



immuneXpresso Tutorial

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Overview

Protective immunity draws on functionality elicited by complex communication of numerous cell types. To date, many principles of individual cell behavior and inter-cellular circuitry have been identified. Yet, the high system complexity, together with tremendous volume of accumulated knowledge, challenge human capability of reasoning over immune data. Complicated inter-cellular relations and whole system effects are difficult to capture or understand. To address the deluge of knowledge and make it accessible for system-level reasoning, we built a Text Mining engine that assembles a machine formatted database of inter-cellular interactions, based on information automatically extracted from PubMed abstracts.

immuneXpresso (iX) identifies directional relations between numerous cell types and regulatory molecules (cytokines and chemokines) these cells employ for inter-cellular signaling in context of thousands of diseases. We do not simply look for cell and cytokine co-occurrences within the same paper abstract or sentence. Sophisticated analysis detects semantically related cells and cytokines to make the inter-cellular communication network as precise and relevant as possible. Interactions captured by iX include both direct cytokine binding/secretion events and more distant, indirect influencing relations, for example cytokines mediating cell differentiation or impacting its proliferation without necessarily binding directly. For each interaction its directionality is identified to indicate which entity is triggering the interaction and which one is the target. As an experimental feature, interaction polarity (called "sentiment" interchangeably), specifying its positive or negative effect (*e.g.* up-regulation or inhibition), as well as the cellular function involved are included, when possible. In addition to interactions, iX collects separate mentions of cells or cytokines in disease context.

iX captures multiple different synonyms and term writing variations for both cells, cytokines and diseases, followed by their normalization to a single representative label/id. For cells and diseases, official Cell Ontology and SNOMED CT are used to allow linkage to other resources.

The iX knowledgebase is heavily filtered, using manual curation and machine learning, to achieve high precision. Don't allow paucity of evidence (possible for rare interactions) or misinterpretation of individual sentences to let you down – the real power stems from standardization, structuring and breadth of the global network.

The literature-derived knowledgebase can serve wide range of uses, from exploring interacting counterparts, extracting disease-specific immune networks, to predicting previously



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unappreciated cell-cytokine interactions or cytokine-disease associations and assisting data interpretation.

Getting Started

To start working with immuneXpresso, specify your search query using the *Query* panel on left and click the *Search* button. The result will be presented on right (Figure 1). Search query is composed of cells and cytokines of interest, together with context information specified within the *Cell*, *Cytokine* and *Disease* sections respectively. You can either select terms of interest from the predefined dictionaries using the search box or upload a file with preselected names. If no search term is specified for some category, the results will not be limited for that category. For example, if a cell search term is specified but there is no cytokine name set, interactions between this particular cell and any cytokine will be presented.

Figure 1

The screenshot displays the immuneXpresso web interface. On the left is the 'Query' panel, and on the right is the 'Results' table.

Query Panel:

- Search Term (e.g. CD4, T cell)
- Filters: Cell, T cell, Cytokine, IL2
- Context Info: Disease (Rheumatoid arthritis), Interaction Type, Article

Results Table:

Cell	Interaction	Cytokine	E-score	Paper #	Articles (Function / % Total)
T cell	+	IL2	5.3	13	See Articles
T cell	→	IL2	4.52	10	Activation / 7.69% Proliferation / 7.69% Other / 84.62% All / 100%
T cell	←	IL2	1.58	9	Proliferation / 40% Activation / 20% Defect / 10% Other / 30% All / 100%
CD4-positive, alpha-beta T cell	+	IL2	3.63	2	See Articles
T cell	-	IL2	2.26	1	See Articles
CD4-positive, alpha-beta T cell	+	IL2	0.9	1	See Articles
helper T cell	+	IL2	8.59	1	See Articles

Within the *Interaction Type* section on left you may specify the required interaction directionality, indicating whether it is the cell or the cytokine that triggers the interaction, and polarity, expressing the nature of the interaction (i.e. positive, like up-regulation, negative, like inhibition, or neutral, like correlation). You can further refine your query by selecting the type and range of years of the publications in the *Article* section. For more details, see [Defining a query](#).



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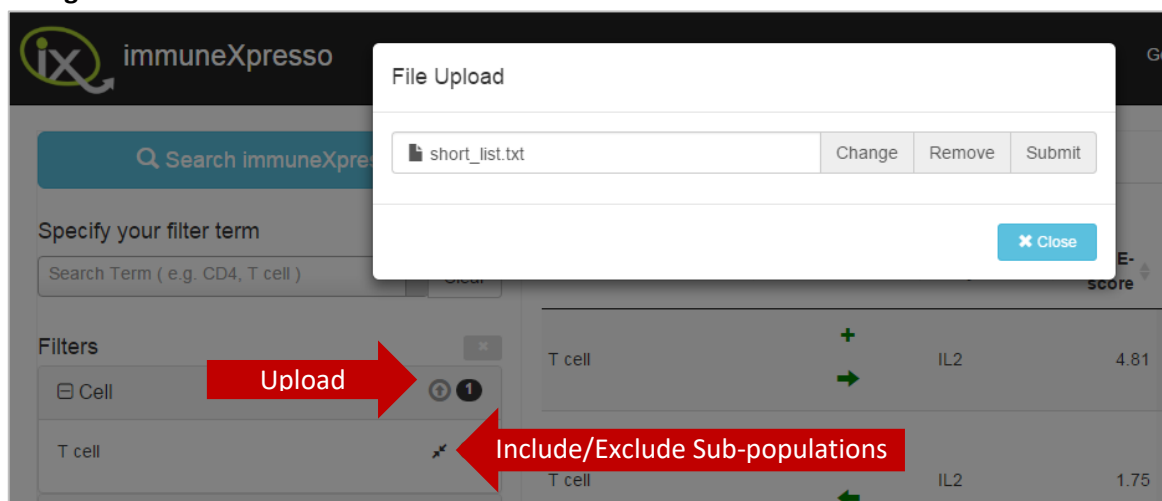
immuneXpresso output is composed of two tabs, as shown on right of Figure 1. The *Interactions* tab presents all the cited interactions between the requested cells and cytokines under the chosen context. For each interaction its direction, sentiment, confidence scores and, when available, cellular biological functions triggered by the particular cytokine are presented. The second, *Co-occurrence* tab presents all the occurrences of either the selected cells or the selected cytokines under the context of interest. Relevant article snippets are reached by following the *Articles* link for the particular suggested interaction or co-occurrence fact. When immuneXpresso captures biological functions for cell-cytokine interactions, a separate link is available for each function as well as the *All* link to see all articles snippets together. For more details, see [Results](#).

The rest of this tutorial describes each of the steps in more details.

Defining a query

1. Select the entities that play a role in the interactions or conditions in question. Either start typing the name of the cell, cytokine or disease of interest in the auto-completion enabled search box or upload a pre-selected list of terms as a .txt file, one term per line (Figure 2).

Figure 2



2. There is an option to exclude cell sub-populations and disease sub-groups from the presented results, by checking the *Include/Exclude* toggle button (Figure 2), e.g. only T-cell (per se) vs. T-cell and Th1, Th2, Th17 etc.

Note, any combination and number of terms is allowed, including multiple terms per category and specifying no term for some or even all entity types. In the latter case, all data available in the iX database is displayed.

3. Once search terms are specified, the query can further be refined by interaction characteristics. Select the directionality of interest in the *Interaction Type* section within the *Query* panel (Figure 1). Specify whether you are interested in interactions triggered by cells, cytokines or both (T-cell secreting IL-2 vs IL-6 activating B-cells). For interactions triggered by a cytokine, the required polarity (called "sentiment" interchangeably) can be specified:



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positive (e.g. activates), negative (e.g. decreases) or neutral (e.g. correlate). More than one option can be selected.

4. If needed, limit the range of publication years in the *Article* section within the Query panel. It is also possible to choose the publication type of interest, e.g. whether results should be limited to review papers only.

Results

The results are presented in two tabs as shown on Figure 1:

1. *Interactions* tab lists interactions between the requested cell types (and their sub-populations if required) and cytokines in the specified context, one row per each interaction. For each interaction its direction, sentiment, confidence scores and, when available, cellular biological functions are presented. *E-score* (enrichment score) is calculated as the ratio of the number of actually observed interaction occurrences to that expected by chance, given cell/cytokine frequencies in the corpus. This score reflects the interaction confidence for cells or cytokines rarely appearing within research papers. Additionally, *Paper #* shows the total number of articles mentioning the particular interaction. Clicking *See Articles* link will present the relevant article snippets, sorted by immuneXpresso confidence of their correctness (Figure 3). In case biological functions are captured, *Interactions* tab will provide a separate article snippets link for each function, as well as the *All* link for seeing all interaction articles together. Article snippet dialog allows switching between different functions by using the *Filter Articles by Function* drop-down menu.

Figure 3

The screenshot shows the immuneXpresso interface. At the top, there are buttons for 'Export' and 'Close'. Below that, the search criteria are 'T cell' and 'IL2', with a red arrow pointing to the word 'Interaction' between them. A dropdown menu labeled 'Filter Articles by Function' is set to 'Proliferation / 40%', with a red arrow pointing to it labeled 'Function Filter'. Below the search bar, it says 'Showing 1 to 4 of 4 entries' and 'Previous 1 Next'. The first article snippet is titled 'Cyclosporin A. Mode of action and effects on bone and joint tissues', with a red arrow pointing to the title and a label 'Click title to go to this article on PubMed'. Below it, there is a 'Leave a comment' button with a red arrow pointing to it.

2. *Co-occurrence* tab lists occurrences of either the chosen cells or cytokines in the requested context. The results are shown for each entity type, separately. The exact number of articles describing co-occurrence of the terms is also presented. *Articles* link can be used for presenting article snippets mentioning the particular cells/cytokines in the requested context.

immuneXpresso offers online feedback capabilities, both for general comments input (on the main application menu-bar) as well as feedback about recognition quality of each particular hit

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(on the Article snippet screen, Figure 3). Use these to point out any specific issues and share your thoughts with us.

Data download

All results can be exported as comma-separated (.csv) files for downstream analyses and network visualization, by clicking *Export* button on top. The resulting data depends on the screen from which Export is initiated:

1. From *Interactions* tab: all semantically-related cell-cytokine pairs matching the specified query, together with their interaction directionality (Actor column, indicating the entity triggering the interaction), polarity and confidence information. Note, official Cell Ontology ID and Label are provided for each cell. The exported .csv file can be used for network visualization (e.g., by importing into the [Cytoscape](#) platform). Cells and cytokines might be shown as nodes, with edges representing the cell-cytokine pairs detected by iX. Interaction polarity and confidence might be represented by edge coloring and width.
2. From *Co-occurrence* tab: all cells or cytokines matching the specified query, together with their confidence information. For cells, official Cell Ontology ID and Label are provided.
3. From *Articles* dialog: article snippets currently presented in the dialog.