

Apply predictive analytics on multi-omics data with InSyBio Biomarkers

October 2025

Insybio Suite v3.4



InSyBio

Intelligent Systems Biology

User Manual

www.insybio.com

InSyBio Biomarkers

Introduction

Biomarkers is a tool for:

- dataset preprocessing and statistical analysis of omics and multi-omics datasets
- training multi-biomarkers machine learning models for disease diagnosis, prognosis and response to therapies
- applying trained models to new data

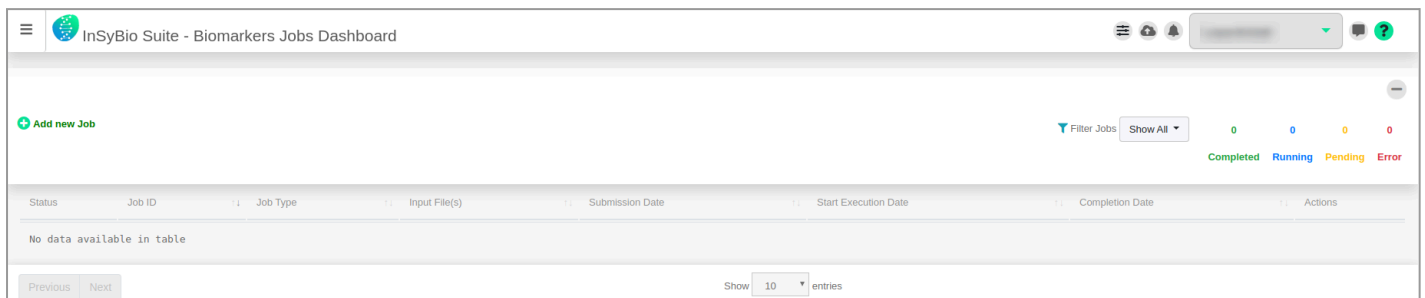
When the user selects the InSyBio Biomarkers tool he will access the Biomarkers dashboard:

Job ID	Name	Description	Submission Date	Start Execution Date	Completion Date	Actions
16	Training Multi-biomarker Predictive Analytics Model	PLC_Labels_80 (PLC_DATA_with missing_with_normalize_80Labels.txt) PLC_data_80_transpos (PLC_DATA_with missing_with_normalize_80datatransposed.txt)	11/8/19 3:30 PM	11/8/19 3:30 PM	11/8/19 4:02 PM	View Results
15	Training Multi-biomarker Predictive Analytics Model	PLC_data_80 (PLC_DATA_with missing_with_normalize_80data (1).txt) PLC_Labels_80 (PLC_DATA_with missing_with_normalize_80Labels.txt)	11/8/19 2:40 PM	11/8/19 2:40 PM	11/8/19 2:52 PM	View Details
14	Testing Multi-biomarker Predictive Analytics Model	Model created from (Preprocessed file from aorta_multi_dataset) and (aorta_labels.txt) (model_13.txt) Testset created from (Preprocessed file from aorta_multi_dataset) and (aorta_labels.txt) after splitting with percentage 0.3 (test_dataset_v_markers_13.txt) Test label created from (Preprocessed file from aorta_multi_dataset) and (aorta_labels.txt) after splitting with percentage 0.3 (test_labels_13.txt)	10/8/19 9:34 AM	10/8/19 9:34 AM	10/8/19 9:34 AM	View Details
13	Training Multi-biomarker Predictive Analytics Model	Preprocessed file from aorta_multi_dataset (preprocessed_data_12.txt) aorta_labels.txt (ferheen_aorta_multiple_conditions_dataset_With_Headers.txt)	9/27/19 2:15 PM	9/27/19 2:15 PM	9/27/19 2:16 PM	View Results
12	Dataset Preprocessing	aorta_multi_dataset (ferheen_aorta_multiple_conditions_dataset_With_Headers.txt)	9/27/19 2:12 PM	9/27/19 2:12 PM	9/27/19 2:12 PM	View Results
11	Testing Multi-biomarker Predictive Analytics Model	Model created from (Preprocessed file from lung_data_no_samples) and (lung_labels.txt) (model_9.txt) Testset created from (Preprocessed file from lung_data_no_samples) and (lung_labels.txt) after splitting with percentage 0.3 (test_dataset_v_markers_9.txt) Test label created from (Preprocessed file from lung_data_no_samples) and (lung_labels.txt) after splitting with percentage 0.3 (test_labels_9.txt)	9/27/19 1:36 PM	9/27/19 1:36 PM	9/27/19 1:36 PM	View Details

The available functionalities in the “Add new Job” button include Biomarkers Dataset Preprocessing, Biomarkers Dataset Statistical Analysis, Training Multi-biomarker Predictive Analytics Model and Testing Multi-biomarker Predictive Analytics Model.

Inside the biomarkers jobs dashboard the user will be able to view his current running, pending, successfully completed and completed with error jobs.

The biomarkers jobs dashboard of a new user will look like the following:



Status	Job ID	Job Type	Input File(s)	Submission Date	Start Execution Date	Completion Date	Actions
No data available in table							

Under the column “Job ID” the table has the identification name of each job. In the column “Job Type” the user will be able to see the type of job, categorized as one of the following: Biomarkers Dataset Preprocessing, Biomarkers Dataset Statistical Analysis, Training Multi-biomarker Predictive Analytics Model and Testing Multi-biomarker Predictive Analytics Model.

In the field “Input File(s)” the user will be able to view the input files of each job. At the field “Submission Date” the dashboard will display the exact date that each job has been submitted. At the field “Start Execution Date” the exact date of the initiation of each job will be displayed. At the field “Completion Date” the completion date of each job will be displayed. Also, at the field “Status”, each job will be either “Completed” or “Pending”, or “Running” or “Error” when an error will have occurred.

Dataset Preprocessing

During preprocessing we filter the dataset, perform normalization, missing values imputation, duplicate measurements averaging and outlier detection with the PCA LOF method.

The screenshot shows the 'InSyBio Suite - Dataset Preprocessing' web interface. It features a header with the InSyBio logo and a user profile 'InSyBio Beta User'. The main form includes input fields for 'Title' and 'Filename', two buttons for file selection ('Select file from Data Store' and 'Go to Data Store to Upload File'), a 'Normalization' dropdown menu currently set to 'Arithmetic Sample-Wise Normalization', a 'Missing values imputation' dropdown set to 'KNN-impute', and three checkboxes for dataset characteristics: 'Does your dataset have samples headers?' (No), 'Does your dataset have features headers?' (No), and 'Does the Normalization use a set of householding molecules?' (unchecked). A green 'Submit Job' button is located at the bottom left of the form.

More specifically, there are two kinds of normalization: arithmetic sample-wise and logarithmic. It should be noted that when the data contain negative numbers the arithmetic normalization should be chosen, since the logarithmic normalization method functions only with non-negative data. If “None” is chosen, no normalization takes place.

There are two kinds of missing value imputation methods as well: average imputation and KNN imputation. Average imputation is a method in which the missing value on a certain variable is replaced by the mean of the available cases¹. On the other hand, the key idea of KNN imputation is that a point value can be approximated by the values of the points that are closest to it, based on other variables². The above missing values imputation methods are relevant only for cases where a missing value does not imply a quantification value of zero. In such cases, missing values should be replaced with zeros before uploading the dataset. If “None” is chosen then no missing value imputation takes place.

Furthermore, if a missing values imputation method is being chosen instead of “None”, the duplicate measurements will be averaged.

The user will be prompted to upload a biomarkers dataset or select one from the Datastore. A biomarkers dataset should have as rows the biomarkers (molecules, or else features) and as columns the samples. Thus, each cell will contain the value of a biomarker in a sample. Also, the user should provide the information if there are

¹ [Single Imputation Methods](https://iriseekhout.com) (iriseekhout.com)

² [The use of KNN for missing values](https://towardsdatascience.com) (towardsdatascience.com)

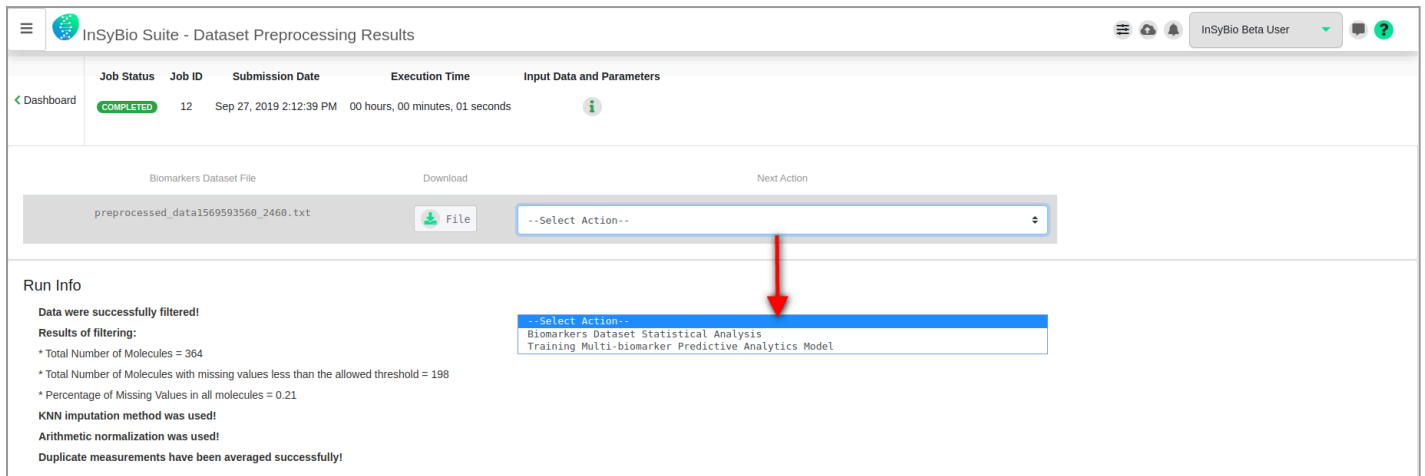
headers inside the dataset (i.e. a samples header, features header, or both or none). To do this you'll have to choose "Yes" or "No" as answers to the questions "Does your dataset have sample headers?" and "Does your dataset have feature headers?". Additionally, the dataset should have its values separated with tabs (have TSV format).

The user can also provide a set of household molecules (biomarkers) to perform geometric normalization of the data additionally to the normalization method already being performed. To do that the user will have to tick the box beside the question "Does the Normalization use a set of householding molecules?", and insert the names of molecules in the box that appears, separated with commas or a new line. Householding molecules should represent a large abundance in the dataset, not have missing values and should not present high variability among the examined phenotypes.

The screenshot shows the 'InSyBio Suite - Dataset Preprocessing' web interface. At the top, there's a header with the InSyBio logo, a hamburger menu, and a user profile 'InSyBio Beta User'. The main section is titled 'Biomarkers Dataset'. It contains several input fields: 'Title:' and 'Filename:'. Below these are two buttons: 'Select file from Data Store' (green) and 'Go to Data Store to Upload File' (blue). The 'Normalization:' dropdown is set to 'Arithmetic Sample-Wise Normalization'. The 'Missing values imputation:' dropdown is set to 'KNN-impute'. There are two dropdowns for 'Does your dataset have samples headers?' and 'Does your dataset have features headers?', both set to 'No'. A checkbox for 'Does the Normalization use a set of householding molecules?' is checked. Below this checkbox is a text area containing 'ATM,TP53,BRCA1,...'. At the bottom left, there's a 'Set of variables for normalization' label and a 'Submit Job' button.

Complex combinations of the above preprocessing methods can be conducted by applying these analysis steps sequentially (e.g. first logarithmic normalization and then arithmetic normalization).

After dataset preprocessing finishes successfully, by selecting "View Results" from the Biomarkers dashboard page the user will view a page like the following:



InSyBio Suite - Dataset Preprocessing Results

Job Status: COMPLETED Job ID: 12 Submission Date: Sep 27, 2019 2:12:39 PM Execution Time: 00 hours, 00 minutes, 01 seconds

Biomarkers Dataset File: preprocessed_data1569593560_2460.txt Download: File Next Action: --Select Action--

Run Info

Data were successfully filtered!

Results of filtering:

- * Total Number of Molecules = 364
- * Total Number of Molecules with missing values less than the allowed threshold = 198
- * Percentage of Missing Values in all molecules = 0.21

KNN imputation method was used!

Arithmetic normalization was used!

Duplicate measurements have been averaged successfully!

In the above page the user will be able to view the Input Data and the Parameters that he chose for the specific job, that is the description of the input file and its name, the normalization method chosen, the missing values imputation method chosen and the set of variables chosen for normalization. Additionally the user will be able to view the Biomarker Job Information, which includes the submission, start, execution and completion date, the total runtime (execution time) and the status.

From the results, the user will be able to download the resulting preprocessed file and choose one of the two actions as a next step.

From this point the actions that the user will be able to select from are to perform statistical analysis of the dataset ("Biomarkers Dataset Statistical Analysis") or to train a predictive analytics model ("Training Multi-biomarker Predictive Analytics Model").

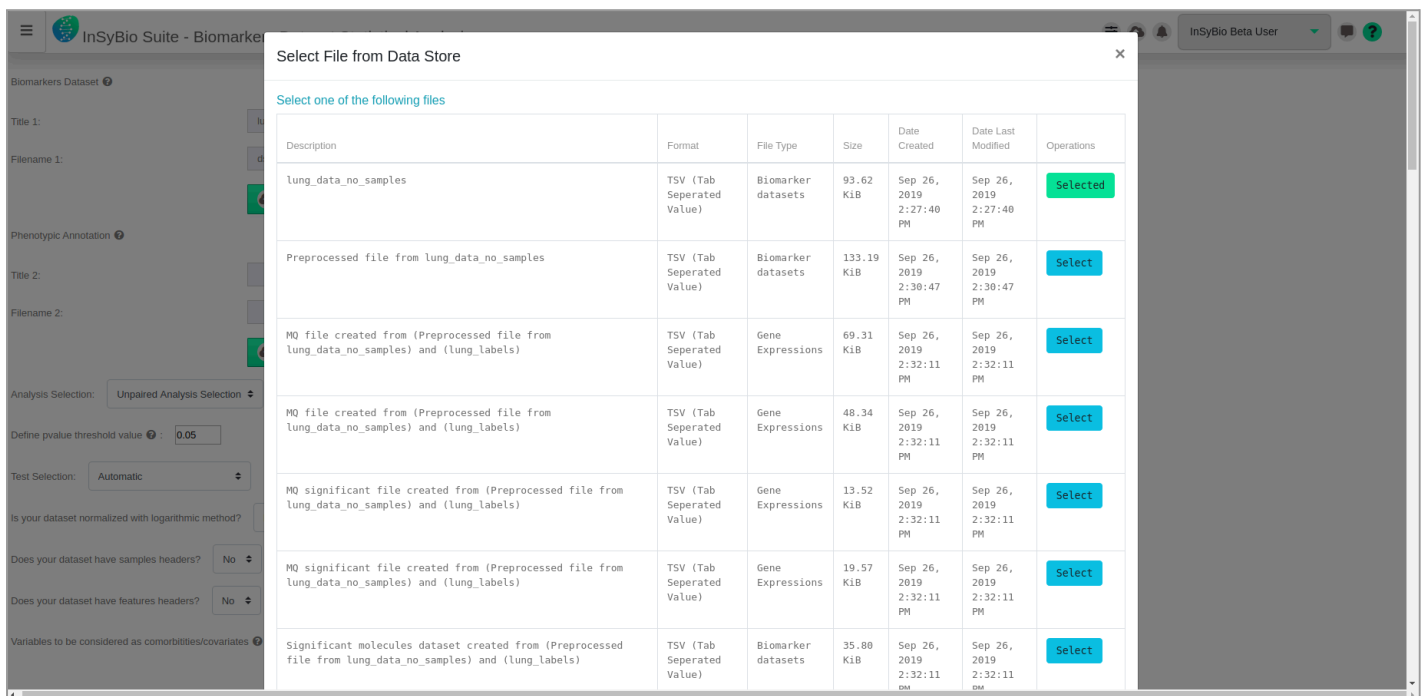
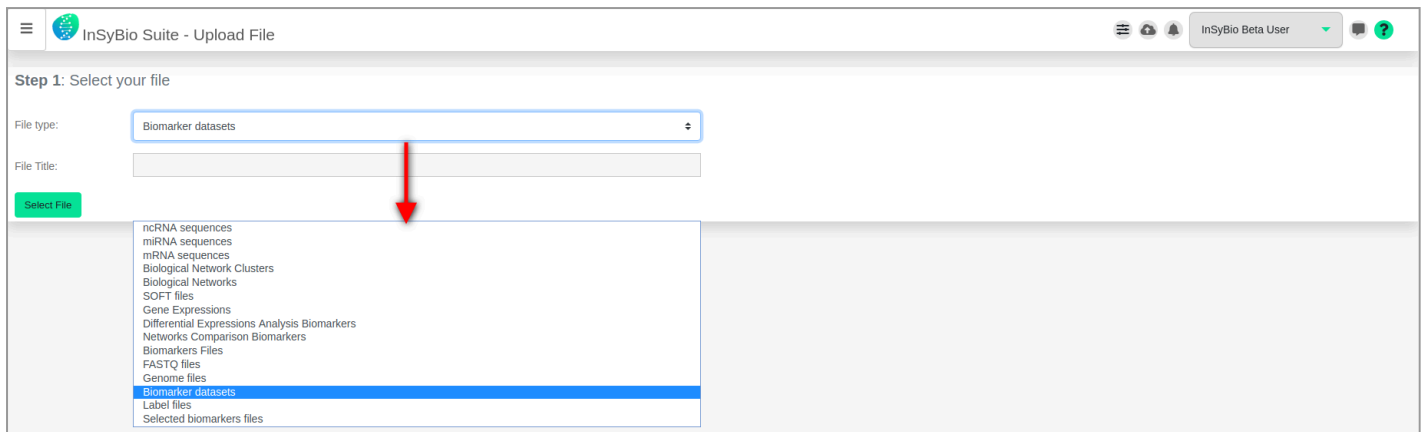
Biomarkers Dataset Statistical Analysis

This page allows the user to perform simple tasks of statistical analysis on a biomarkers dataset including: Differential Expression Analysis, Heatmap construction and spearman correlation table construction.

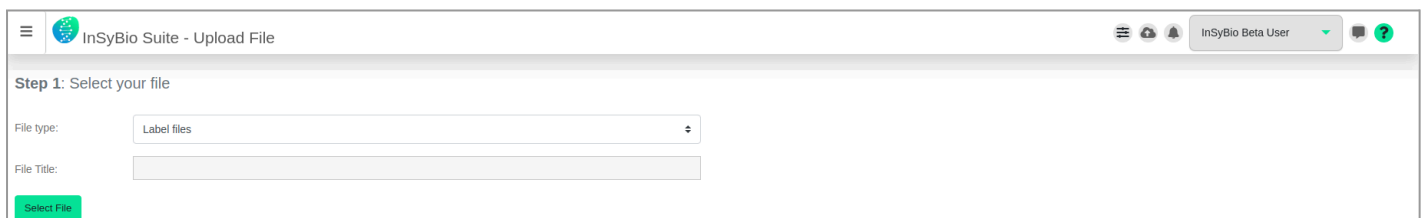
Only variables annotated as genes/transcripts/proteins will be used for differential expression analysis. If a user has uploaded a phenotypic annotation file with more than two columns then multiple tasks will be created with one column of the phenotypic annotation per file. Every phenotypic column can take two or more values. Please note that these analyses are intended for classification problems, where phenotypic columns represent distinct groups or classes.

The screenshot shows the 'InSyBio Suite - Biomarkers Dataset Statistical Analysis' web interface. The top navigation bar includes a menu icon, the suite name, and a user profile 'InSyBio Beta User'. The main content area is titled 'Biomarkers Dataset' and contains two sections for dataset input. The first section, 'Biomarkers Dataset', has fields for 'Title 1:' and 'Filename 1:', followed by two buttons: 'Select file from Data Store' (green) and 'Go to Data Store to Upload File' (blue). The second section, 'Phenotypic Annotation', has fields for 'Title 2:' and 'Filename 2:', followed by the same two buttons. Below these sections are several configuration options: 'Analysis Selection' set to 'Unpaired Analysis Selection', 'Define pvalue threshold value' set to '0.05', 'Test Selection' set to 'Automatic', and three dropdown menus for 'Is your dataset normalized with logarithmic method?', 'Does your dataset have samples headers?', and 'Does your dataset have features headers?', all set to 'No'. A text area for 'Variables to be considered as comorbitties/covariates' contains the text 'ACTA,...'. A green 'Submit Job' button is located at the bottom left of the form.

If the user visits the statistical analysis page after executing the Dataset Preprocessing step, the Biomarkers Dataset file will be pre-chosen for him. Otherwise, he'll have to upload a file on Datastore by selecting "Go to Data Store to Upload File" by selecting as filetype "Biomarker datasets", and then select the uploaded by pressing "Select file from Data Store", as shown in the examples below:



Afterwards, the user will have to either upload or select from the Data Store the phenotypic annotation which pairs the biomarkers dataset. If he uploads the labels file, the user should select as filetype “Label files”, as shown in the next image:



The labels (each one corresponding to a sample) should be all in one row, separated by tabs.

Later on, the user will have to select the type of analysis to be made on the inserted dataset. There are two types of statistical analysis, paired and unpaired analysis.

Afterwards the user will have to insert the p-value threshold value, which is recommended to be 0.05.

Then, the user will choose the kind of test to be performed on the selected dataset: automatic, parametric Ebayes Test Selection, parametric 2-sided Students T-test (or One-way ANOVA Test Selection) or non-parametric Kruskal Wallis (or Mann Whitney Test Selection) test. If the automatic version is chosen, then our algorithm will decide which test to run: the parametric or non-parametric.

Afterwards the user will have to indicate if his dataset was preprocessed using logarithmic normalization or not.

Also, the user will have to insert the information regarding the headers of the input dataset. If the dataset has a sample header, "Yes" should be chosen as an answer to the first question, else "No". If the dataset has a features (biomarkers) header, "No" should be chosen as an answer to the second question.

Finally, the user can also provide a set of household molecules (biomarkers) to perform geometric normalization of the data additionally to the normalization method already being performed. To do that the user will have to insert the names of molecules in the box that appears, separated with commas or a new line.

Householding molecules should represent a large abundance in the dataset, not have missing values and should not present high variability.

When the job is completed in the biomarkers dashboard, the user will be able to select to "View Results" getting to a page like the following:

InSyBio Suite - Biomarkers Dataset Statistical Analysis Results					InSyBio Beta User
Dashboard	Job Status	Job ID	Submission Date	Execution Time	Input Data and Parameters
	COMPLETED	452	Jun 3, 2021 3:01:54 PM	00 hours, 00 minutes, 20 seconds	
Statistical Analysis Results	Heatmap Visualization	Volcano Plots Visualization	Significant Molecules	MQ Files	Beanplots Download
	All Results Download	Run Info			
Statistical Analysis Results (Top 20*)					
*You can download the full results from "All Results Download" tab.					
p-Values top20					
IDs	Pvalue	Adjusted Pvalue	Fold Change		
Age (years)	0.0002198543038503091	0.001539637705193092	0.11894131216350945		
Smoking	0.30975501607977707	0.4439821897143471	0.045543482951146574		
PE side	0.4048341285541227	0.5043748920406902	0.04136139601196409		
PE size (% of lung field)	1.552957646091476e-08	6.677717878193347e-07	0.14482463330009965		
PF RBC (1000_mm3)	0.0142515658857721	0.055710666644381845	0.020712023130608177		
PF NC (1000_mm3)	0.0012351105046412541	0.00590108352217488	-0.01207662263210369		
WBC (1000_mm3)	0.18089351147997134	0.31113656397451067	-0.001529408773678964		
PF NC_WBC ratio	0.0019276367947083362	0.008268638217245846	-0.014508861316051844		
PF mononuclear cells (%)	0.04946379965500796	0.16361102962810326	0.065275263110668		
PF neutrophils (%)	2.857734391286766e-05	0.0006144128941260547	-0.14200804052488997		
PF lymphocytes (%)	0.0005285067062035405	0.00324654119525032	0.0950857147557328		
PF eosinophils (%)	0.5688587616322165	0.6611061283833868	-0.021694287637088732		

In the results page the user will be able to view the Statistical Analysis Results (the top 20 features), the Heatmaps, the Volcano plots, the significant molecules, the molecular quantification (MQ) files and he'll be able to download the Beanplots and all the resulting files. Finally, in the last tab the run information will be displayed.

Training Multi-biomarker Predictive Analytics Model

This page allows users to train their own predictors using a biomarkers dataset, a phenotypic annotation and by providing some parameters.

InSyBio Suite - Training Multi-biomarker Predictive Analytics Model

Biomarkers Dataset

Title 1:

Filename 1:

Phenotypic Annotation

Title 2:

Filename 2:

Do you want to split the dataset in training and testing?

Is your dataset normalized with logarithmic method?

Does your dataset have samples headers?

Does your dataset have features headers?

Variables to be considered as comorbidity/covariates:

What's your Prediction Problem?

☒ Two-Class ☐ Regression ☐ OMni-Class

Predictor Goals

1. Selected Features Minimization	2. Classifier's Accuracy	3. F1 score	4. F2 score
<input type="text" value="1"/>	<input type="text" value="10"/>	<input type="text" value="10"/>	<input type="text" value="1"/>
5. Classifier's Precision	6. Classifier's Recall	7. Classifier's ROC AUC	8. Model Complexity Minimization
<input type="text" value="1"/>	<input type="text" value="1"/>	<input type="text" value="1"/>	<input type="text" value="1"/>

Advanced Options

Multiobjective Optimization Framework Parameters		
Population Size: <input type="text" value="50"/>	Arithmetic Crossover Probability: <input type="text" value="0"/>	Mutation Probability: <input type="text" value="0.01"/>
Generations: <input type="text" value="100"/>	Two Point Crossover Probability: <input type="text" value="0.9"/>	k in k-fold Cross Validation: <input type="text" value="5"/>

These parameters have been tested in various diagnostic and prognostic applications by InSyBio's R&D team and they have proven to provide efficient exploration and exploitation of the search space minimizing also the risk of getting trapped to local optimal solutions. If you are not a bioinformatician with expertise in machine learning, we strongly advice not to change these parameters and to contact our support team if the default values do not provide good predictive models for your dataset.

Firstly the user will have to input a preprocessed biomarkers dataset, selecting it from the Data Store or by uploading it. Then the user will have to insert a phenotypic annotation file.

Later on, the user will have to indicate if his dataset was preprocessed using logarithmic normalization or not.

Afterwards, the user will have to choose to split or not the input dataset to training set and test set, by selecting the percentage ("Filtering percentage") of the original file

that will be the test set. If chosen, the model will be trained using the training set, and the test set will be stored in Data Store for later use.

Then the user will have to insert the information regarding the headers. That is to inform the application if the original dataset has sample headers or feature headers. Optionally, the user will have the option to insert the names of the features that will be used for normalization.

Eventually, the user chooses the kind of prediction problem he has at hand. Later, he can alter the weights of the predictor goals. It is advisable to use the default values. The higher the weight, the more significant the goal.

Finally, the user can alter the multi-objective optimization framework parameters by pressing the button “Show Advanced Options”. Those are the population size, the number of generations, the arithmetic crossover probability, the two point crossover probability, the mutation probability and the number of folds k for the cross validation.

What's your Prediction Problem?

☒ Two-Class
 ☐ Regression
 ☐ Multi-Class

Predictor Goals

1. Selected Features Minimization	2. Classifier's Accuracy	3. F1 score	4. F2 score
<input type="text" value="1"/>	<input type="text" value="10"/>	<input type="text" value="10"/>	<input type="text" value="1"/>
5. Classifier's Precision	6. Classifier's Recall	7. Classifier's ROC AUC	8. Model Complexity Minimization
<input type="text" value="1"/>	<input type="text" value="1"/>	<input type="text" value="1"/>	<input type="text" value="1"/>

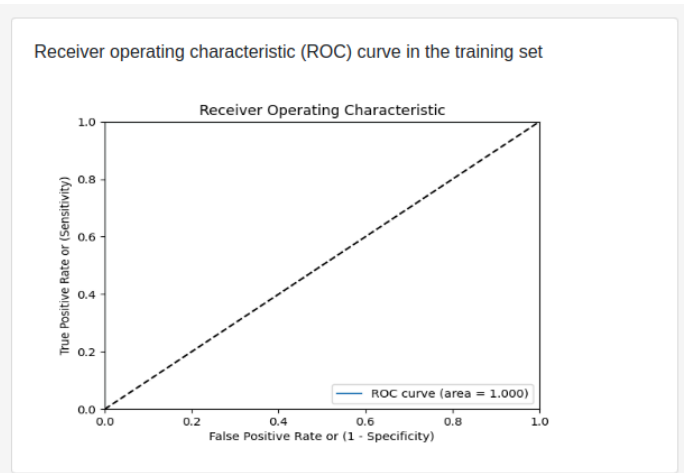
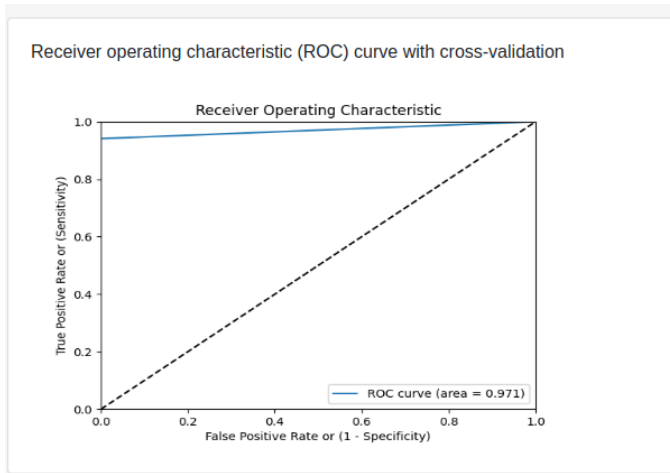
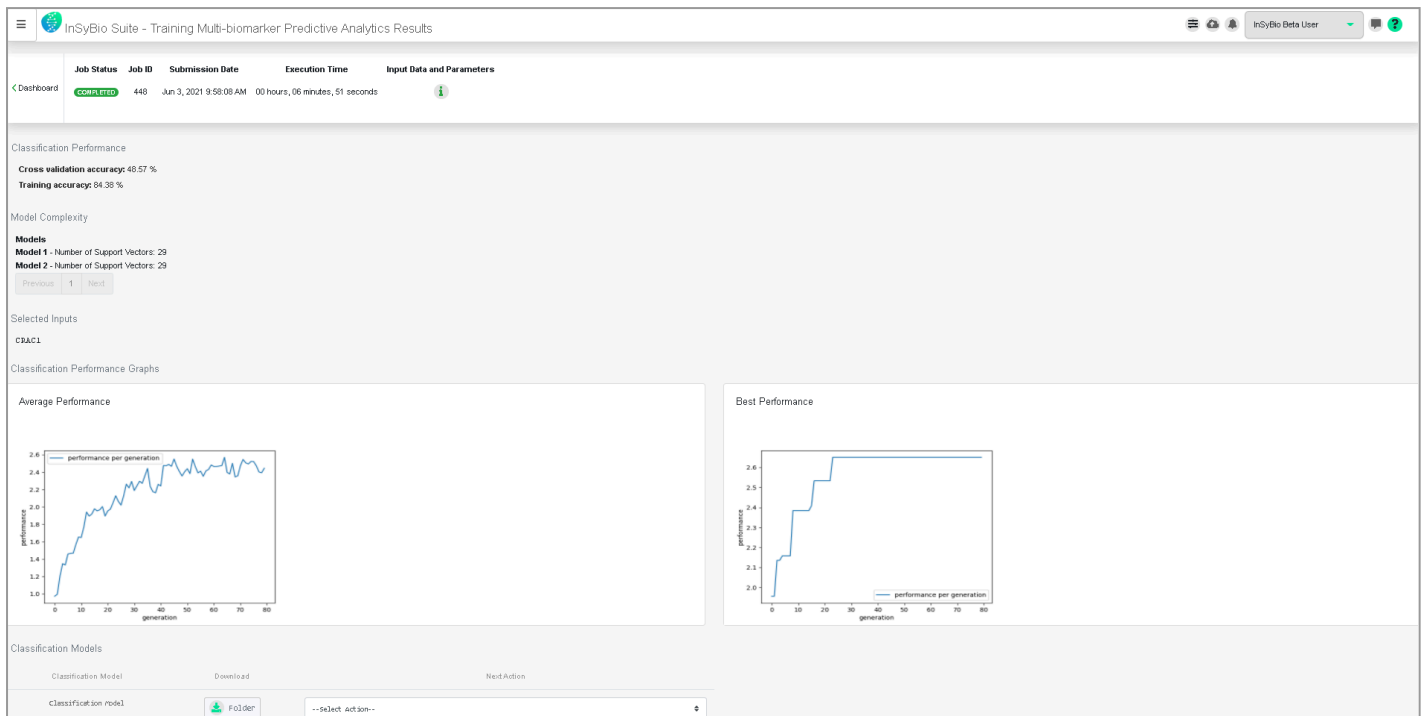
Advanced Options

Multiobjective Optimization Framework Parameters		
Population Size: <input type="text" value="50"/>	Arithmetic Crossover Probability: <input type="text" value="0"/>	Mutation Probability: <input type="text" value="0,01"/>
Generations: <input type="text" value="100"/>	Two Point Crossover Probability: <input type="text" value="0,9"/>	k in k-fold Cross Validation: <input type="text" value="5"/>

These parameters have been tested in various diagnostic and prognostic applications by InSyBio's R&D team and they have proven to provide efficient exploration and exploitation of the search space minimizing also the risk of getting trapped to local optimal solutions. If you are not a bioinformatician with expertise in machine learning, we strongly advice not to change these parameters and to contact our support team if the default values do not provide good predictive models for your dataset.

Submit Job

The result page will have the following form:



As shown, the user will be able to see the input files that he's inserted, the type of prediction problem and the biomarker job information (submission date, start execution date, completion date, execution time and status).

Also the user will be able to view the classification (or regression) performance of the cross validation and of the training set. For the two-class prediction problem the user will be able to see the accuracy, sensitivity, and specificity. For the multi-class prediction problem the user will be able to see only the accuracy and for the regression prediction problem the user will be able to view the root mean square error.

Additionally, the complexity of every model, which is the total number of support vector machines, the number of trees for RandomForest and the number of neurons for the CNN and also, the average and the best performance of the trained model are being displayed.

Two more Roc Curves for the cross validation and the training set are also produced and displayed. An Roc Curve (Receiver Operating Characteristic Curve) is a graph showing the performance of a classification model at all classification thresholds using the True and False Positive Rates.

From this point the user will be able to continue by choosing as a next action the "Testing Multi-biomarkers Predictive Analytics Model".

Testing Multi-biomarker Predictive Analytics Model

This page will allow the users to test the predictors that they have trained in the previous "training" step.

The first input is the model file which will have been autocompleted from the previous step.

The second input file is the test dataset, which can be preprocessed or not preprocessed. If the user has chosen in the training step to split that input dataset, the

form of the test dataset will have been completed with the produced test dataset. In such a case the user should insert that the input dataset doesn't have sample headers but it has feature headers.

The screenshot shows the InSyBio Suite interface for testing a multi-biomarker predictive analytics model. The title bar reads "InSyBio Suite - Testing Multi-biomarker Predictive Analytics Model" and the user is logged in as "InSyBio Beta User". The interface is divided into sections for Model File, Testset File, and Testset Labels (Optional). Each section has input fields for Title and Filename, and buttons to select files from the Data Store or upload files. There are also dropdown menus for dataset preprocessing and headers, and a "Submit Job" button at the bottom.

Model File

Title 1:

Filename 1:

[Select model file from Data Store](#)

Testset File

Title 2:

Filename 2:

[Select file from Data Store](#) [Go to Data Store to Upload File](#)

Testset Labels (Optional)

Title 3:

Filename 3:

[Select file from Data Store](#) [Go to Data Store to Upload File](#)

Is your Dataset already Preprocessed?

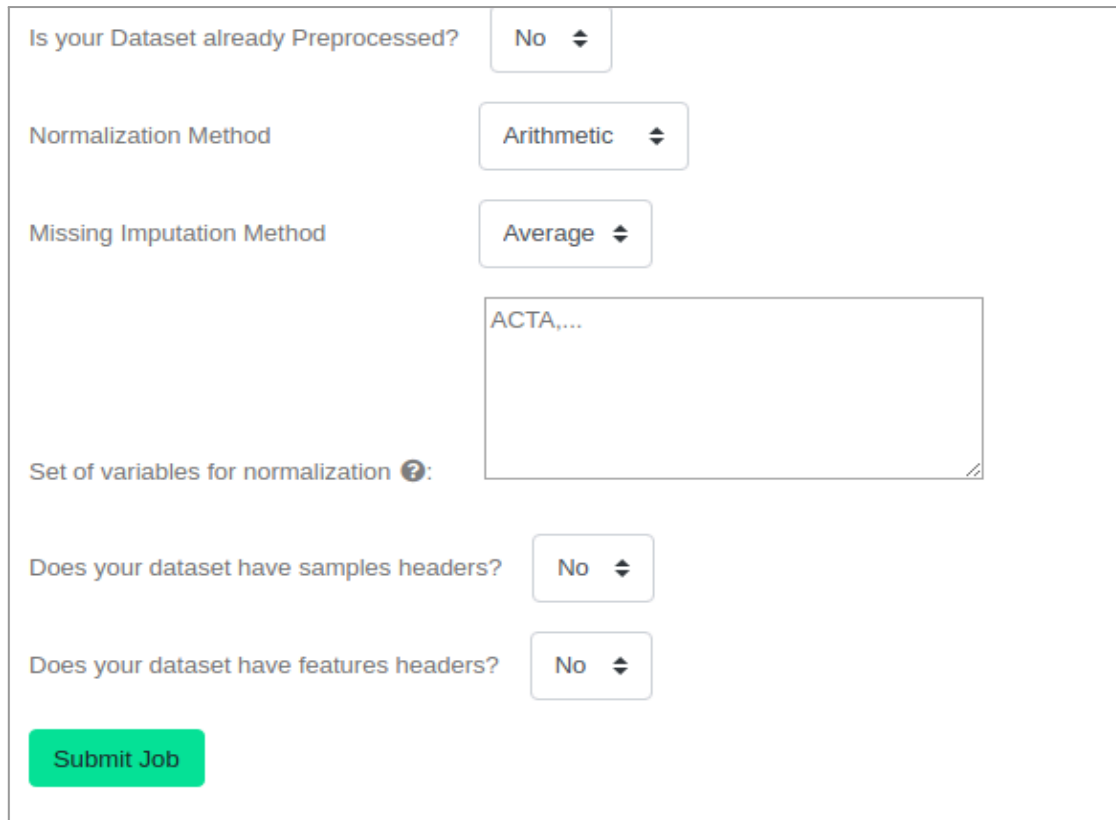
Does your dataset have samples headers?

Does your dataset have features headers?

[Submit Job](#)

The third input are the testset labels, which is optional. If the user inserts the testset labels then he'll receive as an output along with the predicted labels the performance metrics of the prediction.

The user may choose to test a non-preprocessed testset. Then he'll have to choose as normalization and missing imputation methods those methods that he'd chosen to preprocess the training dataset. He may also insert a set of variables for normalization, to use the geometric normalization method.



The screenshot displays a web form for submitting a biomarker job. The form includes several dropdown menus and a text area. The first dropdown is 'Is your Dataset already Preprocessed?' with 'No' selected. The second is 'Normalization Method' with 'Arithmetic' selected. The third is 'Missing Imputation Method' with 'Average' selected. Below these is a text area labeled 'Set of variables for normalization' with a question mark icon, containing the text 'ACTA,...'. The fourth dropdown is 'Does your dataset have samples headers?' with 'No' selected. The fifth dropdown is 'Does your dataset have features headers?' with 'No' selected. At the bottom left is a green 'Submit Job' button.

It should be noted that the input dataset must have the format of the previous functionalities, that is it should have as rows the features and as columns the samples.

The results the user will be getting are the following. Firstly he will view the input data and the chosen parameters, such as the model file, the test dataset file, the labels file, and the type of the problem. Then he'll be able to view the biomarker job information, such as the submission date, the start execution date, the completion date, the execution time, and the status (completed or not). Finally he'll view the predicted labels and the performance metrics. For the two classification problems (two-class, multi-class) he'll view the test set accuracy, specificity, sensitivity and the geometric mean of specificity and sensitivity. For the regression he'll view the testset mean squared error and the test set squared correlation coefficient. The above are being displayed in the following image as an example.

Cloud computing Infrastructurer and Security Certifications

InSyBio Suite and all its tools are running over the cloud computing as a service infrastructure of Vultr (<https://www.vultr.com>), at the Amsterdam (Netherlands) facilities, offering the following security attestations and certifications (SOC 2+ (HIPAA), PCI (Merchant), CSA Star Level 1, ISO/IEC 20000-1:2018, ISO/IEC 27001:2022, ISO/IEC 27017:2015, ISO/IEC 27018:2019).

How to get InSyBio Interact

To request a free one month license of InSyBio Suite please email us at info@insybio.com.

To purchase InSyBio Interact commercial version 3.3 please contact us at sales@insybio.com.

About Us

InSyBio Inc is a bioinformatics pioneer company (www.insybio.com) in personalized healthcare, that focuses on developing computational frameworks and tools for the analysis of complex life-science and biological data in order to develop predictive integrated biomarkers

(biomarkers of various categories) with increased prognostic and diagnostic aspects for the personalized Healthcare Industry.

InSyBio Suite consists of tools for providing integrated biological information from various sources, while at the same time it is empowered with robust, user-friendly and installation-free bioinformatics tools based on intelligent algorithms and methods.

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