

## A tutorial of hipathia, a mechanistic model of pathway activity

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Conventional gene-based approaches ignore the modular nature of most human traits, while pathway enrichment methods produce only illustrative results of limited practical utility. Recently, new methods have emerged that change the focus from the whole pathways to the definition of elementary sub-pathways or circuits within them that have any mechanistic significance. In some cases, this involves the recodification of Process Description pathways into Influence Maps that describe how proteins interact among them to trigger or carry out cell functionalities. The activity of such circuits defined within Influence Map pathways is expected to be better descriptor of cell functional activity than whole pathways of single genes.

Here we present a tutorial on the HiPathia MPA method (1), implemented in a R/Bioconductor package (<http://bioconductor.org/packages/devel/bioc/html/hipathia.html>) as well as in an interactive web application (<http://hipathia.babelomics.org/>). This tutorial demonstrates how to transform decontextualized gene expression measurements into highly-informative cell activity quantitative values how and relate them to phenotypes. Different analyses can be carried out using circuit activities that include differential activity analysis when two conditions are compared or relation of circuit activities to a continuous variable. Since circuits modeled have a functional meaning (any of them trigger one or more cell functions, defined by Gene Ontology terms), the results provide direct clues to understand disease mechanisms or drug modes of action. It is also possible to build predictors directly based on circuit activities, which adds an interesting mechanistic dimension to the prediction process.

In addition to be used to uncover the molecular basis of phenotypes, mechanistic models can also be used to predict what would be the potential effect of one or several interventions (KOs, inhibitions, over-expressions, drugs, etc.) over the system studied. Thus, the PathAct (2) web application (<http://pathact.babelomics.org/>) allows predicting from a holistic perspective what would be the effects of interventions over a specific system.

The HiPathia suite provides a friendly environment to use Influence Map pathways as templates of cell functionality to provide a mechanistic interpretation of transcriptomics data.

1. M. R. Hidalgo et al., High throughput estimation of functional cell activities reveals disease mechanisms and predicts relevant clinical outcomes. *Oncotarget* 8, 5160 (Dec 22, 2017).
2. F. Salavert et al., Actionable pathways: interactive discovery of therapeutic targets using signaling pathway models. *Nucleic Acids Res* 44, W212 (Jul 08, 2016).