**Actionable pathways**
Interactive discovery of therapeutic targets using signalling pathway models

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**Introduction**

Actionable pathways enables the study of the consequences that Knockouts (KOs) or over-expressions of genes can have over signalling pathways. Implements robust models of signalling pathways within an advanced graphical interface that provide a unique interactive working environment in which actionable genes, that could become potential drug targets, can be easily assayed alone or in combinations.

**Load gene expression data**
The measurements of gene expression in a given condition (diseased tissue biopsy, cell line, etc.) is used as reference, then the signaling activity of all the signaling circuits represented in the pathways. It calculates the activity status of all the signaling circuits in which the KEGG pathways analyzed can be decomposed.

Here, we focus on effector proteins, at the end of the pathways, which are the ultimate responsible for the cellular response to stimulus by triggering specific cell functionalities.

Therefore, a signaling circuit is defined here as the sequence of proteins that connect an effector protein back to all the possible receptor proteins from which the signal transmission is initiated upon stimulus reception.

**Select genes to Knockout**
Genes can be selected in two ways, first on is by selecting it manually so the value of the intervention can be defined. Thus, a KO can be simulated by setting a gene contribution to 0 (or to a low value). Conversely, an over-expression of an inactive gene can be simulated by setting its contribution value to 1 (or to a high value).

**Drug effect**
The second way is by the effect of drugs with known targets (as described in DrugBank) over the different signaling pathways can be studied. The added drugs will provide new gene targets that will be used in the signaling calculations.

**View the affected circuits**
Once all the desired interventions have been made, it recalculates the predicted signaling status of the resulting simulated condition. Then, the simulated condition is compared to the reference condition and circuits are colored according to the activity status changes (red edges indicates a significant increase in the signaling status and blue edges a significant decrease).

The genes selected manually are colored in red and the genes affected by drugs are colored in green. The rectangles in the circuits represents the cell functionalities, i.e. Apoptosis.

**Add genes**
The selected genes appear in the Add genes panel where the value of the intervention can be defined.

**Select gene related drugs**
Additionally, any time a gene is selected the Select gene related drug list panel displays all the drugs known to target such gene.

**Add drugs**
The Add drugs search box allows selecting drugs for simulating the effect.

**Conclusions**
PathAct provides a summary of the effect that interventions on one or several genes have over all the signaling circuits in all the modeled pathways. Also it saves a lot of time and resources in trial-and-error experiments by allowing highly focused testing of hypothesis of intervention over a reduced number of signaling circuits. In this way this tool will decisively contribute to the acceleration of the discovery of new drug targets and can facilitate application of targeted therapies in personalized treatments.