

**DATABASE**

# CYTOCON: The manually curated database of human in vivo cell and molecule concentrations

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**Abstract**

Cell and cYTOKine CONcentrations DataBase (CYTOCON DB) is a project undertaken by the InSysBio team and aimed at the development of a database that allows collecting, processing, and visualizing publicly available in vivo human data on baseline concentrations of cells, cytokines, chemokines, and other molecules. Besides manual curation, an important feature of CYTOCON is that most values found in papers are converted from a huge variety of original units (i.e., mg/ml and number of cells per mm<sup>2</sup> of biopsy surface section) to unified units: “pM” for cytokine and “kcell/L” for cell concentration. These features of the database can help researchers facilitate the creation and calibration of quantitative systems pharmacology (QSP) models. Possible applications can be: estimation of the average value or variability of the cell, cytokine or chemokine concentrations for patient groups with different characteristics, such as age, gender, disease severity, disease subtype, etc.; and analysis of correlations among the cell, cytokine, or chemokine concentrations in patients with different characteristics, such as severity of the disease.

**INTRODUCTION**

Currently, the volume of data generated during scientific research is growing exponentially. To collect these data, make it suitable for analysis, and provide appropriate tools for data comparison and visualization, various databases with online access are being developed. Each of the databases has specific features defined by the type of collected data. Indeed, the RCSB Protein Data Bank (PDB)<sup>1</sup> collects info on protein structure and allows us to visualize it,

STRING<sup>2</sup> is a database of known and predicted protein–protein interactions, etc. However, in Quantitative Systems Pharmacology (QSP) modeling, in addition to data on structure, expression level, and distribution of proteins, we also need other types of data.

QSP modeling is a tool that addresses questions arising in the drug development framework in a mechanistic manner.<sup>3–5</sup> To build, calibrate, and validate such types of models, different types of data are utilized.<sup>6–8</sup> For example, to calibrate QSP models of diseases associated with

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immune response, data on baseline concentrations of immune cells and cytokines located in different tissues is required.<sup>9</sup> Unfortunately, few databases provide information about in vivo concentrations of human cells, cytokines, chemokines, and other molecules.<sup>10</sup> One of the reasons is that data available in publications is reported in ways that make it hard to analyze and compare the data across different publications (i.e., the data is not complete, or is expressed in different units or relative units which cannot be easily converted to absolute values applicable for QSP model calibration). All these difficulties force research groups to waste a lot of precious time searching for such data and adapting it to a particular project. Plus, the error rate during data extraction is inevitably high when there is no double control. To overcome the difficulties, we have developed a manually curated online database CYTOCON DB. The most important feature of CYTOCON DB is that the concentrations are converted from a huge variety of original units (i.e., mg/ml and number of cells per mm<sup>2</sup> of biopsy surface section) to unified units: “pM” for cytokine and “kcell/L” for cell concentration. A huge amount of information about patient groups, disease status, and experimental methods is preserved during data extraction and linked to particular concentrations. All these features of CYTOCON DB aim to facilitate access to human baseline in vivo data for scientists so that they can focus more on scientific problems.

## CONSTRUCTION AND CONTENT

### Types of collected data and CYTOCON DB roles

The database was created exclusively to collect and process human in vivo baseline concentrations of cells, cytokines, chemokines, and other active molecules measured in different tissues of the body without specific treatment. We focused on gathering data about various conditions, including autoimmune diseases, different types of cancer, coronavirus disease 2019 (COVID-19), etc. Data manipulation is performed by scientists with advanced degrees (e.g., MSc, MD, PharmD, and PhD) and expertise in biological, medical, and/or pharmaceutical sciences. There are two different roles for the scientists involved in the extraction of data from publicly available sources, annotation process, and data accuracy checks: annotator and reviewer. The annotator reads the paper, and extracts and annotates the data. The reviewer checks the accuracy of data extraction, implements automatic formulas for the conversion from original units to unified units, and manages the process of annotation.

## Structure of CYTOCON DB

In an attempt to structuralize information from articles and avoid mistakes during the annotation process, we included several predefined and continuously updated tables with the values used by annotators during the annotation process. The tables are created and can be updated only by the reviewers. We describe these tables below:

- Sample data
  - *Tissue type*. This table contains information about tissue types: tissue name (blood, epidermis, etc.) and corresponding percentage of interstitial volume from total tissue volume.
- Measurement data
  - *Average types*. This table contains different types of average: mean, median, etc.
  - *Dispersion types*. This table contains different types of dispersion: SD, SEM, interquartile range (IQR), etc.
  - *Experimental method*. This table contains different types of measurement methods: enzyme-linked immunosorbent assay (ELISA), microparticle immunoassay, flow cytometric analysis, etc.
  - *Extraction method*. This table contains three values: (1) taken - data copied and pasted from the article directly; (2) digitized - data digitized from pictures; and (3) calculated - operation-like averaging is performed on the data.
  - *Units*. This table contains information about original unit names (nM, mg/ml, cells/L, etc.) and formulas for converting the original units to pM or kcells/L, if such information exists.
- Disease
  - *Disease name*. This table contains information about disease names: asthma, breast cancer, COVID, etc.
  - *Disease alias*. This table contains information about disease aliases: nocturnal asthma linked to asthma, allergic asthma linked to asthma, etc. Each alias is linked to one disease from the disease name table. Alias is indicated in the result of a query on the primary disease, and vice versa.
  - *Disease attribute*. This table contains information about disease attributes: severity, SCORAD, cancer stage (I-IV), fibrosis stage, etc.
  - *Bind disease attribute to disease*. This table contains information about links between disease attributes and particular diseases: atopic dermatitis - SCORAD, BSA, etc. Non-small cell lung cancer (NSCLC) - N stage of cancer (TNM), M stage of cancer (TNM), etc.
- Species data
  - *Species type*. This table contains two values: cells and molecules.

- *Species name*. This table contains information about species names: granulocyte colony-stimulating factor (GCSF), interleukin-1 receptor antagonist (IL1RA), mature dendritic cells, etc.
- *Species alias*. This table contains information about species aliases: Eotaxin-1 is linked to CCL11 (C-C motif chemokine ligand 11), macrophage inflammatory protein 1 beta (MIP-1b) is linked to C-C motif chemokine ligand 4 (CCL4), etc.  
Each alias is linked to one species from the species name table. Alias is indicated in the result of a query on the primary species, and vice versa.
- *Species attribute*. This table contains two values: molecular weight of different molecules for concentration conversion; cell markers - CD8+, CD4+, CCR4– (CD194–), etc.
- Patient data
  - *Patient attribute*. This table contains information about patient attributes: patient group average age, patient number, patient # men, patient # women, etc.

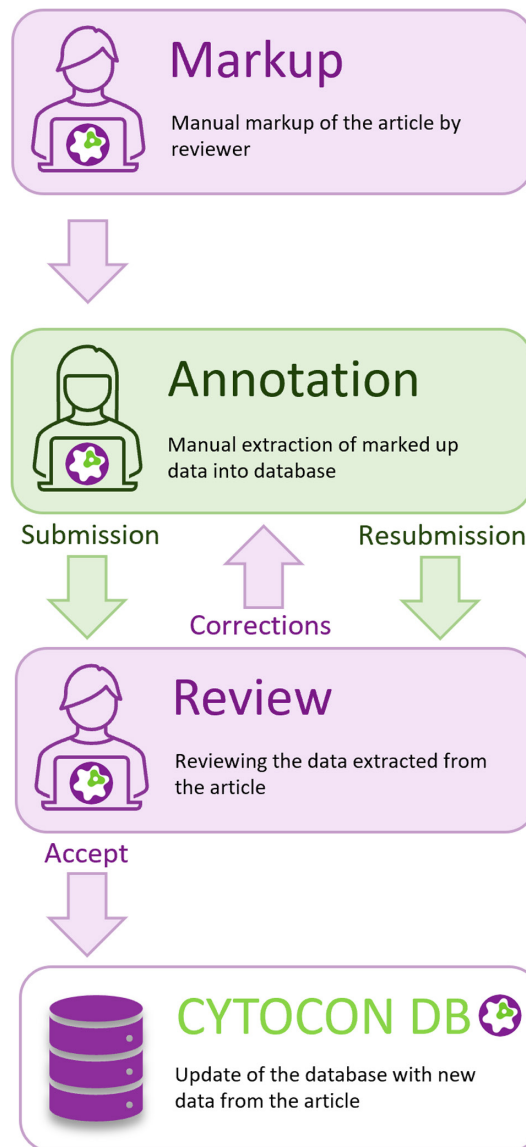
## Workflow

CYTOCON is a manually curated database. An overview of the data collection process is given in [Figure 1](#).

There are three roles in our workflow: reviewer, annotator, and user. Annotator and reviewer roles are nested, meaning that the annotator has access only to annotation options. The reviewer has full access to the database. Users only can work with the query interface.

Annotators cannot create names of objects (cell type, tissue, diseases, etc.) and units. They can only select specific values from a table, thus avoiding duplication and other types of mistakes. The exceptions are the fields with “text” data types, like comments or inclusion/exclusion criteria, etc. If the annotator faces a new unit or cell type, for instance, he/she must ask the reviewer to create a new cell type, unit, etc.

According to the workflow, the reviewer chooses an article, decides which information should be extracted, and creates a markup for the annotator. The annotator extracts data from the article and enters the data in the appropriate form into the database. From this point on, all data manipulations occur in the database. The annotator sends the results of his/her work using the CYTOCON interface to the reviewer. Each form filled by the annotator undergoes thorough revision performed by a professional reviewer. The reviewer checks whether all forms are filled correctly and nothing is missing. If there are errors, the reviewer uses a special comment field, where he/she can leave comments about what



**FIGURE 1** Flowchart of the database construction and validation processes. The annotation workflow was designed in such a way as to provide a satisfactory level of quality control. A group of annotators transfers information from papers to the database, and a group of reviewers verifies the accuracy and completeness of the data. Each member of the CYTOCON team has a degree in biology or medicine.

should be improved in the form, and sends the article back to the annotator. When information is extracted correctly, the reviewer approves the article and new data become available for users. The data for the database are collected only from the published articles that undergo peer review.

Below we describe what we extract from an article step-by-step.

*General article information:* We automatically extract data from the PubMed database for most of the articles, including title, authors, journal, publication date, etc. In

case only the DOI is available, the annotator manually fills all rows.

*Patient groups:* At this step, the annotator creates patient groups and assigns disease types from the disease table.

*Patient group disease attribute:* For each patient group, the annotator extracts information on the disease state (if available), such as duration, severity and specific scores (SCORAD, SLEDAI, FEV1, TNM stages, etc.).

*Patient group attribute:* The annotator retrieves information about the patient characteristics: number, gender, age, body mass index, height, smoking status, treatment status, etc. At this stage, inclusion and exclusion criteria are extracted as well. We preserve most of the relevant information about the patients.

*Patient group species:* The annotator extracts information about concentrations. He/she chooses species type (cell or molecule), species name, average type (mean, median, etc.), dispersion type (SD, IQR, etc.), extraction method (taken or digitized), experimental method (ELISA, immunohistochemistry, etc.), tissue type (blood, tumor, lymph node, etc.), unit (pg/ml, cells/L, %, etc.), link value (a reference to text, table, or figure from the article), then the annotator fills dispersion, average value, and range fields (minimum and maximum value), if relevant.

*Cell markers:* For cells, it is quite important to understand which markers researchers used to define phenotype. The annotator assigns markers to a cell concentration record from a predefined table (CD3+, CD4+, CD8+, IL2+, HLA-DR-, etc.).

## Key features

### Special units

A major part of the published data on cell concentrations is represented as a percentage calculated for the absolute value of some parental cell populations. For example, the count of [PD1+, CD8+, CD3+] cells is typically measured as the percentage of [CD8+, CD3+] cells. Because we want to provide potential users with absolute cell counts, we have implemented an algorithm allowing recalculation of the percentage values to absolute cell concentrations. There are two different cases of such percentage representation, depending on the availability of absolute cell count measured in the parental cell population. If the value is available in a publication, the annotator creates a unit that considers the unique value of the parental cell subset in a particular patient group. If the absolute cell count of a parental cell population is not available, the annotator chooses a unit that is calculated as an average across all appropriate database entries (different publications) with the same disease, tissue, and cell markers ([CD8+, CD3+] cells in our example

above). When the content of the database is updated, the average values for the parental subset are recalculated.

### Units' unification

One of the advantages of CYTOCON DB is the unification of measurement units: “pM” for cytokine and “kcell/L” for cell concentration. For instance, mg/ml for IL-6 will be converted to pM and the number of cells per mm<sup>2</sup> of the biopsy surface section to “kcell/L” for a particular tissue. For some tissues, concentration is available not only for the total tissue volume, but for interstitial volume as well (without cell and structural volumes of the tissue). Information about data conversion is available in the supplementary part of CYTOCON DB.

### Database strengths

- 280 disease types
- 183 tissues/physiological fluids
- 452 molecules (cytokines, chemokines, growth factors, and other molecules, such as PGE2, LTE4, etc.)
- 156 cell types and states
- 34,967 values of cytokine/cell concentrations
- Data extracted from 991 papers/other public sources

CYTOCON DB<sup>11</sup> is updated once a year, with ~20,000 new concentrations added each time. Software updates for the database are released continuously.

### Platform

CYTOCON DB is developed as a web application based on the ASP.NET MVC framework, Microsoft IIS web server, Microsoft SQL Server database, Telerik Kendo UI, and Bootstrap.

### Availability and conditions of use

To access CYTOCON DB Open, please visit <https://cytocon-open.insysbio.com/>

### Copyright status of webpages

Information that is available at this site is within the public domain. Public domain information on CYTOCON DB Open web pages may be freely distributed, copied, and used for both commercial and non-commercial purposes.

However, it is requested that in any subsequent use of this work, CYTOCON DB Open be given appropriate acknowledgment.

## Accessibility policy

InSysBio is making every effort to ensure that the information available on CYTOCON DB Open Web site is accessible to all.

## Privacy policy

InSysBio provides this website as a public service. We do not collect any personally identifiable information about visitors to our websites. We do collect some data about user visits to help us better understand how the public uses the site and how to make it more helpful.

## UTILITY

### General description of QUERY interface

Interaction with CYTOCON DB is quite simple from a user perspective. The query page (Figure 2) includes several options which can be used separately or in combination:

- Species type: cell or molecule
- Species: monocytes, IL-2, etc.
- Tissue type: blood, epidermis, tumor, etc.
- Disease: healthy control, atopic dermatitis, melanoma, etc.
- Patient group attributes: gender, age, treatment, inclusion criteria, etc.
- Cell markers [for cells only]: CD4+, CD2+, HLA-DR-, etc.
- Average type: mean, median, geometric mean, etc.
- Dispersion type: SD, SEM, IQR, etc.
- Experimental method: ELISA, immunohistochemistry, flow cytometry, etc.

Query results can be downloaded in CSV format or accessed directly at the web interface of CYTOCON DB (Figure 2).

### Application of CYTOCON DB in QSP modeling

CYTOCON DB can be used at several stages of QSP modeling.

## Development of a QSP model

At this stage, researchers analyze scientific articles, posters, or reviews to obtain a general understanding of disease pathophysiology and understand which structural components of a potential QSP model (cells, bioactive molecules, compartments, processes, and pathways) are necessary to include in a new QSP model. One of the tools that can help at this stage is CYTOCON DB. You can search for groups of cells, cytokines, and other important molecules located in the tissues that differ between healthy subjects and patients suffering from specific diseases. It can give you insights into disease pathways. Even more, the comparison of the baseline values available in the literature (collected and unified in CYTOCON DB) allows us to make a decision on which species can be implemented in a QSP model as variables or fixed values. For example, Figure 3 represents aggregated data on cell concentrations in patients suffering from melanoma (11 papers – Table S2), NSCLC (34 papers – Table S3), and in healthy persons (140 papers – Table S1). To compose Figure 3 (Table S4) we have used CYTOCON DB to search for both relative and absolute cell concentrations measured for the corresponding patients. We downloaded results in the form of a CSV file, converted it to an Excel spreadsheet (see Appendix S3 for more detailed description). Then filters out all concentrations that cannot be transformed in kcells/L. After we averaged corresponding concentrations measured in the same tissue and for the same patient type and plot the result as a graph. Interestingly, there are four papers for melanoma and three papers for NSCLC that include absolute values of different cells measured in tumor tissue and lymph nodes. This is 36% for melanoma and 9% for NSCLC of the number of papers retrieved from CYTOCON in accordance with the search criteria described above.

A comparison of cell concentrations presented at Figure 3 leads to several conclusions. The amounts of natural killers, B cells, T helpers, cytotoxic T cells, and Tregs is lower in melanoma tumors than in NSCLC. The same conclusion is true for T helper and Tc cells in lymph nodes but number of Tregs demonstrates the opposite trend. Cell counts measured in blood of different patients are very close to each other independently on the diseases considered in the example except white blood cell and neutrophils which are higher for patients with melanoma.

## Calibration of QSP models

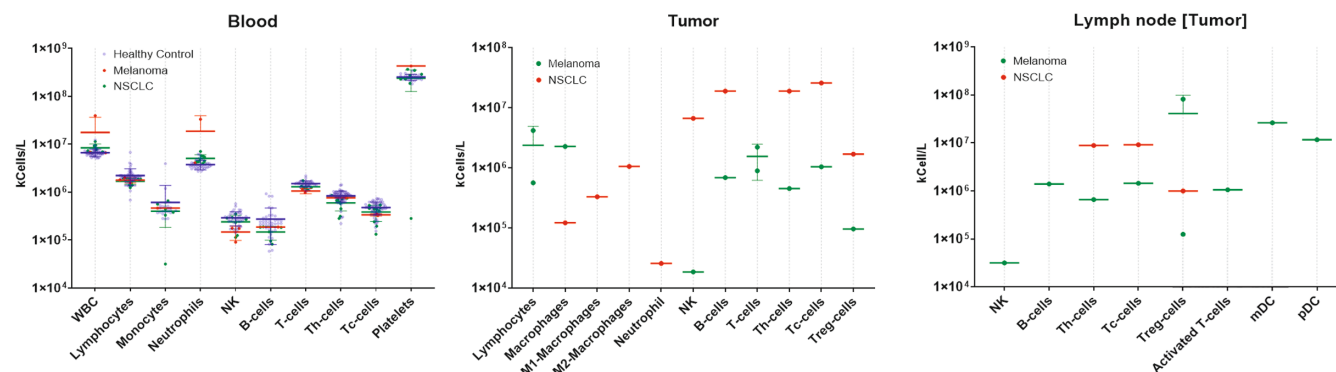
After developing a QSP model, the next step is to calibrate it, meaning to identify parameter values based on available experimental data.<sup>12,13</sup> A typical calibration



**FIGURE 2** Query and output interfaces. Screenshot of the “Query” interface demonstrating a search for concentrations of CD3+ cells in the airway smooth muscles layer. The query page includes several options, which can be used separately or in combination. The major ones are species type, species, tissue type, and disease. Query results are represented as a table and corresponding graph. Results can be exported in CSV format for further analysis.

workflow consists of several consecutive steps, including calibration against in vitro data,<sup>13</sup> baseline in vivo data,<sup>7,9,14</sup> and clinical data describing the response of a patient subpopulation to a particular treatment.<sup>7,9,12,15</sup>

To proceed with calibration against baseline in vivo data, you need to collect baseline values of cells and cytokines from the literature and implement them into the QSP model in terms of units introduced in your



**FIGURE 3** Comparison of cells in different tissues of healthy subjects and patients suffering from melanoma or NSCLC. Data aggregated from various sources on the concentration of cells in blood, lymph node, and tumors from healthy persons or patients suffering from melanoma or NSCLC is represented in CYTOCON DB. Data is shown as Mean  $\pm$  SD. mDC, mature dendritic cells; pDC, plasmacytoid dendritic cells; NK, natural killers; Tc, cytotoxic T-cells; Th-cells, T helpers; Treg, regulatory T-cells; WBC, white blood cells.

model. You need to retrieve hundreds or, in some cases, thousands of values published in dozens or hundreds of scientific papers, understand original units of the data found in the papers, and transform all these units (and corresponding values) into a unified form implemented in your model. The application of CYTOCON DB can facilitate this process. CYTOCON DB was extensively used by our team during the development of QSP models for asthma,<sup>16</sup> atopic dermatitis, chronic obstructive pulmonary disease (COPD),<sup>17</sup> and systemic lupus erythematosus (SLE).<sup>18</sup> In addition, baseline values of cell concentrations in different tissues are often used to calibrate physiologically-based pharmacokinetic/receptor occupancy (PBPK/RO) models, especially when they are focused on describing the pharmacokinetics of monoclonal antibodies and the occupancy of receptors located on the surface of different cells (surface molecules) for mAbs. We have successfully applied CYTOCON DB to inform PBPK/RO models describing CD40/PD1 bispecific mAb,<sup>19</sup> various anti-TIGIT,<sup>20</sup> and anti-PD-L1 mAbs.<sup>21</sup>

### Creation of virtual patient population

Development and calibration of a model with unique parametrization corresponding to an average reference patient is only one part of a typical QSP project. To explore the variability of responses to treatment, a population of virtual patients (VPpop), reliably reproducing both mean/median and dispersion (SD, SEM, and/or other statistics) of clinically measured data, is required. Creation of such reliable VPpop reproducing clinically measured data includes several steps: (I) generation of initial VPpop, (II) filtration of initial VPpop to form plausible VPpop, and (III) filtration of plausible VPpop to form final VPpop

describing clinically measured responses to therapies. To form plausible VPpop, a set of biomarkers implemented in the model as variables should be selected, and physiologically plausible ranges of their values should be identified based on available experimental data. In order to form plausible VPpop, we should filter out all virtual patients (VPs) of initial VPpop which do not match the ranges of the selected biomarkers. These biomarkers typically represent concentrations of cytokines, chemokines, and cells (cell states) measured in different tissues. Application of CYTOCON DB allows us to easily identify the ranges of the biomarkers.

## DISCUSSION

Standardization of data published in articles on biology and medicine is a complex problem that remains poorly explored. Indeed, data can be acquired by using different methods for completely different patient groups even with the same disease. It is also complicated by the fact that data are often represented exclusively as graphs (pictures) and needs to be digitized. Various text recognition approaches have been used to create automatic annotation for databases with some biological data. It works well for proteins and genetic data with some level of accuracy but, unfortunately, there are no databases that provide information about in vivo concentrations of human cells, cytokines, chemokines, and other molecules in conventional ways with automatic annotation, due to the reasons mentioned above (see more details in Appendix S4). We decided to create a manually curated database with several levels of error protection. CYTOCON DB accumulates values of cell and cytokine concentrations experimentally measured in different tissues of healthy subjects and patients suffering

from different diseases. Each value extracted from the literature is accompanied by a proper description of a patient population and disease provided in a particular scientific paper. CYTOCON DB is an online database, meaning that online access was implemented for users, who can search for particular baseline values of cells and cytokines, and for annotators and reviewers, who create content of the database by extracting data from publicly available scientific literature. This database aims to help researchers create QSP models. It has already been utilized in multiple projects focused on the development of QSP and PBPK/RO models of asthma, COPD, atopic dermatitis, SLE, various solid tumors, and hematological malignancies, and it was extremely helpful during model development. We are going to further develop CYTOCON DB, implement new features (see Appendix S4 for more details) and populate the database with new information extracted from the public domain.

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## CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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