GC-TEAR: A rapid and customisable algorithm for growth-coupled strain design

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Summary

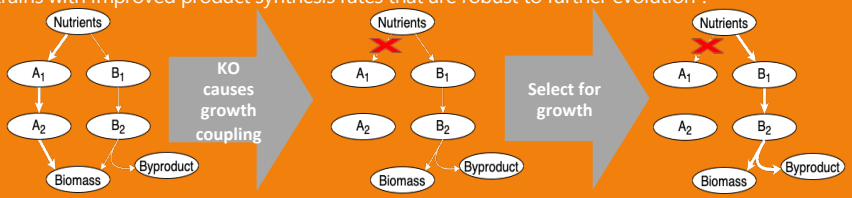
Growth Coupling by Trade-offs and Evolutionary AlgoRithm (GC-TEAR) uses a genetic algorithm to design knockout strategies that couple synthesis of a compound to cell growth.

Rapidly identifies strategies by utilising model reduction and scoring uncoupled designs by how heavily product synthesis affects growth.

Finds designs that better fit user requirements by optimising growth-coupled designs based on a customisable combination of product synthesis rate, productivity, growth rate and coupling strength.

Background- growth coupling

Growth-coupled production is achieved by engineering metabolism such that a desired product is synthesised when growth is maximised. Interventions that enforce coupling create a selective pressure for metabolic flux to be rerouted through the target pathway, which lets adaptive evolution create strains with improved product synthesis rates that are robust to further evolution[1].



WT cell has evolved to use pathway A, as pathway B wastes nutrients by forming a byproduct

Knockout in pathway A causes growth coupling- byproduct synthesis has become necessary for nutrients to be converted into biomass

Selective pressure for fast growth makes cells evolve to increase their usage of pathway B, resulting in more byproduct synthesis

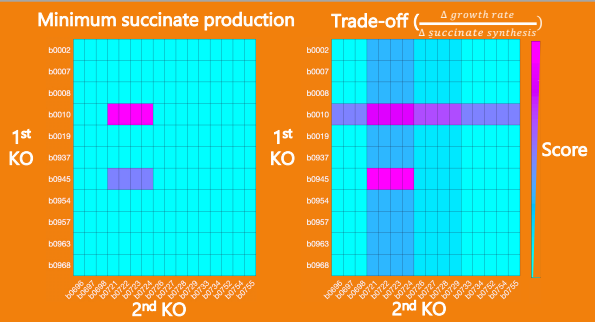
Case study used: coupling succinate production to growth in *E. coli*

Model reduction

E. Coli model	iML1515[2]	Reduced iML1515
Reactions	2712	1178
Targetable reactions	2266	1010
Genes	1516	1106

GC-TEAR removes inactive reactions/genes, pools unbranched pathways into a single reaction, combines genes where knockouts are redundant, and prevents knockouts of genes/reactions necessary for product synthesis from being tested. This reduces the size of the search space.

Fitness landscapes



GC-TEAR uses a genetic algorithm to analyse combinations of knockouts. If minimum product is used to find designs, all uncoupled designs receive the same score. If the strength of the trade-off between growth and product synthesis is used, many of the genes that contribute to coupled solutions receive higher scores than genes that don't, which makes the algorithm focus on them and find growth-coupled designs more quickly.

Rapid design identification

Algorithm	FastPros[4]	OptGene[5]	GC-TEAR
Genetic algorithm?	No	Yes	Yes
Fitness metric	Trade-off	Minimum product	Trade-off + composite
Run time (minutes)	>120	>120	14 (8 if parallel processing enabled)

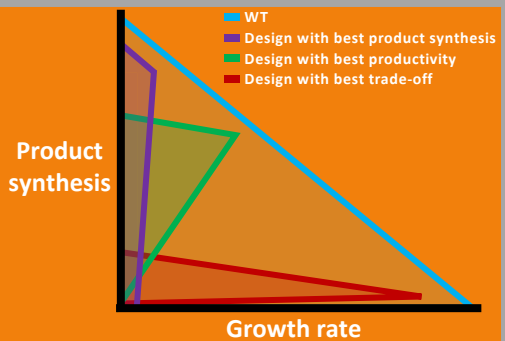
GC-TEAR, FastPros[3] and OptGene[4] were used to identify 3-deletion designs that growth-coupled succinate in the reduced model. The time it took for each to identify at least one growth-coupled design was recorded, with GC-TEAR being substantially faster at finding an initial growth-coupled design.

Customisable design selection metrics

GC-TEAR uses a two-part fitness function. Uncoupled designs are assessed by growth-product trade-offs, while coupled designs are analysed by a combination of product synthesis rate, growth rate, specific productivity and coupling strength.

The weight of each metric is adjustable- so users can define which metrics are most important and then let the algorithm optimise any growth-coupled design it finds according to their requirements.

By allowing users to define the type of design the algorithm favours, GC-TEAR should be able to find designs that are more useful to users.



Example designs that score highly with different metrics. Using a single metric would bias the genetic algorithm towards particular types of design, making it miss designs that represent a good balance.

Conclusions

GC-TEAR can rapidly identify growth coupled strains in this case study.

Designs created should better reflect user desires, as users can control the metrics used to optimise any growth-coupled designs that the algorithm finds.

References

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