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Minireview – Yeast as a model for biology and disease

Systems biology of yeast metabolism

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Abstract

Metabolism underpins cellular function by supplying energy, biosynthetic precursors, and redox balance and in yeast there are thousands of metabolic reactions that are tightly coordinated through multilayered regulation. The yeast *Saccharomyces cerevisiae* has become a central model for studying metabolism and its regulation and following publication of its genome in 1996, this yeast became pivotal in systems biology. Systems biology integrates experimental data with mathematical modeling to analyse complex cellular networks. A major advance for metabolic analysis was the development of flux balance analysis and genome sequencing enabled reconstruction of the first genome-scale metabolic model (GEM) for yeast. This initial GEM described how hundreds of genes, reactions, and metabolites interact across compartments. Subsequent models, including Yeast8 and Yeast9, expanded the coverage and predictive power, and these models enable metabolic comparison, physiological analysis, omics integration, and design of strains that can be used for production of chemicals and biopharmaceuticals. Overall, *S. cerevisiae* remains a cornerstone of systems biology and biotechnology, with continued advances expected in integrative modeling and engineering applications.

Keywords metabolic engineering, metabolism, *Saccharomyces cerevisiae*, genome-scale metabolic models, systems biology

Introduction

Metabolism is at the core of cellular function as it provides the Gibbs free energy required for cell growth and maintenance, building blocks for synthesis of cellular components, and ensures handling of electron flows. In yeast cells, there are thousands of different metabolic reactions and to ensure that the fluxes through these different reactions are coordinated by complex regulatory systems that have evolved. These engage transcriptional regulation, translational regulation, and posttranslational regulation, such as protein modifications and metabolite-enzyme interactions. The yeast *Saccharomyces cerevisiae* has evolved as a very important model organism for studies of these different regulatory processes (Nielsen 2025), illustrated in elucidation of the so-called GAL-regulon that ensures expression of enzymes involved in galactose metabolism (Ostergaard et al. 2000, Ideker et al. 2001, Hong et al. 2011).

When the genome sequence of *S. cerevisiae* became available in 1996 its role as a model organism was further cemented, particularly in the field of systems biology, where the objective is to use mathematical models for description of biological processes for gaining new mechanistic insight into their function. A key driver for this was multilaboratory efforts to functional characterize the yeast genome, e.g. the EUROFAN project (Goffeau 2000), as well as many early developments of omics analysis, e.g. the first genome-wide transcriptome analysis (DeRisi et al. 1997), extensive proteome analysis (Washburn et al. 2001) and protein–protein interaction analysis (Uetz et al. 2000). These studies were instrumental in advancing the fundamental understanding of the physiology of *S. cerevisiae* as well as ensuring an extremely well-characterized genome with a high fraction of the genes being annotated with a function.

Here, I will briefly review how *S. cerevisiae* became a central organism in systems biology, in particular in the field of studying yeast metabolism, and I will at the end give some perspectives on the future of systems biology of yeast metabolism.

Early systems biology studies of yeast metabolism

Systems Biology is the study of complex biological systems by analysing how many different components, i.e. genes, proteins, and metabolites, interact to exert cellular functions. It employs a holistic approach, where experimental data are combined with computational and mathematical modeling to predict biological functions. Even though mathematical models have been used for description of biological processes for a long time, including for studies of evolution and species interactions, e.g. the Lotka–Volterra model that was developed for description of predator–prey interactions, their use for modeling cellular growth and cellular processes expanded in the 1960s when Aris, Fredrickson and

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Table 1 Typical metabolite concentrations, fluxes through the metabolites, and turnover times for key intracellular metabolites in yeast cells.

Metabolite	Net production rate[1] (mmoles/g DW/h)	Concentration level (μmoles/g DW)	Turnover times[2]
ATP	40	2–4	<1 s
Glycolytic intermediates	20	0.1–5.0	<1 s
Amino acids	0.4	50	~5 min[3]

[1]Calculated based on a maximum specific growth rate of about 0.4 h^{-1} and a biomass yield of about 0.1 g DW/g glucose, i.e. typical representative numbers for maximum specific growth rate of *S. cerevisiae*, meaning fermentative metabolism with a very high glycolytic flux. At respiratory conditions, the net production rates of glycolytic intermediates will be about 10-fold lower, but ATP production will be in the same order of magnitude as it scales linearly with the specific growth rate.
[2] For both glycolytic intermediates and amino acids there is some variation. For glycolytic intermediates, glucose-6-phosphate and fructose-1,6-bisphosphate have the highest concentration and they may have turnover times in the order of a few seconds at respiratory conditions. DW: dry weight.
[3] Even though a turnover time of about 5 min for amino acids is much higher than for the other metabolites, this is still short compared with the turnover time for a cell, e.g. a doubling time of 1–2 h for *S. cerevisiae.*

others developed a solid mathematical framework for describing growth kinetics of cells (Tsuchiya et al. 1966). These first models were relatively rudimentary, but in the 1980s they led to the development of quite detailed models for *Escherichia coli*, e.g. the Cornell model that was the first single cell model (Shuler et al. 1979) and several models developed by Lee and Bailey for description of plasmid–cell interaction (see e.g. Lee and Bailey 1984).

For studying metabolism, a major breakthrough was the development of the concept of flux balance analysis by Aiba (Aiba and Matsuoka 1979). Flux balance analysis is based on a simple principle, i.e. that all fluxes producing a specific metabolite equal the fluxes that convert this metabolite to other metabolites. Clearly there cannot always be balancing of fluxes through all the metabolites inside the cells, as this would not allow the concentration of these metabolites to change over time. However, the turnover times of intracellular metabolites, i.e. metabolite concentrations divided by the fluxes through the metabolite, is for most metabolites in the order of seconds due to the very low concentrations of most cellular metabolites (Table 1). This means that just a few seconds without flux balancing can lead to a significant change in the metabolite concentration, and hereby to a new "steady state" condition with flux balancing. Amino acids are present in relatively high concentrations inside the cell due to the relatively high K_m values for binding of amino acids to the tRNAs, and these metabolites therefore have turnover times of intracellular metabolites in the order of minutes (Table 1). However, still compared with the time constant of cellular growth that is in the order of hours flux balancing is a reasonable assumption also for amino acids.

The concept of flux balance analysis basically provides a modelling framework where it is possible to set-up a set of algebraic equations that link all the metabolic fluxes (Fig. 1A). This set of equations can be solved either through measuring a certain set of fluxes, e.g. typically uptake and secretion fluxes from the cell, or through defining an objective function and then use linear programming to identify a set of fluxes that comply with the objective function. The first to use flux balance analysis for characterization of yeast metabolism was van Gulik and Heijnen (van Gulik and Heijnen 1995). Using a 88 metabolic reactions, where the P/O ratio and the ATP maintenance consumption rate was defined as parameters they could calculate metabolic fluxes using linear programming during aerobic growth on glucose and ethanol. Subsequently we developed a slightly simpler model with 37 reactions and 43 metabolites to do flux balance analysis for studies

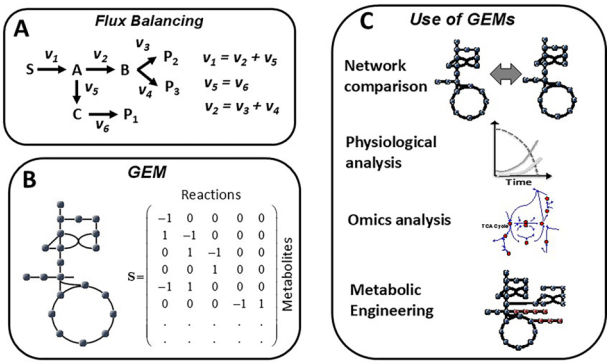

Figure 1 Flux balance analysis (FBA) and its applications. (A) Illustration of the basic concepts of FBA for a simple metabolic network. Balancing around the three metabolites A, B, and C provides three constraints on the six metabolic fluxes. Through measurement of three fluxes, e.g. substrate uptake rate (v_1) and production rate for two of the three products (v_3, v_4, or v_6) the three other fluxes can be calculated. Alternatively, linear programming can be applied by defining an objective function, e.g. optimize production of P_1 in which case $v_1 = v_5 = v_6$ and the three other fluxes are zero. When linear programming is applied it is necessary to define one input flux, e.g. v_1. (B) When the FBA concept is applied to a large metabolic network it is possible to reconstruct a genome-scale metabolic model (GEM), where the stoichiometric coefficients for the different metabolic reactions are assembled in a stoichiometric matrix S. Reactions are in the columns and metabolites in the rows, e.g. metabolite number two is produced in the first reaction and consumed in the second reaction and is not involved in any other reaction. (C) GEMs find a wide range of applications with four typical applications being: (1) comparison of metabolic capabilities of different strains/species; (2) physiological analysis, e.g. identification of essential and nonessential reactions; (3) overlaying the metabolic network with omics type data, e.g. transcriptome or proteome data, to gain new insight into coregulated parts of metabolism; and (4) design of metabolic engineering strategies.

of yeast metabolism at anaerobic growth (Nissen et al. 1997), and by using the model we could calculate the fluxes in the central carbon metabolism of yeast and hereby identify a key role of a mitochondrial alcohol dehydrogenase (Adh3) in maintaining redox balancing in the mitochondria at anaerobic conditions (Nissen et al. 1997). These early flux balance analysis studies were to a large extent relying on earlier work of Oura, who had conducted

foundational work on the metabolism of *S. cerevisiae*. Through a detailed mapping of enzymes in the central carbon metabolism, he showed how biotin deficiency affected yeast metabolism as well as clearly demonstrated how metabolism changed in response to aeration (Oura 1974, Oura 1978). His work was also instrumental in determining the biochemical composition of yeast, which was important for defining the so-called biomass equation, i.e. defining the stoichiometry for conversion of cellular building blocks into biomass. Later studies, including our analysis of anaerobic growth (Nissen et al. 1997), confirmed that the biomass composition of yeast is remarkably constant across different growth conditions, which has been quite important for later modeling efforts.

Flux balance models are often underdetermined systems, meaning that it will not be possible to calculate the fluxes without either measurements of many fluxes or using linear programming, where an objective function has to be defined (Fig. 1A). Even though maximizing growth or minimizing substrate uptake is often found to be a biologically reasonable objective function (Islam et al. 2025), flux balance analysis based on linear programming will not necessarily provide a unique solution in terms of the fluxes as several different operations of metabolism may satisfy the objective function. To overcome this problem, it is necessary to add additional constraints. The use of ^{13}C-labeled substrates coupled with measurements of the labeling pattern in intracellular metabolites, such as amino acids provides such additional constraints (Nielsen 2003). This concept therefore gained much interest in flux quantification in the late 1990s and early 2000s, and we were the first to quantify fluxes in yeast using this concept (Gombert et al. 2001). By analysis of yeast grown in batch and chemostat cultures it was possible for the first time to get insight into how fluxes distribute between the different pathways of the central carbon metabolism at fermentative and respiratory conditions.

Genome-scale metabolic models

Even though the first examples of flux analysis mentioned above enabled much new insight into the function of cellular metabolism, the models were relatively simple and only covered the central carbon metabolism. However, with the availability of the genome sequence of yeast (Goffeau et al. 1996) it became possible to identify all the metabolic capabilities of yeast. This led to the reconstruction of the first genome-scale metabolic model (GEM) for yeast (Forster et al. 2003a), which also was the first GEM for an eukaryal organism and therefore the first model to consider compartmentalized metabolism, i.e. separation of metabolic reactions in the mitochondria and the cytoplasm. This model described how 708 genes encode enzymes carrying out 1145 reactions connecting 825 metabolites. In this first model there were several gaps in the metabolic networks, i.e. not all reactions were associated with an enzyme/gene, that were filled based on knowledge of metabolic capabilities of yeast, e.g. when this model was reconstructed not all enzymes of the ergosterol biosynthetic pathway had been identified but it was known that yeast could synthesize ergosterol so all reactions toward this lipid were included in the model. Besides providing a network of how genes, enzymes and metabolites are connected a GEM is also a mathematical representation of metabolism in the form a stoichiometric matrix that collects the stoichiometric coefficients for all the reactions in the metabolic network (Fig. 1B). This stoichiometric matrix can be directly used to generate the flux balance equations that can be used for calculation of metabolic fluxes.

Over the years the first yeast GEM was further updated by different research groups, e.g. with expanded description of different compartments (Duarte et al. 2004) and lipid metabolism (Nookaew et al. 2008), but in 2008 the yeast research community gathered to reconstruct a consensus GEM for yeast referred to as Yeast1 (Herrgård et al. 2008). This model described how 888 genes encode enzymes carrying out 1761 reactions connecting 1168 metabolites, and it included many more compartments than the original model. Over the years Yeast1 was further updated through adding more reactions and improved connectivity between reactions, enzymes, and genes, but these modifications were not tracked in a formalized fashion. With the introduction of Yeast8, this was changed as the model was reposited in GitHub (Lu et al. 2019), which allowed different researchers to work in parallel on model development like how software engineers work on software development. The Yeast8 paper was a very comprehensive model with 1133 genes, 3949 reactions, and 2680 metabolites, i.e. it added more than 200 new genes compared with Yeast7. In the development of Yeast8, and subsequent models, the Yeast Metabolome Database (Ramirez-Gaona et al. 2017) played a very important role as an annotated resource of identified metabolites in yeast, and this clearly demonstrates the importance of maintaining valuable databases like this as well as the Saccharomyces Genome Database. The model also formed the basis for exploring the pan-metabolism of *S. cerevisiae* through reconstruction of a GEM based on the pan-genome of 1011 yeast strains and using the pan-GEM it was possible to easily reconstruct strain specific GEMs for the 1011 different yeast strains. Hereby variations in yeast metabolism with *S. cerevisiae* strains could be examined, and even though there is a relatively large genomic variation of the 1011 strains, i.e. with the core genome being about 5000 genes with about 1000 auxilliary genes, there is only few metabolic differences among the strains (Lu et al. 2019). With the introduction of the GitHub platform, it was possible to have version control of model improvements, and the whole yeast community could therefore be engaged in model improvements.

This resulted in continuous improvements and launch of several new versions, and in 2024 this led to launch of Yeast9 comprising 1162 genes, 4130 reactions, and 2805 metabolites (Zhang et al. 2024). Besides the expanded coverage of metabolism by Yeast9, the model also had improved quality in terms of connectivity and predictive capabilities (Zhang et al. 2024). The continuous development and improvement of the yeast GEMs illustrate very well that these models can continuously be improved when new knowledge is obtained, and at the same time they represent a library of metabolic knowledge for the organism. More recently machine learning was used to identify so-called underground metabolism of yeast, i.e. reactions carried out due to promiscuity of the enzymes, and this resulted in the generation of a model covering 59 914 reactions covering 16 244 metabolites and linked to 2057 genes (Wu et al. 2026). This model demonstrated how many enzymes can carry out additional functions, which can be challenging in metabolic engineering as it can lead to unpredicted side reactions. This model is therefore a valuable tool for further advancing metabolic engineering of yeast in the future. GEMs have many different applications (Österlund et al. 2012), but among

these four stands out (Fig. 1C): (1) metabolic network comparison; (2) physiological analysis, e.g. genome essentiality; (3) integration with omics analysis; and (4) prediction of metabolic engineering targets. The use of the Yeast8 GEM for analysis of metabolic diversity among different *S. cerevisiae* strains was already mentioned above, but Yeast8 could also be used as a scaffold for generating GEMs for 322 different yeast species (Lu et al. 2021). This enabled analysis of how different metabolic capabilities in these yeast species had been acquired, in many cases through horizontal gene transfer or enzyme promiscuity, but also that gene loss results in loss of metabolic capabilities not required in ecological niches where different yeast species have evolved (Lu et al. 2021). Yeast GEMs have also played an important role in obtaining new physiological insight into yeast metabolism. Initially focus was on getting new insight into gene essentiality (Forster et al. 2003b), but yeast GEMs have also been useful for getting insight into metabolic capabilities for growth on different carbon sources (Lu et al. 2021). GEMs represents a well-curated network graph of how genes, proteins, and metabolites are connected, and they have therefore served as a very important scaffold for analysis of omics data. This was first demonstrated for use of transcriptome data to identify either coregulated metabolic networks or so-called reporter metabolites that are metabolites around which there are large transcriptional changes in response to genetic or environmental perturbations (Patil and Nielsen 2005). This concept enabled much better insight into how metabolism is responding to different perturbations, and it was further developed to also enable analysis of metabolomics data (Cakir et al. 2006). This concept resulted in development of general bioinformatics tools like PIANO for integrative analysis of omics data (Väremo et al. 2013). This approach has been found to easy transfer for analysis of omics data from human cells and was demonstrated to be useful for identification of novel biomarkers for cancer (Gatto et al. 2014, 2016), and it again emphasizes the value of developing experimental and computational concepts for yeast as these easily translate for analysis of human biology.

Probably the most extensive application of GEMs have been in the field of metabolic engineering (Nielsen and Keasling 2016), where GEMs have been used for identification of targets for genetic engineering that will result in improved phenotype for a specific application, e.g. improved production of a specific metabolite. One example of this was identification that CO_2 fixation was a limiting factor for high-level production of 3-hydroxypropionic acid, a chemical that can be used for production of acrylic acid that serves as a precursor for super-absorbent acrylic acid used in e.g. diapers (Qin et al. 2024). Another example is the identification of targets for improved production of heme by yeast which enabled high-level production of human hemoglobin that can be used as a oxygen carrier in blood substitutes (Ishchuk et al. 2022).

Even though there are many examples of how GEMs have been used in metabolic engineering, a limitation has been their predictive power of metabolic fluxes. Through development of enzyme constrained GEMs, so-called ecGEMs, where the flux through each reaction is constrained by the product of the catalytic capacity, given as k_{cat}, and the enzyme concentration (Sanchez et al. 2017) (see Fig. 2). The k_{cat} has been determined for many enzymes and can be collected from various databases (Sanchez et al. 2017), and if not experimentally determined k_{cat} values can be predicted from the amino acid sequence using artificial intelligence (Li et al. 2022a, 2023). If proteomics data is available the enzyme concentration is known for most enzymes, but often proteomics data are not available. In these cases, it can be assumed that the total proteome mass within a cell allocated to enzymes is constant (Sanchez et al. 2017). ecGEMs have been shown to have much improved predictive strength compared with traditional GEMs, and they can describe complex phenotypes. Thus, an ecGEM can explain that the Crabtree effect, i.e. the overflow metabolism happening at high glucose concentrations leading to ethanol production in the presence of oxygen excess, is a result of a proteome mass constraint. Even though the ATP yield on sugar is much lower during fermentation than during respiration, the amount of ATP generated per proteome mass allocated to fermentation is higher than the amount of ATP generated per proteome mass allocated to respiratory metabolism (Yu and Nielsen 2019). At high specific growth rates, where the Crabtree sets in and there is overflow metabolism to ethanol, there is a high demand for ribosomes and proteome mass allocated for ATP generation therefore has to be optimized. With the improved predictive power of ecGEMs they are very well suited for identification of metabolic engineering targets and in a recent study an ecGEM was used to identify targets for improving more than 103 different metabolites (Domenzain et al. 2025). The concept of ecGEMs has been shown to easily transfer for description of other species (Domenzain et al. 2022) as well as it could be extended to cover description of protein secretion and hereby be used for identification of how recombinant protein production by yeast can be improved (Li et al. 2022b).

An extension of ecGEMs are models where reactions describing transcription and translation are added to the model, so-called proteome constrained models (pcGEMs), and such a model has also been reconstructed for yeast (Elsemman et al. 2022). The strength of this model is that it could provide insight into how proteome constraints in different cellular compartments, e.g. the mitochondria, determines phenotype as well as correctly predict how expression of heterologous proteins impacts cellular growth as well as many other fundamental features of cellular biology (Elsemman et al. 2022). The proteome constrained models are far more comprehensive than the ecGEMs, which has caused

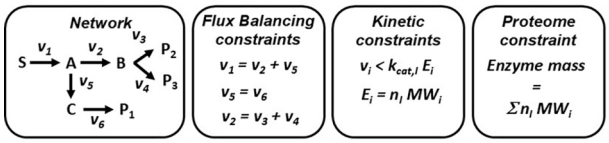

Figure 2 Illustration of the concept of proteome constraints. For a metabolic network model, the flux balancing constraints are combined with kinetic constraints that specify that any flux cannot attain a value larger than the product of the catalytic capacity of the enzyme (k_{cat}) and the enzyme concentration (E_i). The enzyme concentration is given as mass per unit biomass mass, and this is also defined as the product of the number of enzymes per unit of biomass times the molecular mass of the enzyme. Thus, even for enzymes present in low amounts within the cell can still account for a large enzyme concentration of their molecular weight is high. In addition to the flux balancing and kinetic constraints, the cells also need to manage their proteome budget and there is therefore a proteome constraint, i.e. the sum of enzyme concentrations (or enzyme number times enzyme molecular weights) equals the amount of proteome allocated for metabolic enzymes. This is typically about 50% of the proteome mass, and is surprisingly constant across different environmental conditions.

challenges with simulation time. Oftadeh et al. (2021) therefore introduced a simplified formulation of these models, the so-called ETFL formulation, that significantly improved the applicability and also enabled introduction of thermodynamic constraints. The model captured all key features of yeast physiology, i.e. specific growth rate on different carbon sources and the Crabtree effect.

The future of yeast systems biology

The yeast *S. cerevisiae* has evolved to be a very important model organism (Botstein and Fink 2011), and it has therefore also been used extensively for systems biology studies (Nielsen 2025). Thus, many omics technologies were first developed for *S. cerevisiae* and key regulatory pathways were studied using a systems biology approach, e.g. the GAL regulon (Ideker et al. 2001) and the high-osmotic glycerol pathway (Klipp et al. 2005). As discussed above, the development of yeast GEMs has also pioneered development of this model type for other organisms. Even though much experimental research on eukaryal biology has shifted to the use of human cell lines, yeast still serves as an important model organism due to the vast amount of data available for yeast, the ability to carry out well controlled experiments with yeast, and the availability of large strain libraries, e.g. gene deletions and GFP-tagging of all proteins, yeast is still used widely as an eukaryal model organism. This is also due to its important role as cell factory, where it undisputably is the most widely used cell factory for production of fuels, chemicals, foods, beverages, and pharmaceuticals.

Opportunities for future research on systems biology of yeast metabolism would be to add more information about regulation. There has been made attempts to add regulatory pathways to GEMs, but these have been relatively simple models only considering a few regulatory pathways, e.g. the Snf1 pathway (Österberg et al. 2021). To develop fully functional models that will be able to describe functional pathways in response to different environmental conditions, it will be necessary to develop models that integrate everything from nutrient sensing to regulatory pathways involved in gene expression. The challenge with development of such models is that information is still sparce and the kinetics is not sufficiently well understood. However, here AI models may have a role to play as these models are excellent in connecting inputs, i.e. environmental conditions, with outputs, i.e. gene expression, and considering the very large data sets available for gene expression in *S. cerevisiae* it should be possible to develop an AI agent that can connect environmental conditions with gene expression. If developing such an AI agent is combined with a large-language model harvesting information from literature, it will even be possible to map how key regulatory pathways are operating at different environmental conditions. Such AI agents could easily be integrated with ecGEMs or pcGEMs and hereby provide almost complete description of yeast functions. Besides application in metabolic engineering, such models could also be used for identification of aspects of regulation that are functioning but for which there are no mechanistic understanding available and hereby also drive basic biological research.

Thus, there are many opportunities for still advancing systems biology, and I am therefore confident that the yeast *S. cerevisiae* will continue to serve as an important model organism, in particular in the field of systems biology where yeast has clearly demonstrated that models developed for this organism can easily be translated for studies of human biology (Nielsen and Petranovic 2025).

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Author contributions

Jens Nielsen conceptualized and wrote the paper.

Conflicts of interest

Jens Nielsen is the co-founder of Melt&Marble that is a yeast synthetic biology company that produces ingredients for cosmetics and food and co-founder of Chrysea that is a yeast synthetic biology that produces bioactive ingredients for human health and nutrition.

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References

Aiba S, Matsuoka M. Identification of metabolic model: citrate production from glucose by *Candida lipolytica*. *Biotechnol Bioeng* 1979;**21**:1373–86. https://doi.org/10.1002/bit.260210806

Botstein D, Fink GR. Yeast: an experimental organism for 21st century biology. *Genetics* 2011;**189**:695–704. https://doi.org/10.1534/genetics.111.130765

Çakir T, Patil KR, Önsan ZI *et al.* Integration of metabolome data with metabolic networks reveals reporter reactions. *Mol Syst Biol* 2006;**2**:50. https://doi.org/10.1038/msb4100085

DeRisi JI, Iyer VR, Brown PO. Exploring the metabolic and genetic control of gene expression on a genome scale. *Science* 1997;**278**:680–6. https://doi.org/10.1126/science.278.5338.680

Domenzain I, Lu Y, Wang H *et al.* Computational biology predicts metabolic engineering targets for increased production of 103 valuable chemicals in yeast. *Proc Nat Acad Sci USA* 2025;**122**:e2417322122. https://doi.org/10.1073/pnas.2417322122

Domenzain I, Sánchez B, Anton M *et al.* Reconstruction of a catalogue of genome-scale metabolic models with enzymatic constraints using GECKO 2.0. *Nature Com* 2022;**13**:3766. https://doi.org/10.1038/s41467-022-31421-1

Duarte NC, Herrgård MJ, Palsson BO. Reconstruction and validation of *Saccharomyces cerevisiae* iND750, a fully compartmentalized genome-scale metabolic model. *Genome Res* 2004;**14**:1298–309. https://doi.org/10.1101/gr.2250904

Elsemman IE, Rodriguez Prado A, Grigaitis P *et al.* Whole-cell modeling in yeast predicts compartment-specific proteome constraints that drive metabolic strategies. *Nature Com* 2022;**13**:801. https://doi.org/10.1038/s41467-022-28467-6

Förster J, Famili I, Fu P *et al.* Genome-scale reconstruction of the *Saccharomyces cerevisiae* metabolic network. *Genome Res* 2003;**13**:244–51. https://doi.org/10.1101/gr.234503

Förster J, Famili I, Palsson BØ *et al.* Large-scale evaluation of *in silico* gene deletions in *Saccharomyces cerevisiae*. *OMICS* 2003;**7**:193–202. https://doi.org/10.1089/153623103322246584

Gatto F, Nookaew I, Nielsen J. Chromosome 3p loss of heterozygosity is associated with a unique metabolic network in clear cell renal carcinoma. *Proc Nat Acad Sci USA* 2014;**111**:E866–75. https://doi.org/10.1073/pnas.1319196111

Gatto F, Volpi N, Nilsson H *et al.* Glycosaminoglycan profiling in patients plasma and urine predicts the occurrence of metastatic clear cell renal cell carcinoma. *Cell Rep* 2016;**15**:1–15. https://doi.org/10.1016/j.celrep.2016.04.056

Goffeau A, Barrell BG, Bussey H *et al.* Life with 6000 genes. *Science* 1996;**274**:563–7. https://doi.org/10.1126/science.274.5287.546

Goffeau A. Four years of post-genomic life with 6000 yeast genes. *FEBS Lett* 2000;**480**:37–41. https://doi.org/10.1016/S0014-5793(00)01775-0

Gombert AK, Moreira dos Santos M, Christensen B *et al.* Network identification and flux quantification in the central metabolism of *Saccharomyces cerevisiae* under different conditions of glucose repression. *J Bacteriol* 2001;**183**:1441–51. https://doi.org/10.1128/JB.183.4.1441-1451.2001

Herrgård MJ, Swainston N, Dobson P *et al.* A consensus yeast metabolic network reconstruction obtained from a community approach to systems biology. *Nature Biotechnol* 2008;**26**:1155–60. https://doi.org/10.1038/nbt1492

Hong K-K, Vongsangnak W, Vemuri GN *et al.* Unravelling evolutionary strategies for yeast for improving galactose utilization through integrated systems level analysis. *Proc Nat Acad Sci USA* 2011;**108**:12179–84. https://doi.org/10.1073/pnas.1103219108

Ideker T, Thorsson V, Ranish JA *et al.* Integrated genomic and proteomic analysis of a systematically perturbed metabolic network. *Science* 2001;**292**:929–34. https://doi.org/10.1126/science.292.5518.929

Ishchuk OP, Domenzain I, Sánchez BJ *et al.* Genome-scale modeling drives 70-fold improvement of intracellular heme production in *Saccharomyces cerevisiae*. *Proc Nat Acad Sci USA* 2022;**119**:e210845119. https://doi.org/10.1073/pnas.2108245119

Islam MM, Shao W, Batavia M *et al.* Reframing the role of the objective function in its proper context for metabolic network modeling. *Cell Syst* 2025;**16**:101298. https://doi.org/10.1016/j.cels.2025.101298

Klipp E, Nordlander B, Krüger R *et al.* Integrative model of the response of yeast to osmotic shock. *Nature Biotechnol* 2005;**23**:975–82. https://doi.org/10.1038/nbt1114

Lee SB, Bailey JE. Analysis of growth rate effects on productivity of recombinant *Escherichia coli* populations using molecular mechanism models. *Biotechnol Bioeng* 1984;**26**:66–73. https://doi.org/10.1002/bit.260260113

Li F, Yuan L, Lu H *et al.* Deep learning-based k_{cat} predictions enables improved enzyme-constrained model reconstruction. *Nature Cat* 2022a;**5**:662–72.

Li F, Chen Y, Anton M *et al.* GotEnzymes: an extensive database of enzyme parameter predictions. *Nuc Acid Res* 2023;**51**:D583–6. https://doi.org/10.1093/nar/gkac831

Li F, Chen Y, Qi Q *et al.* Improving recombinant protein production by yeast through genome-scale modeling using proteome constraints. *Nature Com* 2022b;**13**:2969. https://doi.org/10.1038/s41467-022-30689-7

Lu H, Li F, Sánchez BJ *et al.* A consensus *S. cerevisiae* metabolic model Yeast8 and its ecosystem for comprehensively probing cellular metabolism. *Nature Com* 2019;**10**:3586. https://doi.org/10.1038/s41467-019-11581-3

Lu H, Li F, Yuan L *et al.* Yeast metabolic innovations emerged via expanded metabolic network and gene positive selection. *Mol Syst Biol* 2021;**17**:e10427. https://doi.org/10.15252/msb.202110427

Nielsen J, Keasling JD. Engineering cellular metabolism. *Cell* 2016;**164**:1185–97. https://doi.org/10.1016/j.cell.2016.02.004

Nielsen J, Petranovic D. Modeling for understanding and engineering metabolism. *QRB Discov* 2025;**6**:e11. https://doi.org/10.1017/qrd.2025.1

Nielsen J. It is all about metabolic fluxes. *J Bacteriol* 2003;**185**:7031–5. https://doi.org/10.1128/JB.185.24.7031-7035.2003

Nielsen J. The power of yeast. *Yeast* 2025;**42**:303–10. https://doi.org/10.1002/yea.70009

Nissen T, Schulze U, Nielsen J *et al.* Flux distributions in anaerobic, glucose-limited continuous cultures of *Saccharomyces cerevisiae*. *Microbiology* 1997;**143**:203–18. https://doi.org/10.1099/00221287-143-1-203

Nookaew I, Jewett MC, Meechai A *et al.* The genome-scale metabolic model *iIN800* of *Saccharomyces cerevisiae* and its validation: a scaffold to query lipid metabolism. *BMC Sys Biol* 2008;**2**:71. https://doi.org/10.1186/1752-0509-2-71

Oftadeh O, Salvy P, Masid M *et al.* A genome-scale metabolic model of *Saccharomyces cerevisiae* that integrates expression constraints and reaction thermodynamics. *Nature Com* 2021;**2**:4790.

Österberg L, Domenzain I, Münch J *et al.* A novel yeast hybrid modeling framework integrating boolean and enzyme-constrained networks enables exploration of the interplay between signaling and metabolism. *PLOS Comp Biol* 2021;**17**:e1008891. https://doi.org/10.1371/journal.pcbi.1008891

Ostergaard S, Olsson L, Johnston M *et al.* Increasing galactose consumption through *Saccharomyces cerevisiae* through metabolic engineering of the *GAL* gene regulatory network. *Nature Biotechnol* 2000;**18**:1283–6. https://doi.org/10.1038/82400

Österlund T, Nookaew I, Nielsen J. Fifteen years of large scale metabolic modeling of yeast: developments and impacts. *Biotechnol Adv* 2012;**30**:979–88. https://doi.org/10.1016/j.biotechadv.2011.07.021

Oura E. Effect of aeration intensity on the biochemical composition of bakers yeast. I. Factors affecting the type of metabolism. *Biotechnol Bioeng* 1974;**16**:1213–25. https://doi.org/10.1002/bit.260160905

Oura E. Biotin and the metabolism of bakers yeast. *Journal of the Institute of Brewing* 1978;**84**:283–7. https://doi.org/10.1002/j.2050-0416.1978.tb03889.x

Patil K, Nielsen J. Uncovering transcriptional regulation of metabolism by using metabolic network topology. *Proc Nat Acad Sci USA* 2005;**102**:2685–9. https://doi.org/10.1073/pnas.0406811102

Qin N, Li L, Wan X *et al.* Increased CO_2 fixation enables high carbon yield production of 3-hydroxypropionic acid in yeast. *Nature Com* 2024;**15**:1591. https://doi.org/10.1038/s41467-024-45557-9

Ramirez-Gaona M, Marcu A, Pon A *et al.* YMDB 2.0: a significantly expanded version of the Yeast Metabolome Database. *Nuc Acid Res* 2017;**45**:D440–5. https://doi.org/10.1093/nar/gkw1058

Sánchez BJ, Zhang C, Nilsson A *et al.* Improving the phenotype predictions of a yeast genome-scale metabolic model by incorporating enzymatic constraints. *Mol Syst Biol* 2017;**13**:935. https://doi.org/10.15252/msb.20167411

Shuler ML, Leung S, Dick CC. A mathematical model for the growth of a single bacterial cell. *Annal N Y Acad Sci* 1979;**326**:35–52. https://doi.org/10.1111/j.1749-6632.1979.tb14150.x

Tsuchiya HM, Fredrickson AG, Aris R. Dynamics of microbial cell populations. *Adv Chem Eng* 1966;**6**:125–206.

Uetz P, Giot L, Cagney G *et al.* A comprehensive analysis of protein-protein interactions in *Saccharomyces cerevisiae*. *Nature* 2000;**403**:623–7. https://doi.org/10.1038/35001009

van Gulik WM, Heijnen JJ. A metabolic network stoichiometric analysis of microbial growth and product formation. *Biotechnol Bioeng* 1995;**48**:681–98.

Väremo L, Nielsen J, Nookaew I. Enriching the gene set analysis of genome-wide data by incorporating directionality of gene expression and combining statistical hypotheses and methods. *Nuc Acid Res* 2013;**41**:4378–91. https://doi.org/10.1093/nar/gkt111

Washburn MP, Wolters D, Yates JR. Large-scale analysis of the yeast proteome by multidimensional protein identification technology. *Nature Biotechnol* 2001;**19**:242–7. https://doi.org/10.1038/85686

Wu K,Liu H, Zhou Y *et al.* Yeast-MetaTwin for systematically exploring yeast metabolism through retrobiosynthesis and deep learning. *Nature Cat* 2026. in press. https://doi.org/10.1038/s41929-026-01523-w

Yu C, Nielsen J. Energy metabolism controls phenotypes by protein efficiency and allocation. *Proc Nat Acad Sci USA* 2019;**116**:17592–7.

Zhang C, Sánchez BJ, Li F *et al.* Yeast9: a consensus genome-scale metabolic model for *S. cerevisiae* curated by the community. *Mol Syst Biol* 2024;**20**:1134–50. https://doi.org/10.1038/s44320-024-00060-7

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