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# A large-scale exploration of cell-free compositions to maximize protein production using active learning

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Chemogenomic and Biological Screening Core Facility



Lysate-based cell-free systems have become a major platform to study gene expression<sup>1-3</sup> but batch-to-batch variation makes protein production difficult to predict<sup>4</sup>. Here we describe an active learning approach<sup>5</sup> to explore a combinatorial space of ~4,000,000 cell-free compositions, maximizing protein production and identifying critical parameters involved in cell-free productivity. We also provide a one-step-method to achieve high quality predictions for protein production using minimal experimental effort regardless of the lysate quality.

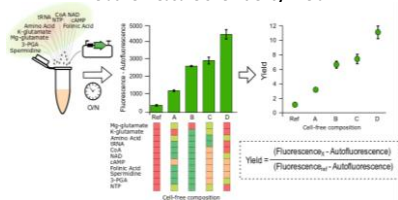
## Cell-free composition:

### A vast combinatorial space to explore

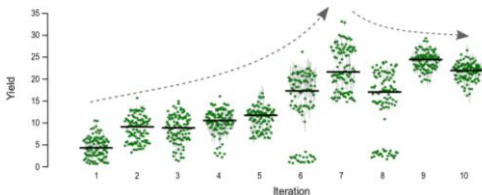
Component	Concentration
Mg glutamate (mM)	0.4 1.2 2 4
K-glutamate (mM)	8 24 40 80
Amino Acid (mM)	0.15 0.45 0.75 1.5
tRNA (mg/ml)	0.02 0.06 0.1 0.2
CoA (mM)	0.026 0.078 0.13 0.26
NAD (mM)	0.013 0.039 0.165 0.33
cAMP (mM)	0.075 0.225 0.375 0.75
Folic Acid (mM)	0.0048 0.0204 0.034 0.068
Spermidine (mM)	0.1 0.3 0.5 1
3-PGA (mM)	3 9 15 30
NTP (mM)	0.15 0.45 0.75 1.5

Combinatorial space =  $4^{11} = 4\,194\,304$  compositions

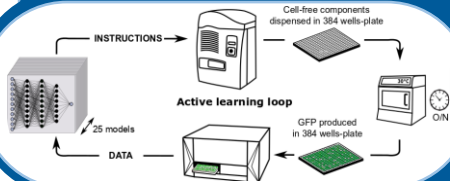
## A relative measure of efficiency: Yield



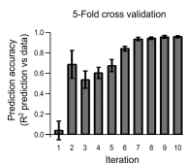
## 34 time Yield improvement after 7 iterations using a home-made lysate



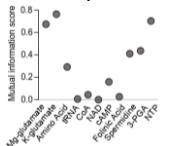
## Active learning loop



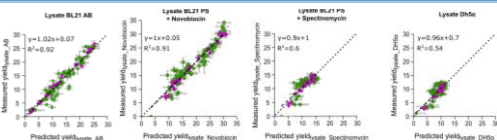
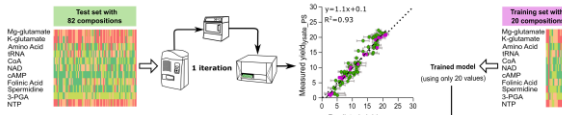
## Prediction accuracy of the models



## Mutual Information analysis



## A one-step method to maximize Yield in cell-free platforms



## References

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