Constraint-Based Workshops

4. GAMS & Sensitivity Analysis
January 17th, 2008
Optimization:

Used when multiple solutions satisfy your equations.
FBA Optimization Problem Statement

- **Objective Function**: A function that is maximized or minimized to identify optimal solutions

- **Constraints**: Place limits on the allowable values the solutions can take on.

Maximize: \( c \cdot v \)

Such that \( S \cdot v = 0 \)

\( LB \leq v \leq UB \)
GAMS Demo License Limits

- MAX CONSTRAINTS  300
- MAX VARIABLES    300
- MAX NON ZERO ELEMENTS  2000
- MAX NON LINEAR ELEMENTS  1000
- MAX DISCRETE VARIABLES  50
GAMS Primer

1. Sets: used as indices in the algebraic equations defining models
2. Parameters: matrices, vectors, or scalars used in the model equations
3. Variables: the variables that are being solved for.
4. Equations: these are the constraints and objective function that define the model
5. Models: set of equations
1. Sets

**Format**

Sets

```
setname1 | index11,index12,... |
setname2 | index21,index22,... |
```

**Example**

Sets

```
i /metabA,metabB/  
j /v1,b1,b2/;
```
2. Parameters

Format
Parameters
scalarname /value/
vectorname(setname1) /index11 value,.../
matrixname(setname1,setname2)
/index11.index21 value
/index12.index22 value... /;

**If you don’t specify and entry the program assumes it is zero

Example
Parameters
Vmax /100/
S(i,j)
/metabA.v1 -1
metabB.v1 1
metabA.b1 1
metabB.b2 -1/;
4. Variables

Format

**Variables**

`Variable1name1`

`Variable1name2(setname);`

Example

**Variables**

V (j)

`objvalue;`

**SIMPLE BOUNDS:**

Constraints on variables can be applied directly to the variables, for example

`V.lo(j)=0;` all elements of V must be ≥ 0

`V.up(j)=Vmax;` all elements of V must be ≤ the parameter Vmax

`V.fx('v1')=0;` The element of V corresponding to v1 is fixed to 0
5. Equations

Format
Equations
Equation1 give description
Equation2(setname) give description;

Equation1.. Give function;
Equation2(setname).. Give function;

Example Equations
MassBalance(i) mass balances around A and B
ObjectiveFunction function to be optimized;

MassBalance(i).. sum(S(i,j)*V(j)) =e= 0;
ObjectiveFunction.. objvalue=e=V('v1');

=e= means =
=\leq= means \leq
=\geq= means \geq
6. Model and Solve Statements

Format
\textbf{model} \textit{modelname} /all/;

or
\textbf{model} \textit{modelname} /list of equations/;

Example
\textbf{model} FBA /all/;

or
\textbf{model} FBA /MassBalance,ObjectiveFunction/;

To solve the model:
solve \textit{modelname} using lp maximizing \textit{objectivevariable};

Example:
solve FBA using lp maximizing objvalue
An Illustrative Example

Consider two variables A and B, which are the amount of toy cars and trucks you can produce.

Do to resource limitations you can make no more than 60 cars a day and no more than 50 trucks a day.

\[ 0 \leq A \leq 60 \]
\[ 0 \leq B \leq 50 \]

You are also limited by shipping such that the number of cars plus twice the number of trucks must be less than 150.

\[ A + 2B \leq 150 \]

You can sell the toys at $20/car and $30/truck your earnings (Z) are given by:

\[ Z = 20A + 30B \]
Graphical Representation of Feasible Solution Space

3 Constraints:
0 ≤ A ≤ 60
0 ≤ B ≤ 50
A + 2B ≤ 150
A + 2B = 150

Feasible Solution Space
Graphical Representation of the Objective Function: $Z = 20A + 30B$

Feasible Solution Space

- Z = 2550
- Z = 2500
- Z = 1500

Optimal value within feasible set
Consider two variables A and B, which are the amount of toy cars and trucks you can produce.

Do to resource limitations you can make no more than 60 cars a day and no more than 50 trucks a day.
* 0 <= cars <= 60
* 0 <= trucks <= 50

You are also limited by shipping such that the number of cars plus twice the number of trucks must be less than 150.
* cars + 2*trucks <= 150

You can sell the toys at $20/car and $30/truck your earnings (E) are given by:
* profit = 20*cars + 30*trucks

Variables:
cars
trucks
profit;

Equations:
constraint1
constraint2
constraint3
earnings;

constraint1.. cars=1=60;
constraint2.. trucks=1=50;
constraint3.. cars+2*trucks=1=150;
earnings.. profit=120*cars+30*trucks;
cars.lo=0;
trucks.lo=0;

model production /all/;
solve production using lp maximizing profit;
Your LST File has all Results

<table>
<thead>
<tr>
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<th>0.016 SECONDS</th>
<th>3 Mb WIN225-148 May 29, 2007</th>
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<tr>
<td>DGAMS Rev 148</td>
<td>x86/MS Windows</td>
<td>01/16/08 15:21:40 Page 5</td>
</tr>
<tr>
<td>General Algebraic Modeling System</td>
<td>Solution Report</td>
<td>SOLVE production Using LP From line 34</td>
</tr>
</tbody>
</table>

**SOLVE SUMMARY**

- **MODEL**: production
- **TYPE**: LP
- **SOLVER**: CPLEX
- **OBJECTIVE**: profit
- **DIRECTION**: MAXIMIZE
- **FROM LINE**: 34

- **SOLVER STATUS**: 1 NORMAL COMPLETION
- **MODEL STATUS**: 1 OPTIMAL
- **OBJECTIVE VALUE**: 2550.0000

Value of Obj. Function (ie. profit)

Solver found an optimal solution
### Constraint and Variable Values

<table>
<thead>
<tr>
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<th>LEVEL</th>
<th>UPPER</th>
<th>MARGINAL</th>
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<tr>
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</table>

**NOTE:** A dot means that the value is zero.
Sensitivity Analysis

Shadow Prices
Reduced Costs
FBA Optimization Problem Statement

• Objective Function: A function that is maximized or minimized to identify optimal solutions

\[ \text{Maximize: } c \cdot v \]

\[ \text{Such that } S \cdot v = 0 \]
\[ \text{LB } \leq v \leq \text{UB} \]

• Constraints: Place limits on the allowable values the solutions can take on.
Shadow Prices

- Tells you how the value for the objective function at the optimal solution would change if you changed the boundaries on the constraints.

Maximize \[ Z = c \cdot v \]
Such that \[ S \cdot v = b \]
\[ v \leq UB \]
\[ v \geq LB \]

Shadow Price \((i) = \frac{dZ}{db_i}\)
Shadow Prices (1 per constraint)

$SP_1 = 5 \rightarrow$ This means if we lower $b_1$ from 60 to 59, the profit would go down to $2550 + (59-60) \times SP_1$ and the solution would change (cars & trucks).

$SP_2 = 0 \rightarrow$ This means if we changed $b_2$ then the profit would change and neither would the solution (cars & trucks), exception being if you made drastic changes to $b_2$. 

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<td>VAR trucks</td>
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<td>VAR profit</td>
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<td>2550.000</td>
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</table>
Graphical Representation of the Objective Function: $Z = 20A + 30B$

Trucks

Cars

Feasible Solution Space

This constraint can move, and it won’t affect the optimal solution

Z = 2550
Reduced Costs

- Tells you how the objective function coefficients ($c_j$) would have to change so that a variable ($v_j$) which is currently zero in the optimal solution, would be non-zero in the new optimal solution using the new values for $c$.
- Or, tells you how the value for the objective function at the optimal solution would change if you forced a variable with value zero to take on a non-zero value.

Maximize $Z = c \cdot v$

Such that $S \cdot v = b$

$v \leq UB$

$v \geq LB$

Reduced Cost ($j$) = $dZ/dv_j$

** Only true when $v_j = 0$ at current optimal solution.
Reduced Costs (1 per variable)

In this case all variables are non-zero so all reduced costs are zero, meaning we don’t have to make any changes to c to get non-zero values for cars and trucks (they already are non-zero)

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<td>-INF</td>
<td>2550.000</td>
<td>+INF</td>
</tr>
</tbody>
</table>
# Metabolic Network Example

### Reaction List

<table>
<thead>
<tr>
<th>Formula</th>
<th>Reaction</th>
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<tbody>
<tr>
<td>$v_1$</td>
<td>A $\rightarrow$ B</td>
</tr>
<tr>
<td>$v_2$</td>
<td>A $\rightarrow$ C</td>
</tr>
<tr>
<td>$b_1$</td>
<td>$\rightarrow$ A</td>
</tr>
<tr>
<td>$b_2$</td>
<td>B $\rightarrow$</td>
</tr>
<tr>
<td>$b_3$</td>
<td>C $\rightarrow$</td>
</tr>
</tbody>
</table>

### S Matrix

$$ S = \begin{bmatrix} -1 & -1 & 1 & 0 & 0 \\ 1 & 0 & 0 & -1 & 0 \\ 0 & 1 & 0 & 0 & -1 \end{bmatrix} $$

### Metabolic Map

- **Maximize**
  $$ Z = c \cdot v = v_1 $$
- **Such that**
  $$ S \cdot v = 0 $$
  $$ 0 \leq v \leq 10 $$
Define S

Define Equations (Z = c \cdot v and S \cdot v = 0)

Apply Variable Bounds: Upper (.up)
Lower (.lo)

Define C, i.e. pick flux to optimize
Before Solve Summary in LST File: Equation Listing

General Algebraic Modeling System
Equation Listing  SOLVE FBA Using LP From line 33

---- massbalance  =E=
massbalance(A)..  - v(v1) - v(v2) + v(b1) =E= 0 ; (LHS = 0)
massbalance(B)..  v(v1) - v(b2) =E= 0 ; (LHS = 0)
massbalance(C)..  v(v2) - v(b3) =E= 0 ; (LHS = 0)

---- objectivefunction  =E=

**objectivefunction..  - v(v1) + Z =E= 0** ; (LHS = 0)

GAMS re-wrote the equation as:  \( Z - c \cdot v = 0 \)
### Constraint and Variable Values

#### EQU massbalance

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>A</td>
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</tr>
<tr>
<td>B</td>
<td>:</td>
<td>:</td>
<td>EPS</td>
</tr>
<tr>
<td>C</td>
<td>:</td>
<td>:</td>
<td>EPS</td>
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</table>

#### EQU objective

<table>
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<td>1.000</td>
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</table>

#### VAR v

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<tbody>
<tr>
<td>v1</td>
<td>:</td>
<td>10.000</td>
<td>10.000</td>
</tr>
<tr>
<td>v2</td>
<td>:</td>
<td>:</td>
<td>10.000</td>
</tr>
<tr>
<td>b1</td>
<td>:</td>
<td>10.000</td>
<td>10.000</td>
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<tr>
<td>b2</td>
<td>:</td>
<td>10.000</td>
<td>10.000</td>
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<tr>
<td>b3</td>
<td>:</td>
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</table>

#### VAR z

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<tbody>
<tr>
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<td>-INF</td>
<td>10.000</td>
<td>+INF</td>
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</table>

\[ S \cdot v = \text{level} \]

\[ Z \cdot c \cdot v = \text{level} \]

### Flux Map

- Flux from A to B: 10
- Flux from B to C: 10
- Flux from C to B: 0
- Flux from B to A: 10
- Flux from C to A: 0
Shadow Prices (1 per constraint)

$SP_A = -1 \rightarrow$

• If we change $b_A$ from zero to 1: we are saying the production of A has to be higher than the consumption of A by 1 unit (remember $S \cdot v = \text{production} - \text{consumption}$).
• A lower consumption of A means that the flux through $v_1$ will have to go down by 1 unit. Hence, $dZ/db_A = -1$.
• For example, if $b_A = 1$ then $Z = 9$.

$SP_C = SP_B = EPS (~0) \rightarrow$ This is because if you added B or C to the network they wouldn’t allow for higher flux through $v_1$.

Metabolic Map

--- EQU massbalance

<table>
<thead>
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<th>LEVEL</th>
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<th>MARGINAL</th>
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<tbody>
<tr>
<td>A</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>B</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>C</td>
<td>.</td>
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<td>-1.000</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>EPS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EPS</td>
</tr>
</tbody>
</table>
Reduced Costs (1 per variable)

**IF FLUX IS NON-ZERO THEN REDUCED COST IS ZERO**
Reduced Cost $v_1 = 0$, because $v_1$ is non-zero ($v_1=10$)
Reduced Cost $b_2 = 0$, because $b_2$ is non-zero ($b_2=10$)
**Exception:** if the non-zero flux is at is simple upper bound ($b_1 \leq 10$) then the shadow price for is reported (shadow price for A is -1)

**IF FLUX IS ZERO THEN REDUCED COST CAN BE NON-ZERO**
Reduced Cost $v_2 = -1$, because if you increase flux through $v_2$ it will reduce flux through $v_1$ thereby reducing $Z$.

<table>
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<tr>
<td>$v_1$</td>
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<td>$v_2$</td>
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<tr>
<td>$b_1$</td>
<td>.</td>
<td>10.000</td>
<td>10.000</td>
<td>1.000</td>
</tr>
<tr>
<td>$b_2$</td>
<td>.</td>
<td>10.000</td>
<td>10.000</td>
<td>.</td>
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<tr>
<td>$b_3$</td>
<td>.</td>
<td>.</td>
<td>10.000</td>
<td>.</td>
</tr>
</tbody>
</table>

**Metabolic Map**

- **A** connected to **B** by **$b_2$**
- **B** connected to **C** by **$b_1$**
- **A** connected to **C** by **$b_3$**
- **$v_1$** and **$v_2$** are fluxes through **A** and **C** respectively.
Conclusions

• You can use shadow prices and reduced costs to evaluate your results.
• For example: If you maximize growth rate and find zero growth, you can identify metabolites which metabolites are needed in order to grow (those with a negative shadow price).
  – This is useful if you are debugging a network.
Central Metabolic Network
(ie. CoreTextbookModel.gms)
Glycolysis

Pentose Phosphate Pathway

TCA Cycle

Oxidative Phosphorylation

101 Genes
63 Metabolites
62 Reactions
Common Flux Abbreviations

- Biomass: this is a drain of biomass components in their appropriate ratios.

- Exchange fluxes (remember + secretion; - uptake)
  - EX_glc_e (glucose)
  - EX_ac_e (acetate)
  - EX_succ_e (succinate)
  - EX_formate_e (formate)
  - EX_etoh_e (ethanol)
  - EX_o2_e (oxygen)
Running FBA

For exchange fluxes, a **negative** value indicates uptake and a **positive** value indicates secretion.

Define Carbon Source and Uptake Rate

Define LowerLimits on Oxygen Uptake Rate

Define Objective Function
### GAMS Results: LST File

#### Non-Zero Fluxes

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<th>Reaction</th>
<th>Flux Value</th>
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<tr>
<td>SUCD1i</td>
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<td>SUCOAS</td>
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<tr>
<td>TALA</td>
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<tr>
<td>AKGDH</td>
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<td>TPI</td>
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<tr>
<td><strong>Obj.L</strong></td>
<td><strong>0.490</strong></td>
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</table>

This is the value of the objective function for the FBA solutions.
FBA Calculations

1. What is the maximum growth rate for glucose aerobic growth (max. glucose uptake rate of 5)?
2. What is the maximum growth rate for glucose anaerobic (no oxygen uptake) growth (max. glucose uptake rate of 5)?
3. What are the by-products that are secreted during maximal glucose anaerobic growth?
4. Can *E. coli* grow anaerobically on acetate? *(hint: to get a feasible solution set lowerlimit to -5 for EX_ac_e and upperlimit to 0)*
5. Looking at the shadow prices for oxygen (o2) do you think that the cells could grow with acetate aerobically?
6. Looking at the reduced costs for the exchange fluxes, what compounds if added would allow for growth?
Glucose Aerobic Growth

Core E. coli Metabolic Network
Glucose Anaerobic Growth

Core E. coli Metabolic Network
FBA Calculations

1. What is the maximum growth rate for glucose aerobic growth (max. glucose uptake rate of 5)?
   • 0.49 1/hr

2. What is the maximum growth rate for glucose anaerobic (no oxygen uptake) growth (max. glucose uptake rate of 5)?
   • 0.197 1/hr

3. What are the by-products that are secreted during glucose anaerobic growth?
   • acetate, ethanol, formate

4. Can *E. coli* grow anaerobically on acetate?
   • No

5. Looking at the shadow prices for oxygen (O2) do you think that the cells could grow with acetate aerobically?
   • Yes, since the shadow price for O2 is negative it means that if you added it growth would increase.

6. Looking at the reduced costs for the exchange fluxes, what compounds if added would allow for growth?
   • akg, fum, glc, lacD, O2, pyr