respectively u_h) is a linear combination of the X (Y) variables. H denotes the dimension of the PLS-DA model. The weight coefficient vector a_h (b_h) is the loading vector that indicates the *importance* of each variable to define the component. For each dimension $h = 1, \dots, H$, PLS-DA seeks to maximize

$$\max_{(a_h, b_h)} \text{cov}(X_h a_h, Y_h b_h), \qquad \text{s.t.} \quad ||a_h||_2 = ||b_h||_2 = 1 \tag{1}$$

where X_h, Y_h are the residual (deflated) matrices extracted from each iterative linear regression (see Lê Cao et al. 2011 for more details). The PLS-DA model assigns to each sample i a pair of H scores (t_h^i, u_h^i) which effectively represents the projection of that sample into the X- or Y- space spanned by those PLS components. As $H << P$, the projection space is small, allowing for dimension reduction as well as insightful sample plot representation. Note that the projection into the Y-space is not used for Discriminant Analysis with PLS-DA.

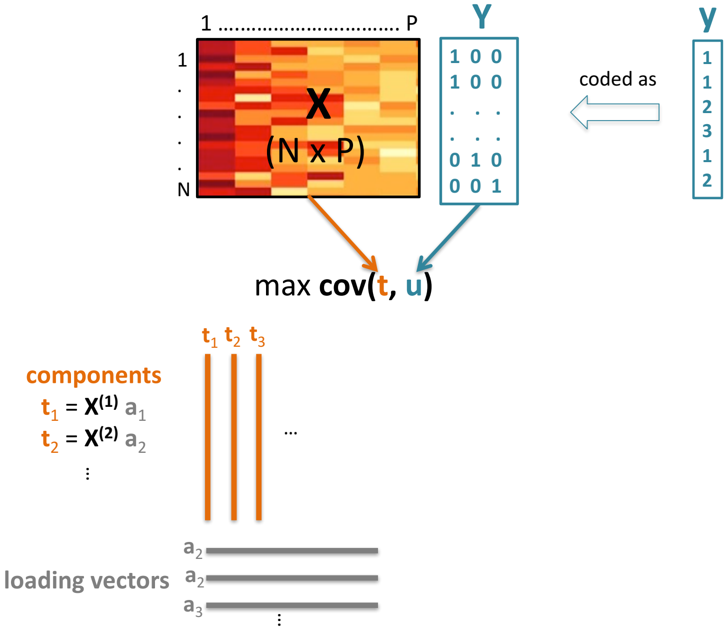


Figure S3: **Example of data matrix decomposition for single 'omics analysis with PLS-DA.** The predictor matrix X is decomposed into a set of components $(t_1, \dots, t_H)$ and associated loading vectors $(a_1, \dots, a_H)$, $\boldsymbol{Y}$ is the outcome coded as a dummy indicator matrix and combined linearly (see exact formula in Equation (1)). $\boldsymbol{X_h}$ is the deflated (residual) matrix starting with $\boldsymbol{X_1} = \boldsymbol{X}$, for $h = 1 \dots H$. H is the dimension of the model - or the number of components.

S3.2 Variable selection with sparse PLS-DA

We developed a *sparse* version of PLS-DA (Lê Cao et al., 2011) which includes an ℓ^1 penalisation (Tibshirani, 1996) on the loading vector a_h to shrink some coefficients to zero. Thus, for each dimension $h = 1, .., H$, sPLS-DA solves:

$$\max_{(a_h, b_h)} \text{cov}(X_h a_h, Y_h b_h), \qquad \text{s.t.} \quad ||a_h||_2 = ||b_h||_2 = 1 \text{ and } ||a_h||_1 \leq \lambda_h \tag{2}$$

where λ_h is a non negative parameter that controls the amount of shrinkage in a_h. The component scores $t_h = X_h a_h$ are now defined on a small subset of variables with non-zero coefficients, leading to variable selection that aims to optimally maximise the discrimination between the K outcome classes in Y. In `mixOmics` we use soft-thresholding to improve usability by replacing the λ_h parameter by the number `keepX` of features to select on each dimension (see 'Choice of parameters' Section in the main article.

S3.3 Extensions of PLS-DA for repeated measurements and 16S microbiome data

PLS-DA and sPLS-DA were extended to account for repeated measurement designs, as described in Liquet et al. (2012) by specifying the argument `multilevel` in the `plsda` and `splsda` functions.

Recent extensions in the package also include sPLS-DA analysis to identify microbial communities for 16S data with an additional `logratio` argument to account for compositional data in microbiome experiment (Lê Cao et al. 2016, see also our `mixMC` framework in `www.mixOmics.org/mixMC`).

S3.4 Workflow for PLS-DA analysis

We provide a full R and Sweave workflow electronically on our website at this link.

S4 N-integration across multiple 'omics data sets with DIABLO

The integration of multiple 'omics datasets measured on the same N biological samples (Figure 1 in main article) is based on a variant of the multivariate methodology Generalised Canonical Correlation Analysis (GCCA, Tenenhaus and Tenenhaus 2011; Tenenhaus et al. 2014), which, contrary to what its name suggests, generalises PLS for N-integration. Multiple data integration is a challenging task, as the analysis can be strongly affected by artefacts of the 'omics technological platforms or by variation between manufacturers, despite being measured on the same biological samples. Our recent development `DIABLO` further improved the implementation of GCCA to include variable selection in a supervised framework and in a user-friendly manner (Günther et al., 2014; Singh et al., 2016). We have applied `DIABLO` to integrate different 'omics experiments arising from different 'omics platforms (*e.g.* transcriptomics, proteomics in Günther et al. 2014, as well as mRNA, proteomics, miRNA and methylation data in Singh et al. 2016), to identify correlated or *co-expressed* 'omics variables that also explain the outcome of interest.

S4.1 `DIABLO` method

We denote Q 'omics data sets $X^{(1)}(N \times P_1)$, $X^{(2)}(N \times P_2)$, ..., $X^{(Q)}(N \times P_Q)$ measuring the expression levels of P_q 'omics variables on the same N biological samples, $q = 1, \dots, Q$. GCCA solves for each component $h = 1, \dots, H$:

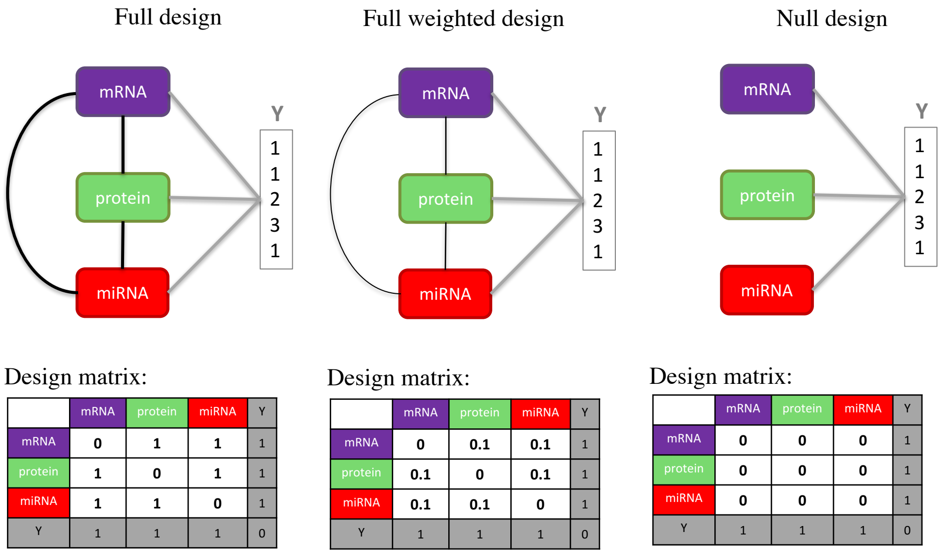
$$\max_{a_h^{(1)},\dots,a_h^{(Q)}} \sum_{q,j=1,q\neq j}^{Q} c_{q,j}\ \mathrm{cov}(X_h^{(q)} a_h^{(q)}, X_h^{(j)} a_h^{(j)}), \qquad \text{s.t.} \quad ||a_h^{(q)}||_2 = 1 \text{ and } ||a_h^{(q)}||_1 \leq \lambda^{(q)} \tag{3}$$

where $\lambda^{(q)}$ is the penalisation parameter, $a_h^{(q)}$ is the loading vector on component h associated to the residual (deflated) matrix $X_h^{(q)}$ of the data set $X^{(q)}$, and $C = \{c_{q,j}\}_{q,j}$ is the design matrix. C is a $Q \times Q$ matrix that specifies whether datasets should be correlated and includes values between zero (datasets are not connected) and one (datasets are fully connected). Thus, it is possible to constraint the model to only take into account specific pairwise covariances by setting the `design` matrix (see Tenenhaus et al. 2014 for more details). Such design thus enables to model a particular association between pairs of 'omics data, as expected from prior biological knowledge or experimental design. `DIABLO` Discriminant Analysis in `mixOmics` extends (3) to a supervised framework by replacing one data matrix $X^{(q)}$ with the outcome dummy matrix Y.

Choice of the design matrix There are different strategies to specify the `design` matrix. One can define the design matrix based on prior biological knowledge (*e.g.* proteomics and transcriptomics 'should be' highly correlated), or based on a data-driven approach. A preliminary multivariate method integrating two data sets at a time (`e.g. pls`) can assess the common information between data sets in an unsupervised analysis, while the performance evaluation of different designs can guide the choice when seeking for a predictive multi-'omics model. Our experience has shown that a trade-off between maximising correlation between datasets and maximising the discrimination of the outcome was required. Assume that $X^{(Q)}$ is set to the outcome dummy indicator matrix. A *full design*, where $c_{q,j} = 1$ for all $q \neq j$, maximises the correlation between datasets while a *null design*, where $c_{q,j} = 0$ for $q, j < Q$ and $c_{q,j} = 1$ for $q, j = Q$, maximises the separation between the outcome classes. In practice, we found that a *full weighted design* where $c_{q,j} = 0.1$ between data matrices and 1 for the outcome led to such trade-off (a correlated and discriminant molecular signature), see Figure S4.

S4.2 Specific outputs to visualise multiple 'omics data sets integration

Several types of graphical outputs are available to support interpretation of the statistical results. To represent samples, `plotIndiv` displays component scores from each 'omics data set individually. Such type



Design matrix:

	mRNA	protein	miRNA	Y
mRNA	0	1	1	1
protein	1	0	1	1
miRNA	1	1	0	1
Y	1	1	1	0

Design matrix:

	mRNA	protein	miRNA	Y
mRNA	0	0.1	0.1	1
protein	0.1	0	0.1	1
miRNA	0.1	0.1	0	1
Y	1	1	1	0

Design matrix:

	mRNA	protein	miRNA	Y
mRNA	0	0	0	1
protein	0	0	0	1
miRNA	0	0	0	1
Y	1	1	1	0

Figure S4: **Example of different design matrices in `DIABLO` for the multi-'omics breast cancer study** (illustrated in the main article). Links or cells in grey are added by default in the `DIABLO` function `block.plsda` and `block.splsda` and do not need to be specified by the user.

of plot enable to visualise the agreement between all data sets at the sample level. The `plotArrow` function also enables similar visualisation (see Section S2). The function `plotDiablo` is a matrix scatterplot of the components from each data set for a given dimension; it enables to check whether the pairwise correlation between two 'omics has been modelled according to the design.

The function `circosPlot` shows pairwise correlations among the selected variables across all data sets. Variables are represented on the side of the circos plot, where colours indicate the type of data, and external (optional) lines display the expression levels with respect to each outcome category. `circosPlot` implement an extension of the method used in `plotVar`, `cim` and `network` described in González et al. (2012).

S4.3 Workflow for `DIABLO` analysis

We provide a full R and Sweave workflow electronically in our website at this link.

S5 P-integration across independent data sets with MINT

The integration of independent data sets measured on the same common P features under similar conditions or treatments (Figure 1 in main article) is a useful approach to increase sample size and gain statistical power. In this context, the challenge is to accommodate for systematic differences that arise due to differences between protocols, geographical sites or the use of different technological platforms to generate the same type of 'omics data (e.g. transcriptomics). The systematic unwanted variation, also called 'batch-effect', often acts as a strong confounder in the statistical analysis and may lead to spurious results and conclusions if it is not accounted for in the statistical model. Here we briefly introduce `MINT`, a PLS-based supervised method that integrates independent studies in a classification framework.

S5.1 `MINT` method

`MINT` (Rohart et al., 2017) is an extension of the multi-group PLS framework (mgPLS, Eslami et al. 2013, 2014), where 'groups' represent independent studies, to a supervised framework with variable selection.

MINT seeks for a common projection space across all studies, defined on a small subset of discriminative variables that consistently discriminate the outcome classes across studies.

In MINT, we combine M datasets denoted $X^{(1)}(N_1 \times P)$, $X^{(2)}(N_2 \times P)$, ..., $X^{(M)}(N_M \times P)$ measured on the same P predictors but from independent studies, with $N = \sum_{m=1}^{M} N_m$. Each data set $X^{(m)}$, $m = 1, \ldots, M$, has an associated dummy indicator outcome $Y^{(m)}$ in which all K classes are represented. We denote X $(N \times P)$ and Y $(N \times K)$ the concatenation of all $X^{(m)}$ and $Y^{(m)}$ respectively. In our MINT framework, each variable from the datasets $X^{(m)}$ and $Y^{(m)}$ is centered and scaled within each study m. For each component h, MINT solves :

$$\max_{a_h, b_h} \sum_{m=1}^{M} N_m \ \mathrm{cov}(X_h^{(m)} a_h, Y_h^{(m)} b_h), \qquad \text{s.t.} \quad ||a_h||_2 = 1 \text{ and } ||a_h||_1 \leq \lambda \tag{4}$$

where a_h and b_h are the global loadings vectors common to all studies, $t_h^{(m)} = X_h^{(m)} a_h$ and $u_h^{(m)} = Y_h^{(m)} b_h$ are the partial PLS-components that are study specific. Residual (deflated) matrices are calculated for each iteration of the algorithm based on the global components and loading vectors (see Rohart et al. 2017). Thus the MINT algorithm models the study structure during the integration process. The penalisation parameter λ controls the amount of shrinkage and thus the number of non zero weights in the global loading vector a. Similarly to sPLS-DA (Section S3.2) MINT selects a combination of features on each PLS-component.

S5.2 Leave-One-Group-Out Cross-Validation for performance assessment

In MINT we take advantage of the independence between studies to evaluate the performance based on a novel CV technique called ‘Leave-One-Group-Out Cross-Validation’ (Rohart et al., 2017). LOGOCV performs CV where each study m is left out once. The aim is to reflect a realistic prediction of independent external studies. The `tune` function implements LOGOCV to choose the optimal number of features `keepX` or the optimal set of features `keepX.constraint` to select in X, as described in ‘Choice of parameters’ Section in the main article. Note that LOGOCV cannot be repeated (no `nrepeat` argument) as the partitioning is not random.

S5.3 Specific graphical outputs for MINT

The set of partial components $t_h^{(m)}, h = 1, ..., H$ provides outputs specific to each study m in `plotIndiv`. The samples plots enable to perform a quality control step to identify studies that cluster outcome classes differently to other studies (i.e. ‘outlier’ studies). The function `plotLoadings` displays the coefficients weights of the features globally selected by the model but represented individually in each study to visualise potential discrepancies between studies. Visualisation of the global loading vectors is also possible (argument `study = ‘all.partial’` or `‘global’`. Note the projection into the Y-space is not useful in MINT.

S5.4 Workflow for MINT analysis

We provide a full R and Sweave workflow electronically in on our website at this link.

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