Application of G-Inverse in Search of Reactions Feasible to the Metabolism of a Species

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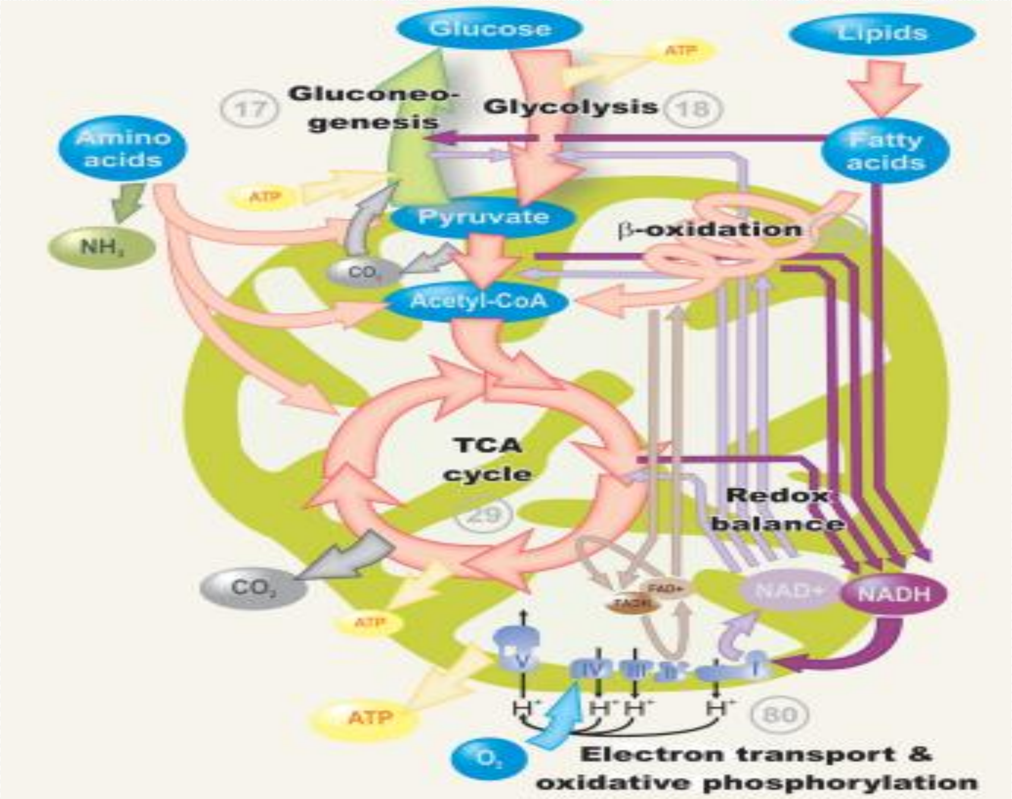
Metabolism



- Metabolism comprises the entire set of chemical reactions that occur in a living organism
- It allows the organism to reproduce, develop, maintain its structure and respond to the environment

Understanding metabolism: A step towards understanding cellular behavior

Analysis of metabolism:

- Construction of a network model and topological analysis
- Set of all reaction would help

  Kinetic Modeling

  Structural Modeling

For different kind of analysis, mass conservation principle should be maintained

All the reactions should be stoichiometrically balanced

What are the problems with databases?

- Inconsistency in Databases
  - Duplication of Reactions
  - Missing reactions
  - Stoichiometrically incorrect reactions
- Using public Databases, serious challenges remain
  - Testing accuracy of all reactions manually is impractical
- Error in one Reaction can turn whole model erroneous

This approach can rid off most of the above

Stoichiometry

- Reaction stoichiometry describes the quantitative relationships among substances as they participate in chemical reactions

- Stoichiometry can be used to calculate quantities such as the amount of products that can be produced with given reactants and percent yield (the percentage of the given reactant that is made into the product)

  i.e. if no residues remains then yield is 100%

- Simply it deals with 'conservation of mass' i.e. if in a chemical reaction mass of reactants is not equal to product

  then it is a 'Stoichiometrilly Incorrect' reaction

Unbalanced Reactions

	E.Coli	M.Tuberculosis	H.pylori
KEGG	4.6%	2.6%	4.1%
BioCyc	0.6%	1.4%	1.5%

Stoichimetrically Incorrect Reaction

$$N_2 + H_2 \rightarrow NH_3$$

Table of Mass

Reactant Elements	Product Elements
N 2	N 1
H 2	H 3

This reaction is unbalanced by both N & H

After balancing…

$$N_2 + 3H_2 = 2\ NH_3$$

Now stoichiometry describe exactly one molecule of nitrogen (N2) reacts with three molecules of hydrogen (H2) to produce two molecules of ammonia

Balancing Chemical Reactions

$$Al + O_2 \rightarrow Al_2O_3$$

We can balance this equation easily

1st try to make mass of each molecule in either side equal

$$2Al + 1.5\ O_2 \rightarrow Al_2O_3$$

This fraction part is horrible thing

Now multiplying each side by 2 we get

$$4Al + 3O_2 = 2Al_2O_3$$

If the equation is like this

$$C_{14}H_{14}O_4 + C_{21}H_{30}N_7O_{17}P_3 + O_2 \rightarrow C_{11}H_6O_3 + C_{21}H_{29}N_7O_{17}P_3 + C_3H_6O + H_2O$$

The task is not easy….

Let us take an example from Database

Reaction No. “RXN-8386”

"CPD-8191" + "NADPH" + "OXYGEN-MOLECULE" -> "PHYTOALEXIN-CMPD" + "NADP" + "ACETONE" +"WATER"

$$C_{14}H_{14}O_4+C_{21}H_{30}N_7O_{17}P_3+O_2 \text{-->} C_{11}H_6O_3+C_{21}H_{29}N_7O_{17}P_3+C_3H_6O+H_2O$$

Table of Mass

Reactant Elements	Product Elements
C 35	C 35
H 44	H 43
O 23	O 22
N 7	N 7
P 3	P 3

This reaction is unbalanced by H & O

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How to Solve?

To solve the problem concept of G-inverse and its properties are used

What is G-inverse?

For a mxn matrix A, its G-inverse is an nxm matrix X satisfying certain Properties

$$A\,XA = A$$

$$XA\,X = X$$

$$(A\,X)^T = A\,X$$

$$(XA)^T = XA$$

All properties are satisfied with Moore-Penrose Inverse

Solving with Generalized Inverse:

The purpose of constructing a generalized inverse is to obtain a matrix that can serve as the inverse in some sense for a wider class of matrices

Why Generalized Inverse used here?

- Usual inverse matrix is defined only for non-singular square matrix
- Most Reaction matrices constructed from chemical equations are non square & they may be a singular one

Feasibility of Reaction

Let a reaction Matrix A_{mn}

Calculate the Rank of A_{mn}

Rank equal to Column , the reaction is infeasible

Rank equal to Column-1 , reaction is unique

Rank <=column-2, Multiple reaction can be possible

Decisions & Computational steps

Moore-Penrose inverse is calculated as X_{nm} using iterative method

Solution matrix is $S_{nn}=I_{nn}-X_{nm}A_{mn}$

Columns elements of S_{nn} holds the fractions of the coefficients

With suitable multiplier we can find the actual coefficients

Computational approach from the beginning

…… Now the task becomes Easy

Examples from Database

Unique Solution

Reaction No.”RXN-7712”

2-KETOGLUTARATE + CARBON-DIOXIDE" + NAD(P)H -> threo-d(s)-iso-citrate+ NAD(P)

$$C_5H_6O_5+CO_2+C_{21}H_{30}N_7O_{17}P_3 \rightarrow C_6H_8O_7+C_{21}H_{29}N_7O_{17}P_3$$

Table of Mass

Reactant Elements	Product Elements
C 27	C 27
H 36	H 37
O 24	O 24
N 7	N 7
P 3	P 3

This reaction is unbalanced by H

Examples from Database

Reaction Matrix:

A=

$C_5H_6O_5$	CO_2	$C_{21}H_{30}N_7O_{17}P_3$	$C_6H_8O_7$	$C_{21}H_{29}N_7O_{17}P_3$	
5	1	21	-6	-21	C
6	0	30	-8	-29	H
5	2	17	-7	-17	O
0	0	7	0	-7	N
0	0	3	0	-3	P

Rank of the reaction matrix is 4=column-1, so the reaction is unique

$$C_5H_6O_5+CO_2+2C_{21}H_{30}N_7O_{17}P_3=C_6H_8O_7+2C_{21}H_{29}N_7O_{17}P_3$$

Examples from Database

With multiple solutions

Reaction No. “RXN-8386”

$C_{14}H_{14}O_4+C_{21}H_{30}N_7O_{17}P_3+O_2 \dashrightarrow C_{11}H_6O_3+C_{21}H_{29}N_7O_{17}P_3+C_3H_6O+H_2O$

Table of Mass:

The reaction matrix is:

A=

	$C_{14}H_{14}O_4$	$C_{21}H_{30}N_7O_{17}P_3$	O_2	$C_{11}H_6O_3$	$C_{21}H_{29}N_7O_{17}P_3$	C_3H_6O	H_2O
C	14	21	0	-11	-21	-3	0
H	14	30	0	-6	-29	-6	-2
O	4	17	2	-3	-17	-1	-1
N	0	7	0	0	-7	0	0
P	0	3	0	0	-3	0	0

Rank of the matrix is 4 so multiple solutions are possible

$962C_{14}H_{14}O_4+1112C_{21}H_{30}N_7O_{17}P_3+1188O_2=1079C_{11}H_6O_3+1112C_{21}H_{29}N_7O_{17}P_3+533C_3H_6O+2454H_2O$

&

$40C_{14}H_{14}O_4+32C_{21}H_{30}N_7O_{17}P_3+17O_2=37C_{11}H_6O_3+32C_{21}H_{29}N_7O_{17}P_3+51C_3H_6O+32H_2O$

Examples from Database

Guessing the solution of infeasible reaction

Reaction No.:“1.17.1.2-RXN”

"|delta(3)-isopentenyl-pp|" + "|NAD(P)|" + "WATER" -> "E-4-HYDROXY-3-METHYLBUT-2-EN-1-YL-DIPH" + "|NAD(P)H|"

$$C_5H_{12}O_7P_2 + C_{21}H_{29}N_7O_{17}P_3 \rightarrow C_5H_{12}O_8P_2 + C_{21}H_{30}N_7O_{17}P_3$$

Table of Mass

Reactant Element	Product Elements
C 26	C 26
H 41	H 42
O 24	O 25
P 5	P 5
N 7	N 7

This Reaction is unbalanced by H and O

Examples from Database

$C_5H_{12}O_7P_2 + C_{21}H_{29}N_7O_{17}P_3 \rightarrow C_5H_{12}O_8P_2 + C_{21}H_{30}N_7O_{17}P_3$

Reaction Matrix:

$$A = \begin{bmatrix} & C_5H_{12}O_7P_2 & C_{21}H_{29}N_7O_{17}P_3 & C_5H_{12}O_8P_2 & C_{21}H_{30}N_7O_{17}P_3 \\ & 5 & 21 & -5 & -21 \\ & 12 & 29 & -12 & -30 \\ & 7 & 17 & -8 & -17 \\ & 2 & 3 & -2 & -3 \\ & 0 & 7 & 0 & -7 \end{bmatrix}$$

Rank of its reaction matrix is equal to its column so the reaction is not feasible with present set of reactants and products

We can suggest some feasible reactions

Examples from Database

Adding "WATER" we can balance it

$H_2O+C_5H_{12}O_7P_2+2C_{21}H_{29}N_7O_{17}P_3=C_5H_{12}O_8P_2+2C_{21}H_{30}N_7O_{17}P_3$

This reaction is unique as now the rank of its reaction matrix is column-1

The same reaction shown in previous slide can be balanced by adding "OXYGEN" and "PROTON"

$O_2+H+2C_5H_{12}O_7P_2+C_{21}H_{29}N_7O_{17}P_3=2C_5H_{12}O_8P_2+C_{21}H_{30}N_7O_{17}P_3$

Feasible reactions can be verified experimentally

Examples from Database

Another example

"RXN66-316":

CPD-4579+NAD(P)H+OXYGEN-MOLECULE -> CPD-4580+NAD(P)+**2**WATER

$C_{28}H_{46}O_2+C_{21}H_{30}N_7O_{17}P_3+O_2 \rightarrow C_{28}H_{44}O_2+C_{21}H_{29}N_7O_{17}P_3+2H_20$

Table of Mass

Reactant Elements	Product Elements
C 49	C 49
H 76	H 77
O 21	O 21
N 7	N 7
P 3	P 3

This reaction is still unbalanced by H

We found if the coefficient of water is **2**

Then the balanced equation should be

$C_{28}H_{46}O_2+2C_{21}H_{30}N_7O_{17}P_3+O_2=C_{28}H_{44}O_2+2C_{21}H_{29}N_7O_{17}P_3+2H_20$

Implications

- Identify the reaction where mass is conserved or not
- Identify the reaction which cannot be balance with present set of reactants & products

  -Experimentalist can look on this to identify the missing reactants and/or products

  -With the help of known chemical space(known biochemical molecules) one can try to identify the possible missing molecule
- One can also balance the unbalanced reaction(if feasible)
- This method can suggest multiple solution of reactions which satisfy the condition Rank<=Column-2

Ultimately help in correct modeling

Thank You..

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