Reinforcement learning optimization of reaction routes on the basis of large, hybrid organic chemistry – synthetic biological, reaction networks data

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Electronic Supplementary Information

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S1 Commercial and natural building blocks

The naturally available building blocks include cofactors and free metabolites, adopted from Blaβ et al.[1] A full list of these molecules can be found on 'Natural precursors' spreadsheet of the Excel file 'SI.xlsx'. These molecules were manually curated from Kyoto Encyclopaedia of Genes and Genomes database (KEGG) database. In total, it has 34 cofactors and 123 free metabolites (157 in total). The corresponding Reaxys molecule IDs are also listed in the table if these molecules are in Reaxys.

It is common in Reaxys that one molecule canonical SMILES string is linked with multiple Reaxys ID, owing to their high order difference (isotopes, stereoisomers, etc.) or simply Reaxys database noise. In this way, one KEGG molecule is usually identical with multiple Reaxys molecules in canonical SMILES.

For the local database to hybrid both the organic synthesis and synthetic biological data, we mainly used Reaxys identification system. We only added KEGG molecule or reaction IDs to the local database if these molecules were not on Reaxys. From the local database perspective, the total number of naturally available building blocks is 451.

The commercial molecules are split into Reaxys and KEGG molecules, labelled with their molecule IDs, can be found in 'Reaxys commercial molecules' and 'KEGG commercial molecules' spreedsheets of 'SI.xlsx', and the number of commercially available building bocks are 24,397 and 249 respectively. These molecules are sorted by ascending prices, and the prices are the minimum available prices by suppliers.

S2 RMSE an Correlations of the MLP models

The Multi-layer Perception (MLP) was developed to mimic the relationship between the 2049 inputs (2048 from Morgan Fingerprint, and 1 from residual depth). From the chemical, biological and hybrid environments, the scaled root mean square errors (RMSEs) and Pearson correlation coefficients are similar, and stable over the 20 iterations of optimisation.

Table S1 summarises the scaled RMSEs and correlations between the predicted expected costs and true expected costs of molecules in the test dataset for the three environments, where scaled RMSE is RMSE divided by mean of test dataset, determined by Eq. S1, and correlation is determined by Eq. S2. In the equations, n indicates the number of observations, y_i indicates the expected costs of molecule i in the test dataset, and $\tilde{y}_i$ indicates the predicted expected costs of molecule i. Y and $\tilde{Y}$ are the vectors for test and predicted results respectively, $cov(Y, \tilde{Y})$ is the covariance between the two vectors, and σ is standard deviation.

$$RMSE = \frac{\sqrt{\frac{\sum_{i=1}^{n}(y_i - \tilde{y}_i)^2}{n}}}{mean_Y} \quad \text{Eq. S1}$$

$$Corr. = \frac{Cov.(Y, \tilde{Y})}{\sigma_Y \sigma_{\tilde{Y}}} \quad \text{Eq. S2}$$

Table S1 The scaled RMSEs and correlations between predicted expected costs and true expected costs of molecules in the test dataset over the 20-iteration optimisation, from chemical, biological and hybrid environments.

Iteration	Chemical env.		Biological env.		Hybrd env.	
no.	RMSE	Corr.	RMSE	Corr.	RMSE	Corr.
0	31.81%	52.72%	59.88%	62.01%	35.60%	77.58%
1	34.98%	59.38%	28.94%	60.61%	29.70%	53.55%
2	32.03%	60.84%	39.62%	63.85%	35.88%	64.35%
3	26.39%	52.57%	45.66%	54.87%	40.45%	58.77%
4	39.92%	58.71%	44.04%	56.87%	40.39%	60.70%
5	51.65%	57.68%	46.59%	57.64%	52.11%	55.07%
6	44.13%	70.85%	45.30%	63.95%	44.39%	67.62%
7	13.08%	54.46%	29.32%	55.18%	55.12%	42.10%
8	35.35%	54.61%	49.32%	85.42%	30.28%	69.15%
9	35.97%	59.66%	49.42%	59.15%	52.69%	60.33%
10	28.23%	50.41%	56.83%	65.58%	43.67%	70.22%
11	39.45%	50.55%	32.92%	57.80%	25.02%	75.25%
12	38.23%	76.46%	48.83%	58.90%	44.20%	74.09%
13	49.60%	65.15%	37.82%	68.85%	37.66%	78.88%
14	37.25%	67.45%	40.92%	56.26%	46.96%	54.76%

15	48.70%	62.60%	44.13%	63.33%	28.90%	59.47%
16	41.05%	64.87%	34.55%	57.01%	37.64%	48.28%
17	36.92%	67.67%	29.69%	57.44%	29.09%	57.29%
18	37.30%	62.48%	44.67%	61.85%	53.39%	57.98%
19	43.60%	78.08%	34.62%	65.02%	35.60%	68.36%

S3 Drug molecules

The full list of drug molecules with canonical SMILES string over 10 is shown in the 'Drug molecules' spreedsheet of 'SI.xlsx'. The statistics of costs to make drug molecules determined from the final value network 'decision maker' using the biological, chemical and hybrid reactions pools are shown in 'Drug synthesis expected cost' spreadsheet 'SI.xlsx', uploaded with the SI.

References

1. Blaß, L. K.; Weyler, C.; Heinzle, E., Network design and analysis for multi-enzyme biocatalysis. *BMC Bioinformatics* **2017,** *18* (1), 366.