CROSSPLAN: Systematic Planning of Genetic Crosses to Validate Mathematical Models

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ABSTRACT

Mathematical models of cellular processes can systematically predict the phenotypes of novel combinations of multi-gene mutations. Searching for informative predictions and prioritizing them for experimental validation is challenging since the number of possible combinations grows exponentially in the number of mutations. Moreover, keeping track of the crosses needed to make new mutants and planning sequences of experiments is unmanageable when the experimenter is deluged by hundreds of potentially informative predictions to test.

We present CROSSPLAN, a novel methodology for systematically planning genetic crosses to make a set of target mutants from a set of source mutants [1]. We base our approach on a generic experimental workflow used in performing genetic crosses in budding yeast. We prove that the CROSSPLAN problem is NP-complete. We develop an integer-linear-program (ILP) to maximize the number of target mutants that we can make under certain experimental constraints. We apply our method to a comprehensive mathematical model of the protein regulatory network controlling cell division in budding yeast. We also extend our solution to incorporate other experimental conditions such as a delay factor that decides the availability of a mutant and genetic markers to confirm gene deletions. The experimental flow that underlies our work is quite generic and our ILP-based algorithm is easy to modify. Hence our framework should be relevant in plant and animal systems as well.

This paper opens up a new area of research: how to automatically synthesize efficient experimental plans for making large numbers of mutants carrying perturbations in multiple genes. Moreover, the

principles used in CROSSPLAN can be directly extended to other organisms where siRNA or CRISPR-based screens are effective. Thus the growing community of biomedical scientists who are beginning to use CRISPR-based approaches to plan multiple, combinatorial gene perturbations will find our approach to be very relevant to their research.

KEYWORDS

experiment planning, genetic crosses, multi-gene mutants, integer linear program, mathematical model simulations

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