



Multi-Feasibility Variable Selection

Ali Fathi¹, Mohammad Rashid¹, Shayan Ranjbarzadeh¹, *Mojtaba Tefagh¹

¹ Sharif Optimization and Applications Laboratory, Department of Mathematical Sciences, Sharif University of Technology, Tehran, Iran

*Correspondence: mtefagh@sharif.edu

Abstract— Background: In a large number of application areas, it is desirable to obtain sparse solutions. In the case of nonconvex problems, which appear in various circumstances, there is no certain tractable method to find an answer with the minimum number of nonzero elements, where it is usually approximated by a convex problem. In computational biology, one of the well-known problems is the *flux variability analysis*, FBA, in which we find a set of reaction fluxes in a cell consistent with constraint vectors with maximum cell growth.

Aim of the study: In this paper, first, we address five variations of the FBA problem designed in the !Optimizer 2021 competition to solve a more general nonconvex variation of the FBA by having many constraints and using sparse methods. In the first two problems, we seek to find the sparsest vectors, and in the next three problems, our goal is to find the matrix V satisfying some constraints with jointly sparse columns. Then, we provide methods and algorithms to overcome these problems, released by the Panda team as the winner solution in this competition.

Materials and Methods: The main algorithm is weighted l1-norm minimization, in which we solve a weighted l1-norm problem in each iteration, but our weight updating method is different from conventional methods. Using randomness is a new technique in the process of updating weights. We also extend this idea to find jointly sparse matrices. All materials can be found in the Codes and data availability section.

Results: Although the data size for this competition is significantly huge, our linear algorithm spends only a short time finding the near-optimal solution. A benchmark of our main algorithms, which outperforms other methods in speed and accuracy, is provided in the Results section of this paper.

Conclusions: By providing this fast algorithm for the multi-column variations of the FBA, it is now possible to include many different constraint data to solve an FBA problem simultaneously, which helps researchers accurately reconstruct new organisms' metabolic networks in a polynomial time.

Keywords—*Metabolic Networks Optimization, Flux Balance Analysis, Sparse Optimization, Linear Optimization, Separation Method.*

I. Competition Motivations and Background

In inverse optimization models, one wants to learn the parameters of a family of optimization problems in a way that some desirable points would become optimal for their associated instances [14]. In this contest, we consider the following class of parameterized feasibility *linear programs* (LP) extensively studied in the field of *constraint-based reconstruction and analysis* (COBRA)

$$(1) \quad \begin{aligned} & \text{find} && v \\ & \text{subject to} && S^I v = 0, \\ & && l^I \preceq v \preceq u^I, \\ & && I = \{i_1, i_2, \dots, i_k\} \subseteq \{1, 2, \dots, n\}. \end{aligned}$$

where $S = [S_1, S_2, \dots, S_n]$ is an $m \times n$ stoichiometric matrix whose columns S_i characterize the stoichiometry of the biochemical reactions happening inside a cell,

$$l = \begin{bmatrix} l_1 \\ l_2 \\ \vdots \\ l_n \end{bmatrix} \quad \text{and} \quad u = \begin{bmatrix} u_1 \\ u_2 \\ \vdots \\ u_n \end{bmatrix}$$

are lower and upper bound vectors of dimension n as determined by the growth media capacity and thermodynamic constraints, while the subvectors

$$l^I = \begin{bmatrix} l_{i_1} \\ l_{i_2} \\ \vdots \\ l_{i_k} \end{bmatrix} \quad \text{and} \quad u^I = \begin{bmatrix} u_{i_1} \\ u_{i_2} \\ \vdots \\ u_{i_k} \end{bmatrix}$$

as well as the submatrix $S^I = [S_{i_1}, S_{i_2}, \dots, S_{i_k}]$ contain the corresponding entries and columns, respectively.

A metabolic network comprises the collection of all chemical pathways of the metabolism of an organism, *e.g.*, a bacterium. In systems biology, it is observed that if we reconstruct a metabolic network by determining the set of indices I representing its reactions, whether the associated organism is viable or not under circumstances specified by l and u can, to some extent, be predicted by whether LP (1) is feasible or not [10]. Moreover, numerous experiments have demonstrated the consistency of cell viability predictions derived by the feasibility of LP (1) with wet lab measurements [8].

Turning this argument around, one may try to reconstruct a genome-scale metabolic network, given a list of viable and nonviable scenarios, by exploiting the fact that all the solutions to different instances of LP (1) have the same sparsity pattern because they belong to different strains of the same species [5, 6]. Therefore, one may select the candidate I by utilizing methods based on joint group sparsity. Other possible applications of this developed framework include, but are not limited to, signal processing [4], astrophysics [13], photoplethysmography [2, 3], and inverse scattering problem [12, 11].

II. Problem Formulation and Methods

The competition task was broken into five gradually complicating rounds, with the main sparse reconstruction problem at the last round. In this section, we present the problem formulations of each round and provide our methods and algorithms for them, from the first round to the fifth.

Round 1: Steady-state flux distributions

The s_{ij} entry of S represents the molar rate of either consumption (if $s_{ij} \leq 0$) or production (if $s_{ij} \geq 0$) of the metabolite i in the reaction j per unit of dry cell weight. If all the metabolites are in mass balance at specific concentrations, *i.e.*, $Sv = 0$, we say that the metabolic network is in the steady-state condition.

In this round, we were supposed to find the vector v of the rates of reactions subject to the constraints

$$(2) \quad Sv = 0, \quad l^1 \preceq v \preceq u^1,$$

as predicted by *flux balance analysis* (FBA) [7], *i.e.*,

$$(3) \quad \begin{array}{ll} \text{find} & v \\ \text{subject to} & Sv = 0, \\ & l^1 \preceq v \preceq u^1. \end{array}$$

To fulfill this task, we simply used a usual LP optimization code with objective function set to 0, *i.e.*, maximize $0^T v$. Also, the code and the answer produced by the next round could be used here as a feasible vector. Our Julia code for this round, placed in a jupyter notebook file, could be found [here](#).

Round 2: Convex relaxation of cardinality optimization problems

In this round, we were required to find the most sparse flux vector satisfying the constraints

$$(4) \quad Sv = 0, \quad l^1 \preceq v \preceq u^1,$$

by minimizing $\|v\|_0$, *i.e.*,

$$(5) \quad \begin{array}{ll} \text{minimize} & \|v\|_0 \\ \text{subject to} & Sv = 0, \\ & l^1 \preceq v \preceq u^1, \end{array}$$

and the biological intuition behind the theory is to minimize the total enzyme load imposed on the organism [9].

To do so, some different algorithms were tested in this round (such as the dual-density method [?] and five other algorithms), but the most successful one was a method called *weighted l_1 -norm minimization* [15], which we explain here in detail. The weighted algorithm optimizes the following problem:

$$(6) \quad \begin{array}{ll} \text{minimize} & \sum_{i=1}^n w_i |v_i| \\ \text{subject to} & Sv = 0, \\ & l^1 \preceq v \preceq u^1. \end{array}$$

This objective function, the weighted sum of the absolute values of the elements of v , is a generalization of approximating l_0 -norm by l_1 -norm. Substituting w with $\vec{1}_n$, the weighted problem would be simply the l_1 -norm minimization. Also, defining a set of zero indices I_z and putting $w_i \approx \infty$ for each $i \in I_z$, and $w_i = 0$ otherwise, makes this problem to find some sparse solution in which $v_{I_z} = 0$, which implies that this formulation includes all sparse optimization problems of interest by having the appropriate weights. To find the most proper weights, we use an iterative algorithm. The weights are iteratively updated according to the optimal solution v of the previous step, and the current problem with these weights would

be solved to get a new optimal vector v and so it continues. There are many possible update rules for w ; for instance, a choice for converging to a sparse result could be like the following rule:

$$(7) \quad \begin{aligned} w^{(0)} &= \vec{1}_n \\ w_i^{(t+1)} &= \frac{1}{|v_i^{(t)}| + \epsilon} \end{aligned}$$

By this rule, after solving the problem on step t to get $v^{(t)}$, weights for the next iteration are defined inversely related to the magnitude of elements of $v^{(t)}$. If $v_i^{(t)}$ is small for some index i , its corresponding weight in the next iteration, $w_i^{(t+1)}$, is set to a large amount, to try to force it to zero (if possible). The intuition behind it is that if some elements of v are near to 0, reducing them by some ϵ and compensating this reduction by the elements of v with large magnitudes, has probably an insignificant effect on l_1 -norm (and the approximate objective function) but a significant effect on l_0 -norm, which is increased only when some elements of v are set to *absolute zero*. Note that ϵ prevents numerical issues (such as division by zero) and was set to 10^{-5} in our best practice result (we will discuss later that ϵ plays some other roles in the theoretical analysis).

A variation of rule (7) was used in our final solution, named NW4 [16], which is as follows

$$(8) \quad \begin{aligned} w^{(0)} &= \vec{1}_n, \\ w_i^{(t+1)} &= \frac{1 + (|v_i^{(t)}| + \epsilon)^p}{(|v_i^{(t)}| + \epsilon)^{p+1}}, \end{aligned}$$

in which p is some modifiable parameter and was empirically set to 0.8 to get the best result on the competition's data. By setting p to 0, this rule would be the same with rule (7) (up to a constant 2 which makes no change in the objective function).

However, NW4 was not the final update rule we used. As mentioned earlier, this converging-to-sparse rule is just a heuristic and could fall into some local optima. To prevent this issue, we added some randomness to the algorithm in the following way:

$$(9) \quad \begin{aligned} w^{(0)} &= \vec{1}_n \\ w_i^{(t+1)} &= \frac{1 + (|v_i^{(t)}| + \epsilon)^p}{(|v_i^{(t)}| + \epsilon)^{p+1}} \times r_i^3 \\ r_i &\sim \text{Unif}[0, 1] \end{aligned}$$

The distribution of randomness and the way it has appeared in w are set empirically to make the best results.

The mentioned updating rules (7) and (8) are not merely heuristics. The theory behind the weighted algorithm is using some convex (or concave) function to approximate l_0 -norm, called merit function, $\Phi_\epsilon(v)$ such that:

$$(10) \quad \lim_{\epsilon \rightarrow 0} \Phi_\epsilon(v) = \|v\|_0$$

In general, Φ_ϵ is a convex function to make the final problem a convex one. However, Φ_ϵ is sometimes chosen to be a non-convex function, but is then approximated by a linear function afterward (which transforms

the original problem to LP):

$$(11) \quad \Phi_\epsilon(v) \approx \Phi_\epsilon(v^{(t)}) + \nabla \Phi_\epsilon(v^{(t)})^T \cdot (v - v^{(t)})$$

For instance, one famous choice for approximating l_0 -norm is by the logarithmic function

$$(12) \quad \Phi_\epsilon(v) = \sum_{i=1}^n \log(|v_i| + \epsilon),$$

which satisfies property (10). Approximating this Φ_ϵ with a linear function results in the following weights

$$(13) \quad w^{(t+1)} = \nabla \Phi_\epsilon(v^{(t)}) = \left(\frac{1}{|v_1^{(t)}| + \epsilon}, \dots, \frac{1}{|v_n^{(t)}| + \epsilon} \right)^T,$$

which is exactly rule (7). The merit function Φ_ϵ for NW4 rule has a few variations which could be found at [16], and we don't include the details here.

Round 3: Exact multi-feasibility variable selection

The goal of this round, is to find the unknown matrix V with jointly sparse columns which satisfies the following constraints

$$(14) \quad SV = 0, \quad L \preceq V \preceq U.$$

Joint sparsity for an arbitrary set of sparse vectors means that all members of the set share a common sparse support set, *i.e.*,

$$(15) \quad \begin{aligned} & \text{minimize} \quad \|V\|_{2,0} \\ & \text{subject to} \quad SV = 0, \\ & \quad \quad \quad L \preceq V \preceq U, \end{aligned}$$

where the mixed norm is defined as follows

$$(16) \quad \|X\|_{p,q} = \|(\|x'_1\|_p, \|x'_2\|_p, \dots, \|x'_m\|_p)\|_q.$$

To the end of this paper, we assume that $x_1^T, x_2^T, \dots, x_m^T$ are the rows of X in this definition, but some authors use another convention of considering the columns instead of rows. Apart from the difference in notation, the two definitions become clearly equivalent to one another if applied to the transpose matrix.

To solve this problem, we approximated $l_{2,0}$ -norm with $l_{1,1}$ -norm

$$(17) \quad \begin{aligned} & \text{minimize} \quad \|V\|_{1,1} = \sum_{j=1}^c \|v_j\|_1 \\ & \text{subject to} \quad Sv_j = 0 \quad \forall j, \\ & \quad \quad \quad l_j \preceq v_j \preceq u_j \quad \forall j, \end{aligned}$$

in which c is the number of columns in V and v_j denotes the j -th column of V .

To justify this approximation, first, we see that in $\|V\|_{p,0}$, the p -norm of rows together with the l_0 -norm, determines whether a row is all-zero or not. Both $p = 1$ and $p = 2$ (and other values for p) fulfill this job. In fact, we have exact equality, *i.e.*, $\|V\|_{1,0} = \|V\|_{2,0}$. Afterward, l_0 -norm in $\|V\|_{1,0}$ is replaced with l_1 -norm to get $\|V\|_{1,1}$. To emphasize, it could be mentioned that the structure of rows and columns in $l_{2,0}$ -norm is not maintained well, but as discussed, this approximation could be better understood when viewed as the combination of two steps, *i.e.*, relaxing l_2 -norm by l_1 -norm and then l_0 -norm by l_1 -norm. Besides, we will replace l_1 -norm approximation by a similar weighted sum as in (6) to maintain the l_0 -norm structure more precisely. Also, the successes of these approximations are demonstrated in practice.

Problem (17) is LP and can be consequently solved efficiently. However, there are some other advantages to this form. Namely, this problem could be separated into c independent problems

$$(18) \quad \begin{aligned} & \text{minimize} && \|v_j\|_1 \\ & \text{subject to} && Sv_j = 0, \\ & && l_j \preceq v_j \preceq u_j, \end{aligned}$$

for $1 \leq j \leq c$. Separation helps in the case that if the solver is super-linear (e.g., $O(n^{1+\delta})$ for an arbitrary δ), having c distinct problems of size n would be solved faster than a problem of size $c \times n$.

As mentioned before, we need to make some changes to (17) to keep the l_0 -norm structure in the $l_{2,0}$ -norm. It could be done by applying the weighted algorithm, exactly like (6). The modified problem would be as the following

$$(19) \quad \begin{aligned} & \text{minimize} && \sum_{i=1}^n w_i \|v'_i\|_1 \\ & && = \sum_{j=1}^c (\sum_{i=1}^n w_i |(v_j)_i|) \\ & \text{subject to} && Sv_j = 0 \quad \forall j, \\ & && l_j \preceq v_j \preceq u_j \quad \forall j, \end{aligned}$$

in which v'_i denotes the i -th row of V . As the problem has remained linear, it could be separated again as in the following:

$$(20) \quad \begin{aligned} & \text{minimize} && \sum_{i=1}^n w_i |(v_j)_i| \\ & \text{subject to} && Sv_j = 0, \\ & && l_j \preceq v_j \preceq u_j, \end{aligned}$$

The weights are updated just the same as in the algorithm for round 2, but by substituting $\|v_i^{(t)}\|_2$ or $\|v_i^{(t)}\|_1$ instead of $|v_i^{(t)}|$. For example, for rule (7):

$$(21) \quad \begin{aligned} w^{(0)} &= \vec{1}_n \\ w_i^{(t+1)} &= \frac{1}{\|v_i^{(t)}\|_2 + \epsilon} \end{aligned}$$

The code for this round is available [here](#).

Round 4: Multi-feasibility variable selection in the presence of error

In this round, it is requested to find the unknown matrix V with jointly sparse columns when the matrix SV is constrained to have jointly sparse rows and $L \preceq V \preceq U$, i.e.,

$$(22) \quad \begin{aligned} & \text{minimize} && (\|V\|_{2,0}, \|(SV)^T\|_{2,0}) \\ & \text{subject to} && L \preceq V \preceq U. \end{aligned}$$

Here in fact, this multi-criterion objective is meant to be interpreted as follows [1]:

$$(23) \quad \begin{aligned} & \text{minimize} && \|V\|_{2,1} + \lambda \|(SV)^T\|_{2,1} \\ & \text{subject to} && L \preceq V \preceq U. \end{aligned}$$

In other words, it indicates that freeing every $Sv_j = 0$ equation would make a λ penalty. Similar to the previous round, weighted algorithm and separation are utilized to solve this multi-columns problem,

but this time some $Sv_j = 0$ equations are freed:

$$(24) \quad \begin{aligned} & \text{minimize} && \sum_{i=1}^n w_i \|v'_i\|_1 \\ & \text{subject to} && Sv_j = 0 \quad \forall j \in J, \\ & && L \preceq V \preceq U, \end{aligned}$$

First, we calculate c variables d_1, \dots, d_c to determine a proper set J , which is meant to represent the constraints to be satisfied:

$$(25) \quad \begin{aligned} d_j = & (\min \|v_j\|_1 \text{ s.t. } Sv_j = 0 \text{ and } l_j \preceq v_j \preceq u_j) \\ & - (\min \|v_j\|_1 \text{ s.t. } l_j \preceq v_j \preceq u_j) \end{aligned}$$

Here d_j is a heuristic of the advantage gained by freeing column j , measured by the fall in l_1 -norm. Then, if this proxy of benefit suggests an improvement more than λ , we would free its corresponding constraint, *i.e.*,

$$(26) \quad J = \{j \mid d_j < \lambda\}.$$

Every other detail is exactly similar to the previous round. The code for this round is available [here](#).

Round 5: Multi-feasibility/infeasibility variable selection

Making some small changes in the previous task, in this round we are going to solve (15) with the additional constraint that at most K columns of SV may have nonzero entries, *i.e.*,

$$(27) \quad \begin{aligned} & \text{minimize} && \|V\|_{2,0} \\ & \text{subject to} && \|(SV)^T\|_{2,0} \leq K, \\ & && L \preceq V \preceq U. \end{aligned}$$

To address the importance and the biological intuition of this formulation, suppose that \tilde{L} and \tilde{U} have t columns denoted by $\tilde{l}_1, \tilde{l}_2, \dots, \tilde{l}_t$ and $\tilde{u}_1, \tilde{u}_2, \dots, \tilde{u}_t$, respectively. Consider the following feasibility problems for $1 \leq k \leq t$

$$(28) \quad \begin{aligned} & \text{find} && v \\ & \text{subject to} && S^I v = 0, \\ & && \tilde{l}_k^I \preceq v \preceq \tilde{u}_k^I, \end{aligned}$$

where I is defined as follows

$$(29) \quad I = \{i \mid \max_j |V_{ij}| > 0\}.$$

According to the biological model, we know that these feasibility problems should be infeasible for the ground truth I , which represents the underlying metabolic network, and the lower and upper bounds \tilde{L} and \tilde{U} , which represent the different growth environments or other conditions.

Therefore, we will validate each solution V by the percentage of the infeasible instances of (28) for the corresponding I . Note that, solving (27) helps to get a better score since we know *a priori* that the smaller the set of indices I , the higher the probability of infeasibility for each LP of the form (28).

Our proposed method to solve (27) is similar to the one in round 4. The problem that we solve is as follows:

$$(30) \quad \begin{aligned} & \text{minimize} && \sum_{i=1}^n w_i \|v'_i\|_1 \\ & \text{subject to} && Sv_j = 0 \quad \forall j \in J, \\ & && L \preceq V \preceq U. \end{aligned}$$

Again, the heuristic coefficients are defined similarly:

$$(31) \quad \begin{aligned} d_j = & (\min \|v_j\|_1 \text{ s.t. } Sv_j = 0 \text{ and } l_j \preceq v_j \preceq u_j) \\ & - (\min \|v_j\|_1 \text{ s.t. } l_j \preceq v_j \preceq u_j) \end{aligned}$$

This time, we free the K most advantageous columns, *i.e.*,

$$(32) \quad J = \{j \mid d_j < K\text{-th maximum coefficient in } d_1, \dots, d_c\}$$

The code for this round is available [here](#).

III. Preprocessing and Data manipulations

To make our codes more efficient and faster, some data modifications have been used. We review the most important ones of them:

Ignoring non-zero elements:: In round 2, if for some elements of v like v_i we have $0 < l_i (\leq v_i)$ or $0 > u_i (\geq v_i)$, then it is intrinsically impossible to have $v_i = 0$. Therefore, it is mishandling to try to make it zero (as the effort of increasing sparsity). Thus, v_i could be taken out from the sparsity objective function to give the model more freedom over these elements. The same matter exists in rounds 3, 4, and 5, where we have $L \preceq V \preceq U$ and if there is any element $L_{i,j} > 0$ or $U_{i,j} < 0$, as it forces $V_{i,j} \neq 0$, it would be impossible for that row i to play a role in joint-sparsity and therefore, this row could be taken out from the joint-sparsity objective function. In a more formal way:

$$(33) \quad \forall i [\exists j [(L_{i,j} > 0) \vee (U_{i,j} < 0)] \Rightarrow w_i = 0]$$

Setting definite elements:: If for some elements we have $l_i = u_i$ ($L_{i,j} = U_{i,j}$ in the last rounds), v_i ($V_{i,j}$) would be set to that definite value too, and there is no need to contain that variable in our optimization problem. In the case of the data for this competition, this equaled value has always been 0 (*i.e.*, $l_i = 0 = u_i$ or $L_{i,j} = 0 = U_{i,j}$), and setting v_i ($V_{i,j}$) to zero, is like deleting those variables from the problem without any further effort. These deletions have made the size of the problems in this competition significantly smaller and have caused the running time to drop considerably.

Sparsity lower-bound analysis:: As mentioned, those rows in which $L_{i,j} > 0$ or $U_{i,j} < 0$ induce $V_{i,j} \neq 0$ and therefore define a lower bound for $\|V\|_{2,0}$. This lower bound could be modified. Let the algorithm result be \bar{v} , and I_{nz} be the set of indices of all non-zero elements of \bar{v} . Roughly speaking, it is expected that for most of those $i \in I_{nz}$, forcing v_i to zero would cause the problem to get infeasible. As $|I_{nz}|$ is comparatively small, we can test it by checking $|I_{nz}|$ feasibility problems. If knocking-out $i \in I_{nz}$ made the problem infeasible, we can take $w_i = 0$ and increase our lower bound. Doing so in the competition has ensured us that our final results are adequately close to optimal, as the distance between our $\|V\|_{2,0}$'s and the calculated lower bounds have been satisfactorily small.

IV. Results

In this [link](#) created by the organizer committee, you can find 7 datasets for each round of the competition. These datasets consist of the metabolic models of the organisms Escherichia Coli, Salmonella, Cricetulus Griseus, Phaeodactylum Tricornutum, Mus Musculus, Homo Sapiens, and the BiGG Universal Model, increasing by size respectively. In the actual competition, 3 of these datasets for each round

were requested to be worked on. The performance of our codes on this comprehensive 7×5 datasets are summarized in the table (I).

Table I. The data and the benchmarks for our algorithms

Round	Dataset	m	n	c	s.c.	Running Time
1	E. Coli	72	95	1	-	0.119 ± 0.270 ms
	Salmonella	2436	3357	1	-	7.563 ± 3.607 ms
	P. Tricornutum	2172	4456	1	-	10.16 ± 3.57 ms
	C. Griseus	4456	6663	1	-	25.44 ± 9.85 ms
	Mus Musculus	8404	13094	1	-	72.02 ± 33.97 ms
	Homo Sapiens	8399	13543	1	-	71.92 ± 32.04 ms
	Universal Model	15638	28301	1	-	0.161 ± 0.003 s
2	E. Coli	72	95	1	8	3.221 ± 0.505 ms
	Salmonella	2436	3357	1	5	47.15 ± 4.25 ms
	P. Tricornutum	2172	4456	1	93	0.125 ± 0.007 s
	C. Griseus	4456	6663	1	95	0.193 ± 0.012 s
	Mus Musculus	8404	13094	1	101	0.428 ± 0.027 s
	Homo Sapiens	8399	13543	1	106	0.482 ± 0.040 s
	Universal Model	15638	28301	1	514	1.055 ± 0.042 s
3	E. Coli	72	95	20	9	0.249 ± 0.005 s
	Salmonella	2436	3357	20	53	14.96 ± 0.15 s
	P. Tricornutum	2172	4456	50	592	70.33 ± 39.00 s
	C. Griseus	4456	6663	30	329	89.41 ± 3.47 s
	Mus Musculus	8404	13094	50	422	294 ± 3 s
	Homo Sapiens	8399	13543	100	564	640^* s
	Universal Model	15638	28301	200	2820	2380^* s
4	E. Coli	72	95	20	9	0.283 ± 0.008 s
	Salmonella	2436	3357	20	53	17.28 ± 0.16 s
	P. Tricornutum	2172	4456	50	592	78.66 ± 39.01 s
	C. Griseus	4456	6663	30	329	97.46 ± 3.47 s
	Mus Musculus	8404	13094	50	422	336 ± 4 s
	Homo Sapiens	8399	13543	100	564	741^* s
	Universal Model	15638	28301	200	2820	3032^* s
5	E. Coli	72	95	20	9	0.234 ± 0.023 s
	Salmonella	2436	3357	20	47	14.00 ± 0.26 s
	P. Tricornutum	2172	4456	50	544	60.95 ± 21.36 s
	C. Griseus	4456	6663	30	306	61.95 ± 1.01 s
	Mus Musculus	8404	13094	50	383	378 ± 121 s
	Homo Sapiens	8399	13543	100	528	584^* s
	Universal Model	15638	28301	200	2653	3124^* s

In this table, m is the number of the metabolites (*i.e.*, the number of rows in the S), n is the number of the reactions (*i.e.*, the number of columns in the S or the number of rows in the V), and c is the number of columns in the V , L or U (which is 1 for the case that v is a vector in first two rounds). The sparsity

score, $s.c.$, is equal to $\|v\|_1$ for round 2 and is equal to $\|V\|_{2,0}$ for rounds 3, 4, and 5. The gained score of each round in the competition has had a strong relationship with this parameter. Note that as round 1 is a feasibility problem, sparsity means nothing there.

In the datasets for round 4, the parameters λ are 7.125, 251.775, 133.68, 333.15, 392.82, 203.145, 212.2575, respectively, which force a huge penalty for releasing $Sv_j = 0$ constraints and, therefore, have resulted in the same result with round 3 according to our heuristic (25), which have made the set J in (26) to contain all the columns for all datasets. In the datasets for round 5, the K parameters have been 4, 4, 10, 6, 10, 20, 40, respectively.

In our performance testing, the number of the iterations in the weighted algorithm has been set to 20 for the round 2, 10 for the first six datasets in the rounds 3, 4, and 5, and 5 for the BiGG universal model in the latter three rounds. Benchmarking has been done by the Julia library **BenchmarkTools**, using 10000 samples or any less number of samples during 300 seconds limit of running (containing at least one sample). The aggregated results in the table are included in the $mean \pm std$ s/ms format, or the $time*s$ format for the huge datasets on which only one sample has been taken.

All codes have been run on a home MacBook Pro PC with a 2.2 GHz Quad-Core Intel Core i7 processor, 16 GB 1600 MHz DDR3 memory, and Intel Iris Pro 1536 MB graphics.

Additionally, a benchmarking for the preprocessing ideas, run on the round 1 datasets, is reported in the table (II):

Table II. The benchmarking for our preprocessing ideas

Dataset	Running Time - No Process	Running Time - Processed
E. Coli	0.37 ± 0.65 ms	0.119 ± 0.270 ms
Salmonella	0.354 ± 0.009 s	7.563 ± 3.607 ms
P. Tricornutum	0.410 ± 0.013 s	10.16 ± 3.57 ms
C. Griseus	1.273 ± 0.012 s	25.44 ± 9.85 ms
Mus Musculus	4.758 ± 0.160 s	72.02 ± 33.97 ms
Homo Sapiens	4.811 ± 0.043 s	71.92 ± 32.04 ms
Universal Model	22.21 ± 0.17 s	0.161 ± 0.003 s

which shows a significant improvement to the running time.

V. Codes and data availability

Each round has contained three turns, which are three datasets to be judged. The Julia codes, written in Jupyter-notebook for each round (.ipynb file) and the data for all turns (folders T1, T2, and T3) for each round are provided in these URLs:

- Round 1: https://github.com/Optimizer-Competition-Pandas/Round_1
- Round 2: https://github.com/Optimizer-Competition-Pandas/Round_2
- Round 3: https://github.com/Optimizer-Competition-Pandas/Round_3
- Round 4: https://github.com/Optimizer-Competition-Pandas/Round_4
- Round 5: https://github.com/Optimizer-Competition-Pandas/Round_5

Note that the **MathOptInterface** package is used for parsing the optimization problems, and the **GLPK** is used as the linear programming solver.

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