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A consensus *S. cerevisiae* metabolic model Yeast8 and its ecosystem for comprehensively probing cellular metabolism

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Genome-scale metabolic models (GEMs) represent extensive knowledgebases that provide a platform for model simulations and integrative analysis of omics data. This study introduces Yeast8 and an associated ecosystem of models that represent a comprehensive computational resource for performing simulations of the metabolism of *Saccharomyces cerevisiae*--an important model organism and widely used cell-factory. Yeast8 tracks community development with version control, setting a standard for how GEMs can be continuously updated in a simple and reproducible way. We use Yeast8 to develop the derived models panYeast8 and coreYeast8, which in turn enable the reconstruction of GEMs for 1,011 different yeast strains. Through integration with enzyme constraints (ecYeast8) and protein 3D structures (proYeast8^{DB}), Yeast8 further facilitates the exploration of yeast metabolism at a multi-scale level, enabling prediction of how single nucleotide variations translate to phenotypic traits.

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Results

Recording community developments of yeast GEMs with GitHub.

Increasing the scope of the yeast metabolic network.

Expanding Yeast8 to enable enzyme constraints.

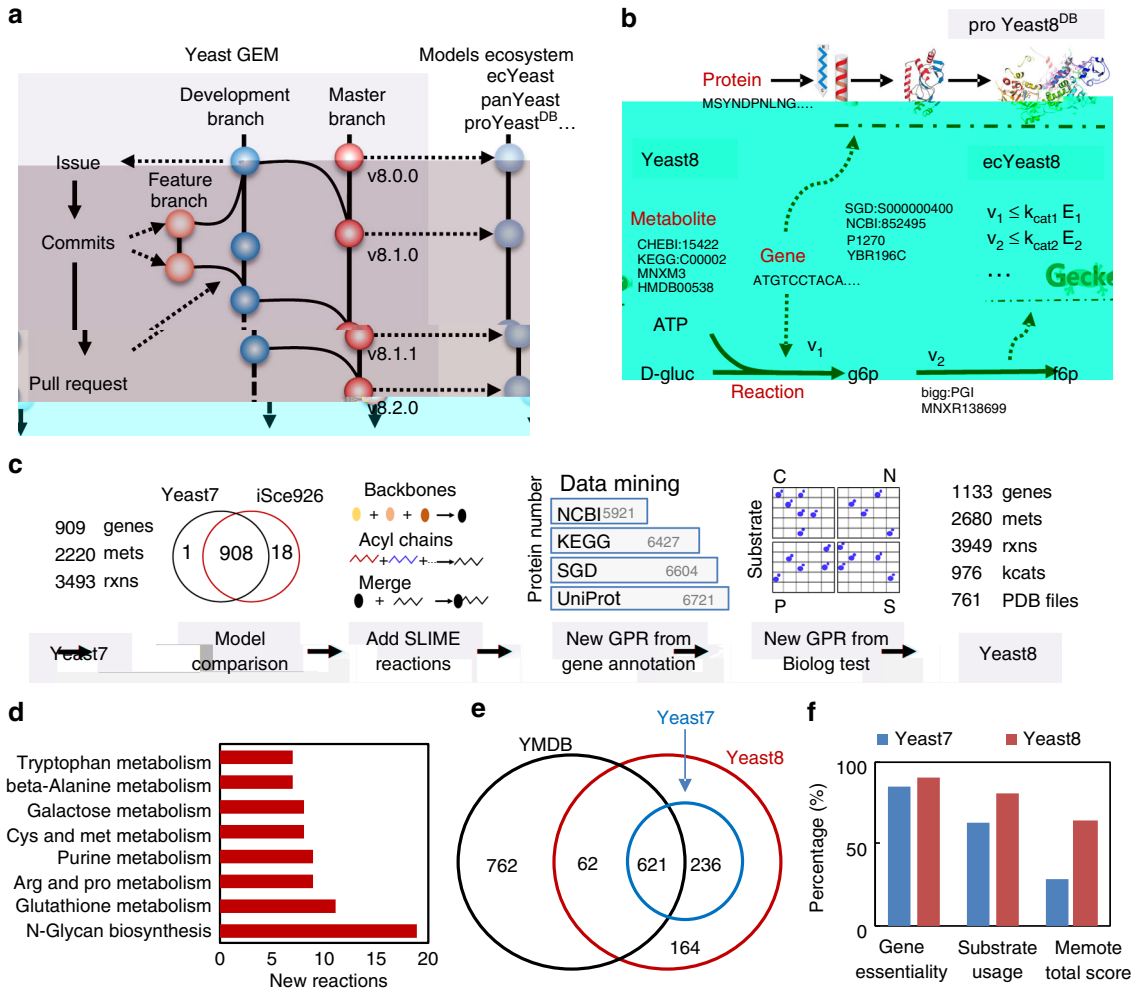

Fig. 1 Framework of the yeast GEM project. **a** Recording model updates in a community way using GitHub. **b** In Yeast8, genes, metabolites and reactions are annotated with their corresponding IDs from different databases, which simplifies translation between namespaces. Yeast8 forms the basis of the model ecosystem from which proYeast8^{DB}, ecYeast8, etc., are derived. **c** Major steps of development from Yeast7 to Yeast8. **d** Subsystem statistical analysis for the reactions added to Yeast8. **e** Metabolomics mapping between Yeast7, Yeast8 and the YMDB database. **f** Comparison of Yeast7 and Yeast8 in percent accuracy of gene essentiality and substrate usage analysis, as well as in memote test total scores (divided by 100)

8 - (1). 8 1,011 [42], - fi fi 8 fl ( ) (- (_ . 2 _). 8, . 6). fl . fi (_) 3969 4013 (_ . 3 . 7). (_ . 2), . . A 8 . fl , , fl 3895 , 2666 892 . -3 (1) 478 , 147 , 1, . A fi *S. cerevisiae*[39]. 8 [26]. (8) fi

Generation of panYeast8 and coreYeast8.

(. 8). . 1011 *S. cerevisiae* - 8 8, . *S. cerevisiae* 1011 (. 6)[40]. 8 fl [41], fi *S. cerevisiae* ,

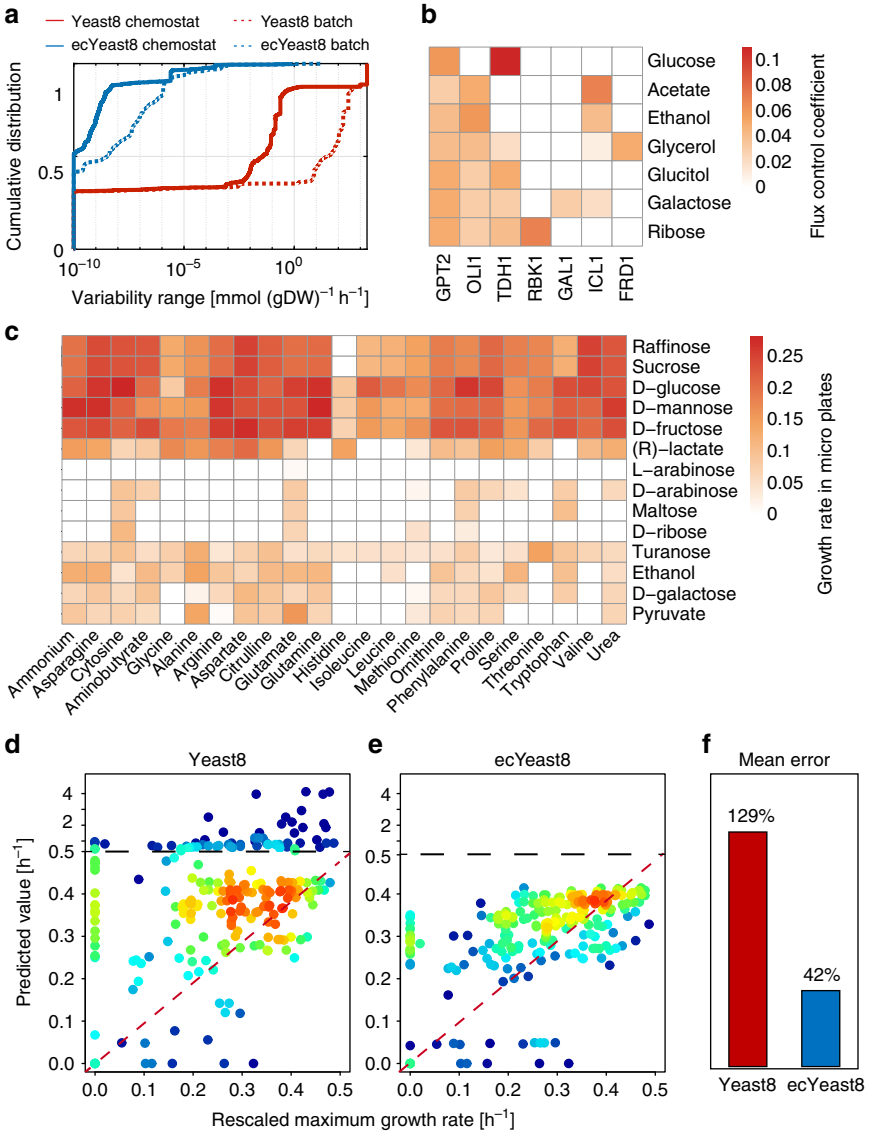

Fig. 2 ecYeast8 with enzyme constraints shows improved fit over the regular Yeast8 metabolic model. **a** Comparison of model performance between ecYeast8 and Yeast8 based on flux variability analysis (FVA). **b** Flux control coefficient analysis with ecYeast8 simulated on different carbon sources in minimal medium with the growth as the objective function. **c** Growth rate of *S. cerevisiae* S288C in micro-plate under different combinations of carbon and nitrogen sources. **d**, **e** Prediction of maximum specific growth rates under different combinations of carbon and nitrogen sources using Yeast8 (**d**) and ecYeast8 (**e**), the red colour zones mean that the data points are overlapped due to higher density. **f** Mean errors for comparison of measured and predicted growth rates using Yeast and ecYeast8

E. coli [8],
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(1, 2).
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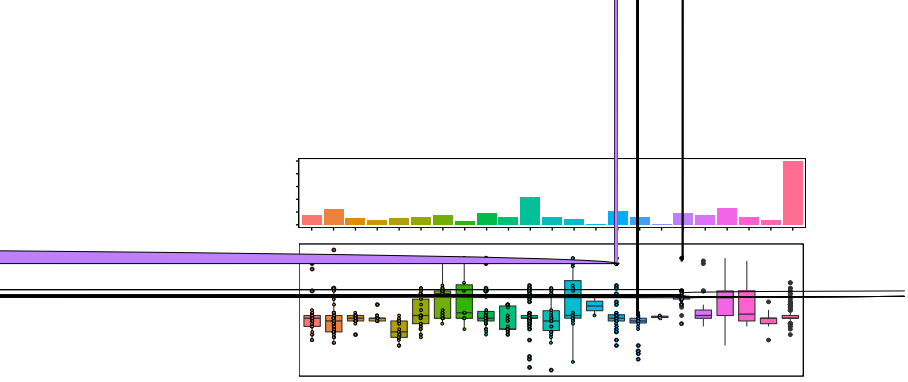
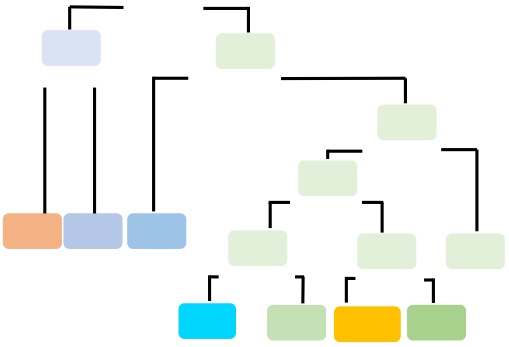
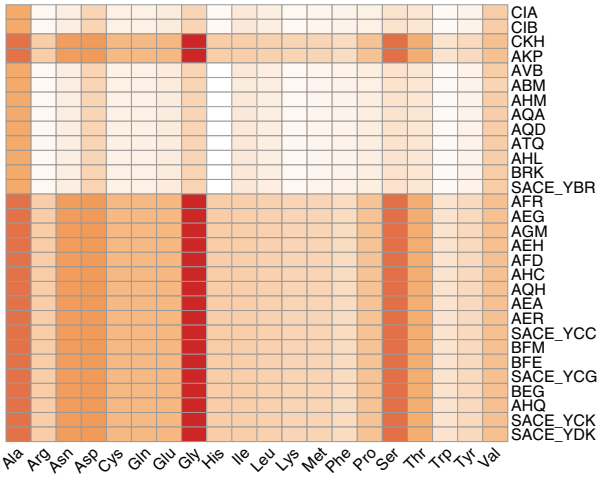
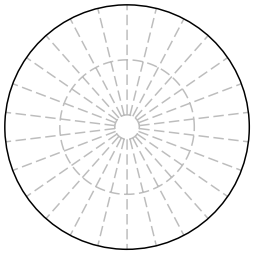
Evaluation of 1011 strain-specific GEMs. 1011 , 20
(1011 (. 3)
) 26
(. 3).
. A
“ ”

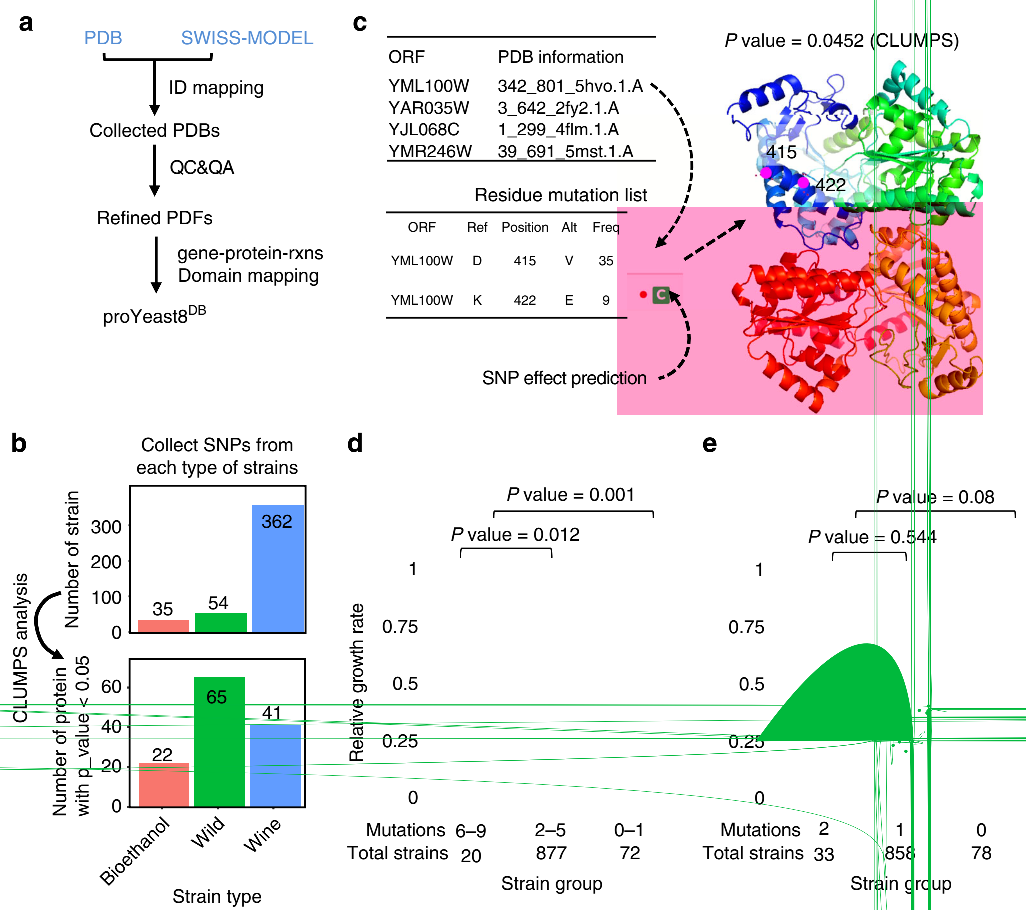








(. 3). fl . A [40] A ((, 1). . 3). fi fi , , fi (. 7). 1,011 , A fi (. 7 , .). , - ( ) [40].



Characteristics of metabolism displayed with proYeast8DB. . A fi ... fi (2) ... fl ... 11), ... B fi ... 8, ... 8B ... (... 9 ... 4). ... 43. ... B fi ... fi ... B fi ... (... 30 ... 2, ... 9 –). ... A ... 6.7[44] (... 3 ... 16,258,509 ... 1011 *S.* ... 4). ... *cerevisiae* ... 40 ... (... (*P* = 0.0001) ... (*P* ... 10 ...) ... fi ... ( ) ... = 0.0003), ... ( ). ... *S. cerevisiae*. B ... (... (*P* ... 10 ...) ... = 0.02), ... (*P* = 0.02), ... fi ... A ... fi ... 3 ... 8B ... 45, ... fi ... fi ... A ... (... 10 ...). ... *S. cerevisiae* ... B ... (4). ... *P* ... 0.05,

fi

fi (_ . 4). _ ’ (*P* = 0.018)

’ (*P* = 0.006, -

5),

-

[46,47].

,

B

(100 , A 035 , 068 ,

246)

(*P* = 0.041, 6),

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[48] (:// /)

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S. cerevisiae . _ , fi

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42 fi

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Systematic analysis of ecYeast8 and proYeast8^{DB}.

8 8^{B} (_ . 5)

fi . B

.[40] (_ . 5),

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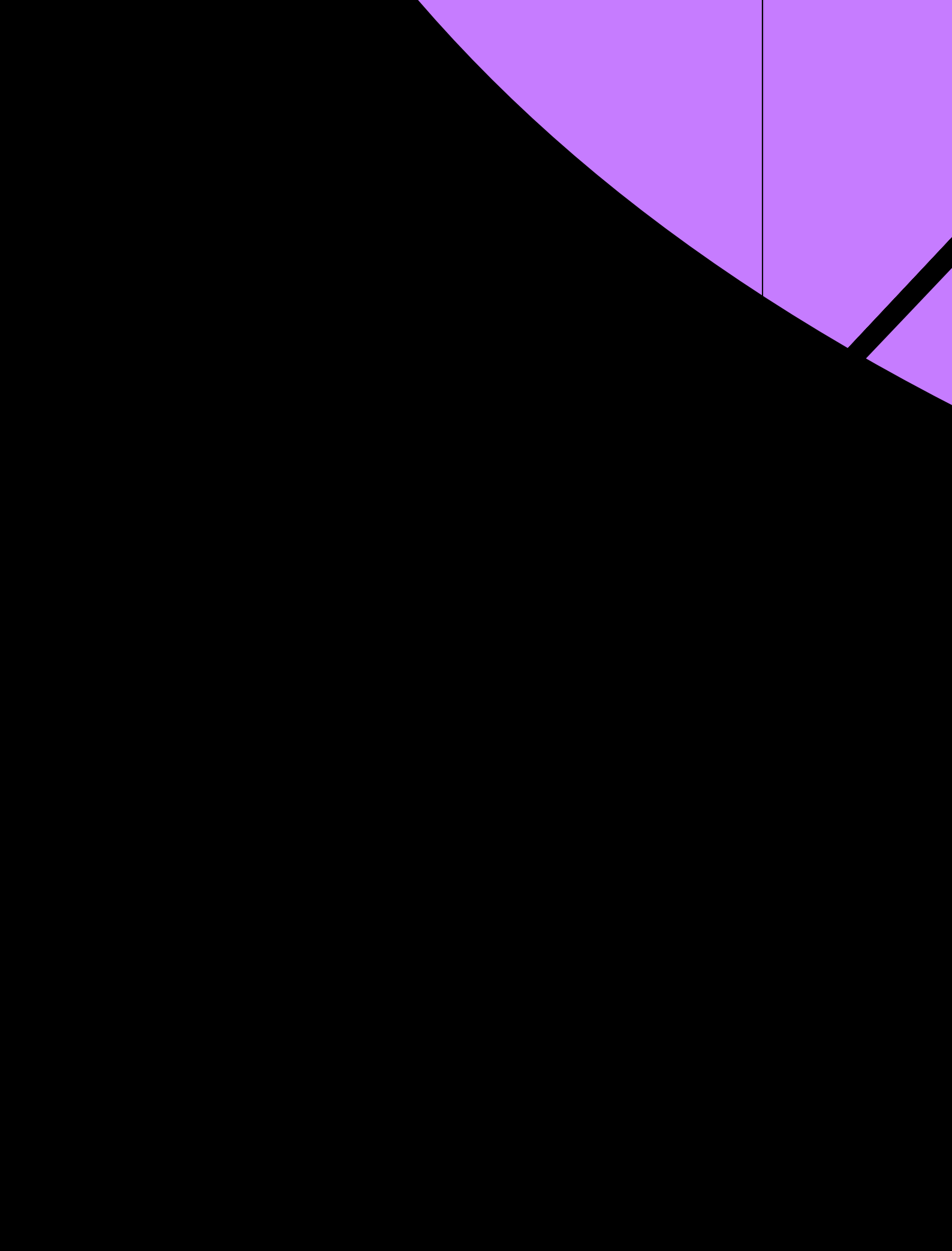
8^{B} fi



Methods

Tracking model changes with version control.

General procedures used to standardise annotation of metabolites and reactions.

Model update from Yeast7 to Yeast8.

Model validation with varied experimental data sources.

Visualisation of Yeast8.

Generation of ecYeast8.

$$-\frac{1}{k}v + e = 0 \quad (3)$$

$$0 \le e \le [E] \quad (4)$$

$$v \le k \cdot [E] \quad (5)$$

Simulations with ecYeast8.

$$= \left(\frac{v_{} - v}{v}\right) / \left(\frac{1.001k^{ij} - k}{k}\right) \quad (6)$$

$$A = \frac{+}{+ + +} \quad (1)$$

$$= \frac{\times - \times}{\sqrt{(+)(+)(+)(+)}} \quad (2)$$

Re-annotation of the pan-genome from the 1011 yeast genome-sequencing project. (8), [40]. , 1011 . A - 6081 - *S. cerevisiae* 288 , 1715 ( ). 7796 , . B , 4940 2846 6081 *S. cerevisiae* 288 , - ( ) 8 A 774 *S. cerevisiae* 288 [40] , [35], [65], (BB) [66]. BB 80% fi 8. , . A , fi - (:// / / /) (:// /#/ /). , BB (-) , , B , , , , , , ,

Generation of panYeast8, coreYeast8 and strain specific GEMs. ( ) - , (A). : (1) A B , 'A B ' 8; (2) A B , 'A B' '(A B) (B)'. , 51 13 8. A , , 8 , , fi

B .

CLUMPS method to calculate *p*-values of mutation enriched PDB files.

[45], A
3

$$A = \sum n\, n\, e^{-\frac{d^2}{2\tau^2}} \tag{7}$$

d fi ( ) α
. t fi
6 . n n :

$$n = \frac{N^m}{\theta^m + N^m} \tag{8}$$

N
$\theta = 2$ $m = 3$
( )
(2)
. A
[45].
fi
A
A 10^4
P
A A P fi

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Acknowledgements

1 §, (10 1016517), A 2020 A (686070 720824).

Author contributions

., B. ., ., B. ., B. 8 8 1,011 fi 8 B. 8 B. .A., ., .B., A fi .

Additional information

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