COmplex PAthway SImulator: A Tool for Modeling Complex Immunological Systems

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Introduction: New discoveries in immunology have triggered the production and development of novel, efficient and cost-effective tools to analyze complex immunological networks and target experimental approaches. The goal of the Center for Modeling Immunity for Enteric Pathogens (MIEP) is to support powerful software that can drive classical immunology in a targeted fashion by developing computational and mathematical intracellular pathways models controlling cellular differentiation, such as CD4+ T cell and macrophage differentiation, as well as models mimicking the immune cell distribution upon infection with *Helicobacter pylori* or *Enteroaggregative E. coli*. The **Complex Pathway Simulator, COPASI**, [1] is a platform-independent, user-friendly software tool that allows easy access to powerful numerical methods for simulation and analysis of biochemical reaction networks and complex systems. The combination of COPASI and experimental data and immunological knowledge and novel discoveries allow multitask analysis and calculation of steady-states, time-courses and parameter estimations, among other functions.

COPASI is freely available and can be obtained from www.copasi.org . The website also contains discussion, tutorials and support from the users and developers. It runs on all major operating systems (Linux, Mac OSX, Windows). Two versions are provided: one with an easy to use graphical user interface that allows editing the model, running calculations, and viewing the results (see screenshots). The other version is a command line tool that can be used for batch processing or for interfacing with other software tools. A new version of COPASI 4.7 (Build 34) was released just before the Cellular Systems Biology conference. The following sections will highlight some new features and improvements of this and the preceding releases.

Events: COPASI has full support for modeling discrete changes to the model state that are triggered by arbitrary conditions ("Events"). This is useful for phenomenological modeling of events like cell division, for flexible modeling of experimental setups, or for model analysis and *in silico* experimentation.

User interface improvements: To improve the handling of large models the tables of reactions, species and other model elements can now be sorted by different criteria. It is also possible to apply filters to find elements in a large model more easily.

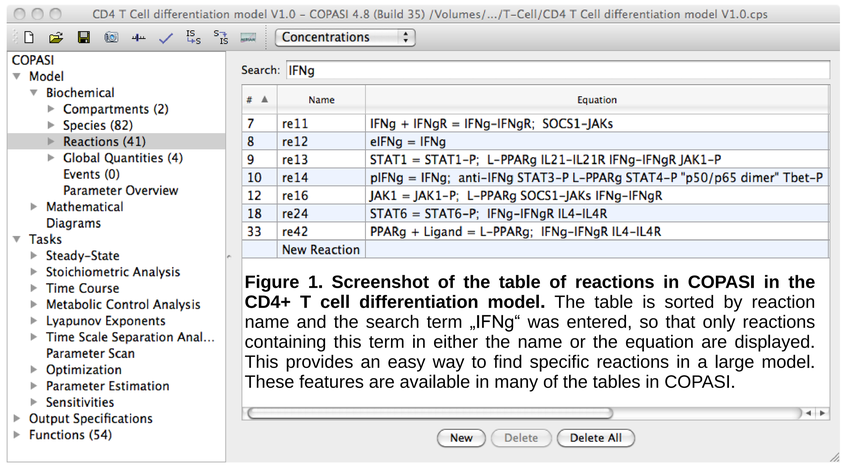

Figure 1. Screenshot of the table of reactions in COPASI in the CD4+ T cell differentiation model. The table is sorted by reaction name and the search term „IFNg" was entered, so that only reactions containing this term in either the name or the equation are displayed. This provides an easy way to find specific reactions in a large model. These features are available in many of the tables in COPASI.

Annotation improvements: Text notes in XHTML format can now be added to each model element and stored both in COPASI and SBML files. Links to web resources in the notes are now also supported. Elementary modes New algorithms were included for the more efficient calculation of elementary modes for large models. For some large models, the computation time decreases by several orders of magnitude compared with older versions. Also the display of elementary modes is much improved.

SBML [2] support: COPASI imports the preliminary SBML level3 rc format. (In addition to import and export of different versions SBML level1 and level2).

Sensitivity analysis: COPASI also allows the calculation of sensitivities of the model with respect to various parameters. Generally a sensitivity is a measure for how much a specific "observable" (this means any number that can be obtained by numerical analysis of the model) changes when a given parameter is modified. Moreover, COPASI allow the user to run **Metabolic Control Analysis (MCA)**, which quantifies how variables such as fluxes and species concentrations depend on network parameters, thus giving an opportunity to the user to detect which are the concentrations of different species for some reactions to occur and consequently, obtain a specific output in the model.

These two tools allow immunologists to detect key pathways and fluxes that can be easily modulated and, at the same time, detect those one that are solid a non-influenced by other parameters. Also, In the case of the CD4+ T cell differentiation model we could detect reactions that were causing instability to the model and thus, give robustness to those areas of the model that needed it.

Stochastic simulation: Due to a collaboration with Ao-ping Hou and Yang Cao (Virginia Tech) COPASI features a number of new stochastic simulation algorithms. In addition to the exact stochastic integration that COPASI always supported it now allows much faster simulation with the approximate **Tau-Leap** method. We have also implemented an innovative method **(Adaptive SSA/Tau-Leap)** that partitions the system dynamically in parts that are simulated with Tau-Leap or the direct method, respectively. This new algorithms combines the accuracy of the direct method with speed advance from the Tau-Leap method.

Time course and concentration analysis: After stimulation of the system, the concentrations of internal species can change in time. COPASI allow the user to check specific concentrations in a user-friendly way and detect unexpected behaviors (Figure 2A). The Scanning task is another feature of COPASI that allow the user to check the trend of a specie when concentrations of specific molecules are increased gradually in the system (Figure 2B). Time-course studies and gradients in concentrations can be used together to check if concentrations are also increased in time as other concentrations in the system are increased (Fgiure 2C).

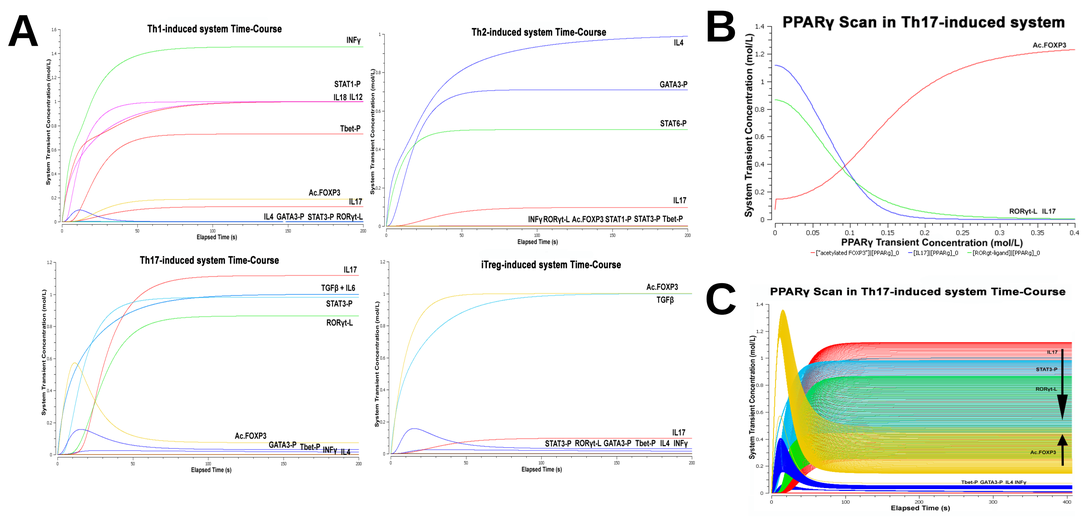

Figure 2. Output specifications for Time-courses, Scans and combined tasks using the CD4+ T cell differentiation model. Time-course in silico studies were run to check different stimulations on CD4+ T cell differentiation, mimicking the four phenotypes: Th1, Th2, Th17 and iTreg (A). The scan task was performed to check the behavior of IL-17, FOXP3, RORγt and STAT-3 upon activation of PPARγ in CD4+ T cells (B). This trend was also checked in time using combined tasks (C).

Parameter estimation task: Parameter estimation is the process of calculating model parameters based on experimental data. These data can be the result of time course or steady-state experiments or both and its nature varies from flow cytometry data, gene expression, or proteomics analysis, among others. COPASI reads a the dataset, which may be comprised of several files each including possibly multiple experiments. After the load of the dataset COPASI fits one or more parameters that are specified by the user to that dataset.

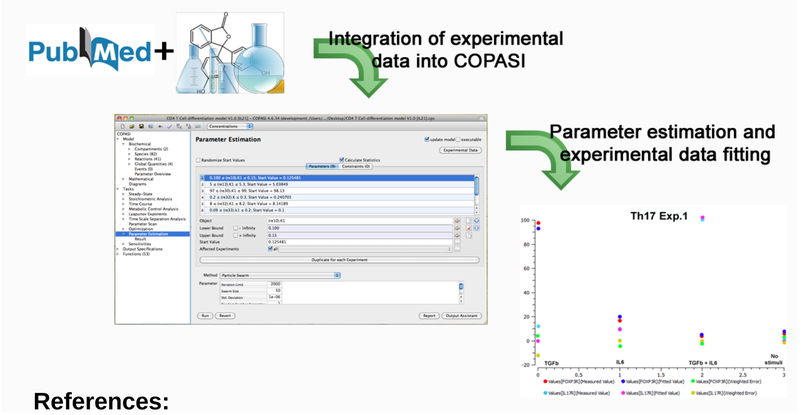

Figure 3. Flow chart showing Parameter Estimation process fluxes. Data can be obtained from literature or from own experimental designs and be easily inserted in the model to run parameter fitting.

References:

1)Hoops, S. et al. (2006), COPASI – a Complex Pathway Simulator, Bioinformatics 22, 3067 – 3074

2)Hucka, M. et al. (2003) The Systems Biology Markup Language (SBML): A Medium for Representation and Exchange of Biochemical Network Models, Bioinformatics 19(4), 524-531

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