SORS: Synthetic lethality in cancer research via genetic Minimal Cut Sets

Objectives

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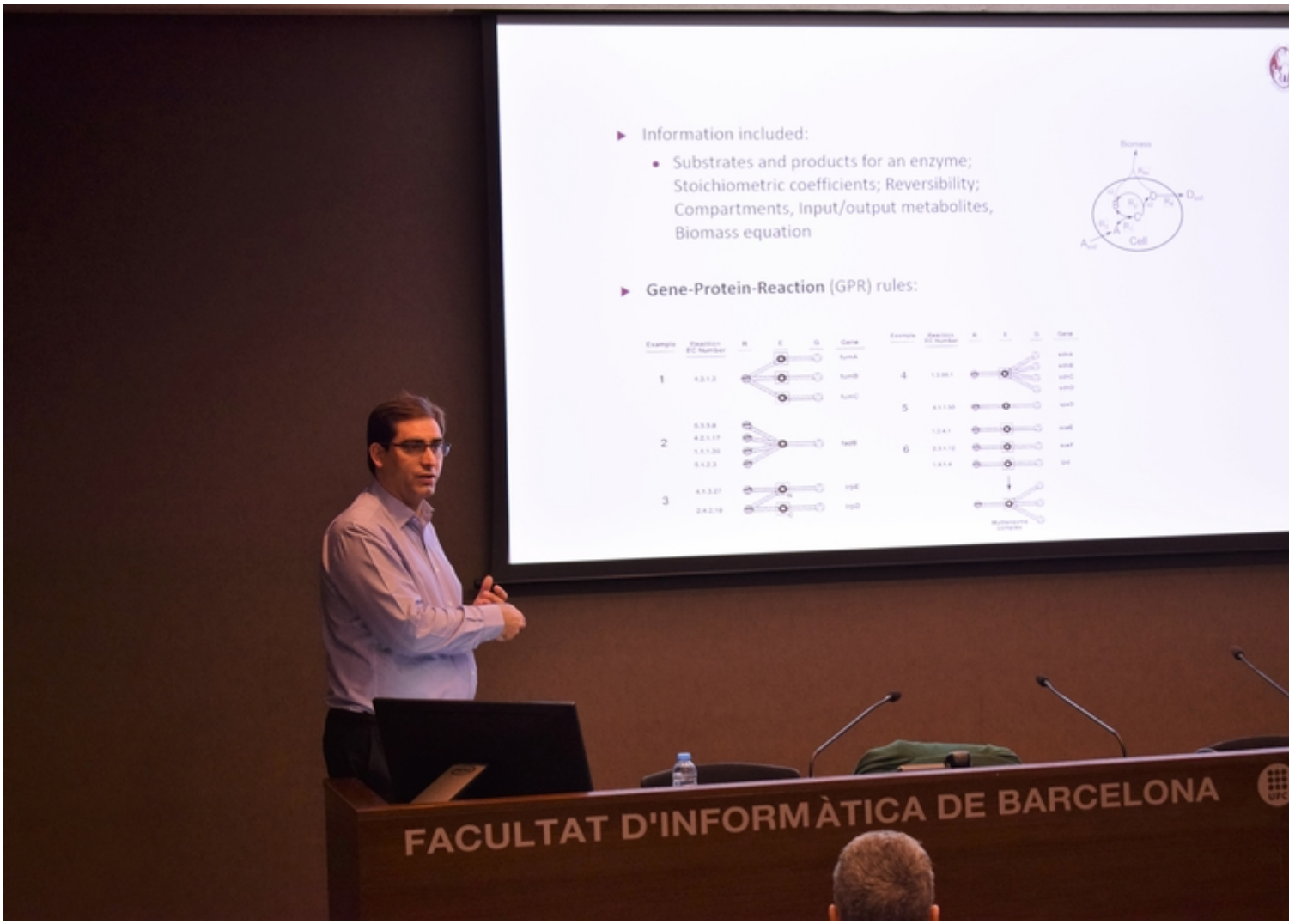
Abstract: Synthetic lethality is a promising approach in precision medicine and cancer as it largely expands the number of possible drug targets and creates an opportunity for selectivity. The increasing evidence of metabolic reprogramming of cancer cells makes it ideal to exploit the concept of synthetic lethality. A number of in-silico tools have been developed to target cancer metabolism using a synthetic lethality approach. In particular, constraint-based modeling (CBM) for genome-scale metabolic networks has received much attention. Here, we present a novel CBM approach to synthetic lethality that is based on the concept of genetic Minimal Cut Sets (gMCSs). With respect to existing methods, our approach avoids the step of network contextualization and integrates –omics data in a more natural and objective manner. In addition, it enables not only the detection metabolic targets but also response biomarkers for them. To illustrate our approach, we first show the results of an experimental proof-of-concept in multiple myeloma (MM), where we validated the therapeutic potential of RRM1 inhibition in different MM cell lines. We also predicted a metabolic signature based on gene expression data that explained the response to RRM1 inhibition in different cancer cell lines. Second, we show preliminary results of a study where response biomarkers for the effectiveness of Methotrexate in different cancer types is predicted following our methodology. This new algorithm, freely available in the COBRA Toolbox, undoubtedly opens new avenues to develop precision medicine strategies in complex and unaddressed clinical questions involving heterogeneous molecular data.

Short bio: Professor Francisco J. Planes is the deputy-director of the Biomedical Engineering and Sciences Department at University of Navarra. Since 2008, his research has been focused on the area of Bioinformatics and Systems Biology, particularly in developing novel mathematical models

and algorithms for the analysis of metabolic networks in the context of high-throughput technologies (genomics, transcriptomics, proteomics, metabolomics and meta-omics) with applications to biotechnology, health, ecology and pharmacology. In the last years, the activity of Dr. Planes has mainly concentrated on cancer metabolism, namely on the development of novel algorithms to identify drug targets and response biomarkers in cancer using genome-scale metabolic networks and –omics data.



Speakers

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