Constraint-Based Workshops

4. GAMS & Sensitivity Analysis

January 17th, 2008

Optimization:

Used when multiple solutions satisfy your equations.

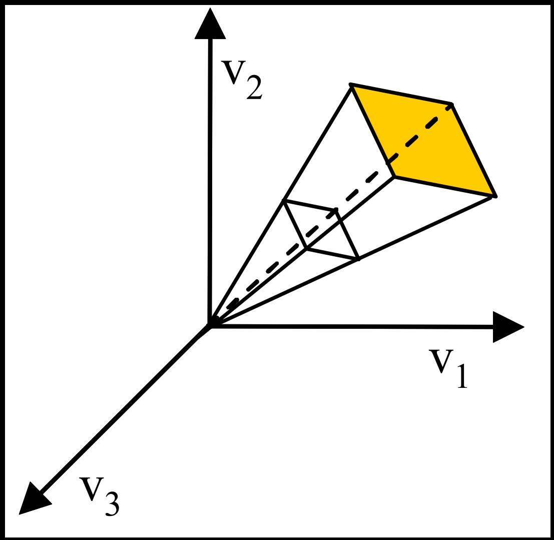
FBA Optimization Problem Statement

- 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 indeces 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

<u>Format</u>

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

<u>Example</u>

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

4. Variables

Format

Variables

Variablename1

Variablename2(*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

<u>Format</u>

Equations

Equation1 give description

Equation2(*setname*) *give description*;

Equation1.. Give function;

Equation2(*setname*).. Give function;

<u>Example</u>

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 =

=l= means ≤

=g= means ≥

6. Model and Solve Statements

Format

model *modelname* /all/;

or

model *modelname* /list of equations/;

Example

model FBA /all/;

or

model FBA /MassBalance,ObjectiveFunction/;

To solve the model:

solve *modelname* using lp maximizing *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.

$$0 \leq A \leq 60$$

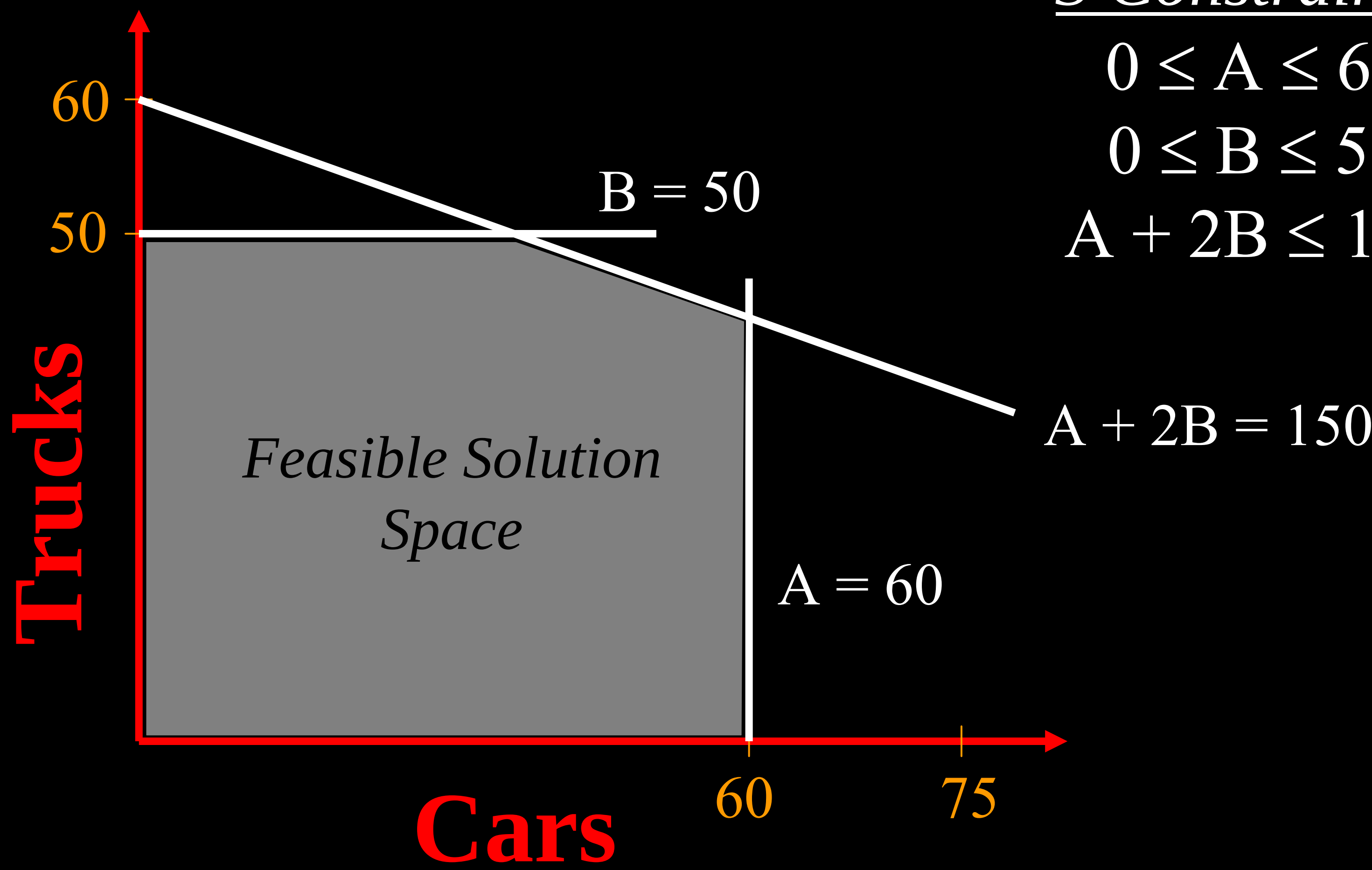
$$0 \leq B \leq 50$$

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



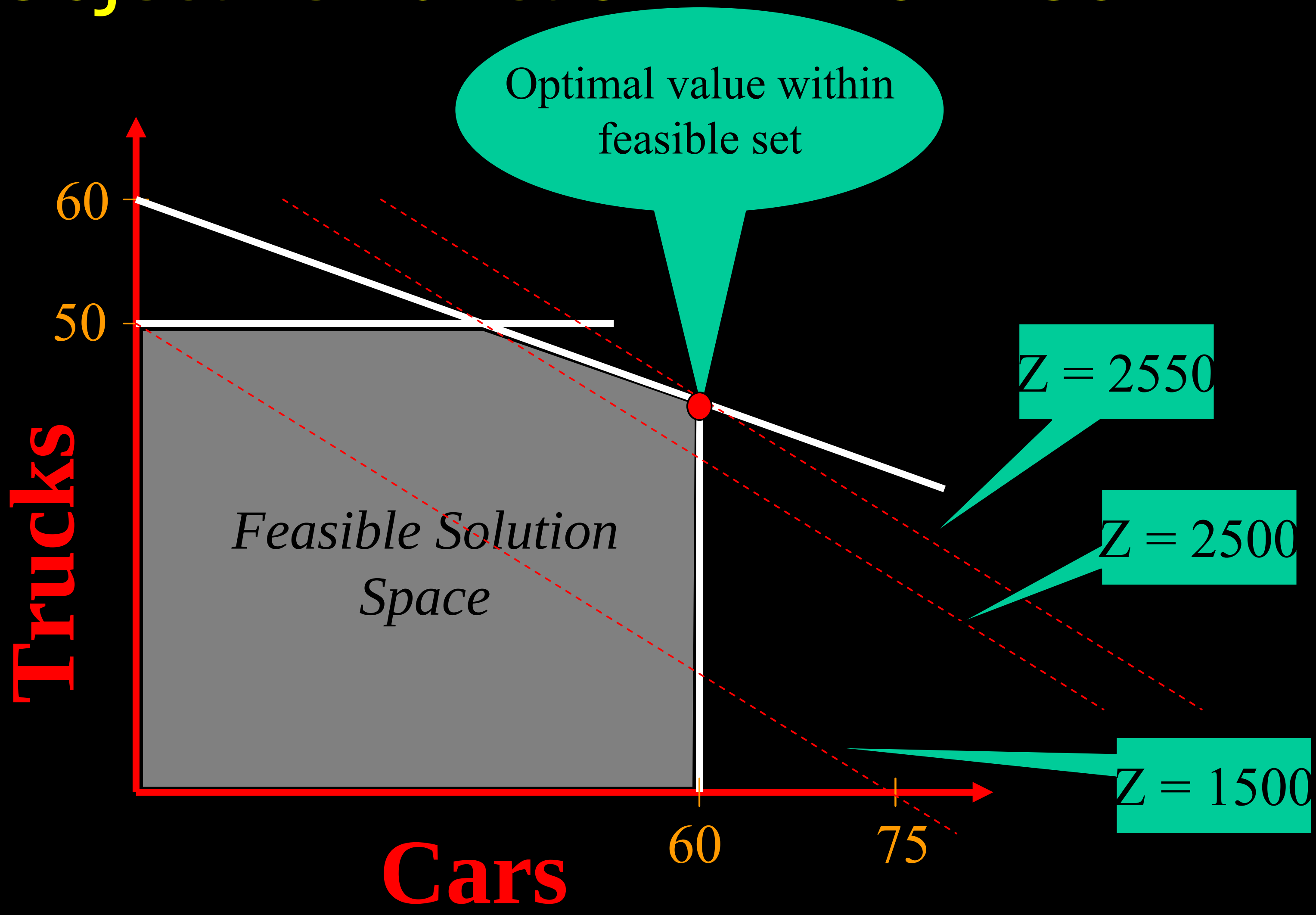
3 Constraints:

$0 \le A \le 60$

$0 \le B \le 50$

$A + 2B \le 150$

Graphical Representation of the Objective Function: Z=20A+30B



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carstrucks.gms

Run GAMS (F9)

```
*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 (Z) are given by:
*   profit = 20*cars + 30*trucks


variables
cars
trucks
profit;

equations
constraint1
constraint2
constraint3
earnings;

constraint1.. cars=l=60;
constraint2.. trucks=l=50;
constraint3.. cars+2*trucks=l=150;
earnings.. profit=e=20*cars+30*trucks;

cars.lo=0;
trucks.lo=0;

model production /all/;
solve production using lp maximizing profit;
```

1: 1 Modified | Insert | Run GAMS (F9)

Your LST File has all Results

```
EXECUTION TIME       =        0.016 SECONDS      3 Mb  WIN225-148 May 29, 2007
GAMS Rev 148  x86/MS Windows                               01/16/08 15:21:40 Page 5
G e n e r a l   A l g e b r a i c   M o d e l i n g   S y s t e m
Solution Report     SOLVE production Using LP From line 34


               S O L V E      S U M M A R Y

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

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

 RESOURCE USAGE, LIMIT          0.031      1000.000
 ITERATION COUNT, LIMIT         1         10000
```

Solver found an optimal solution

Value of Obj. Function (ie. profit)

Constraint and Variable Values

	LOWER	LEVEL	UPPER	MARGINAL
---- EQU constrain~	-INF	60.000	60.000	5.000
---- EQU constrain~	-INF	45.000	50.000	.
---- EQU constrain~	-INF	150.000	150.000	15.000
---- EQU earnings	.	.	.	1.000

	LOWER	LEVEL	UPPER	MARGINAL
---- VAR cars	.	60.000	+INF	.
---- VAR trucks	.	45.000	+INF	.
---- VAR profit	-INF	2550.000	+INF	.

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
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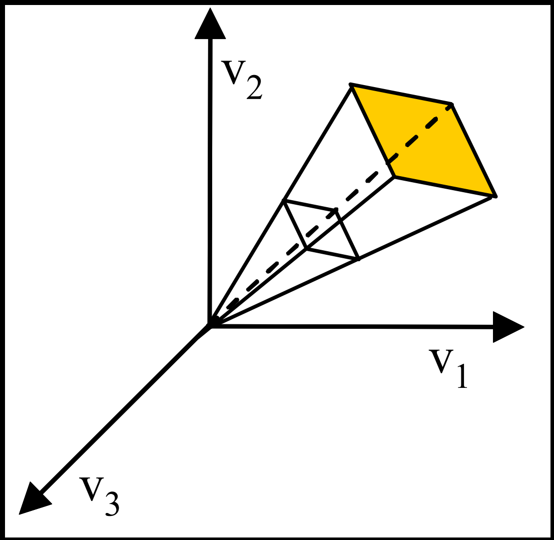
Maximize: $c \cdot v$

Such that $S \cdot v = 0$

$LB \leq v \leq UB$



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.

$$\begin{aligned} \text{Maximize} \quad & Z = c \cdot v \\ \text{Such that} \quad & S \cdot v = b \\ & v \leq UB \\ & v \geq LB \end{aligned}$$

$$\text{Shadow Price (i)} = dZ/db_i$$

Shadow Prices (1 per constraint)

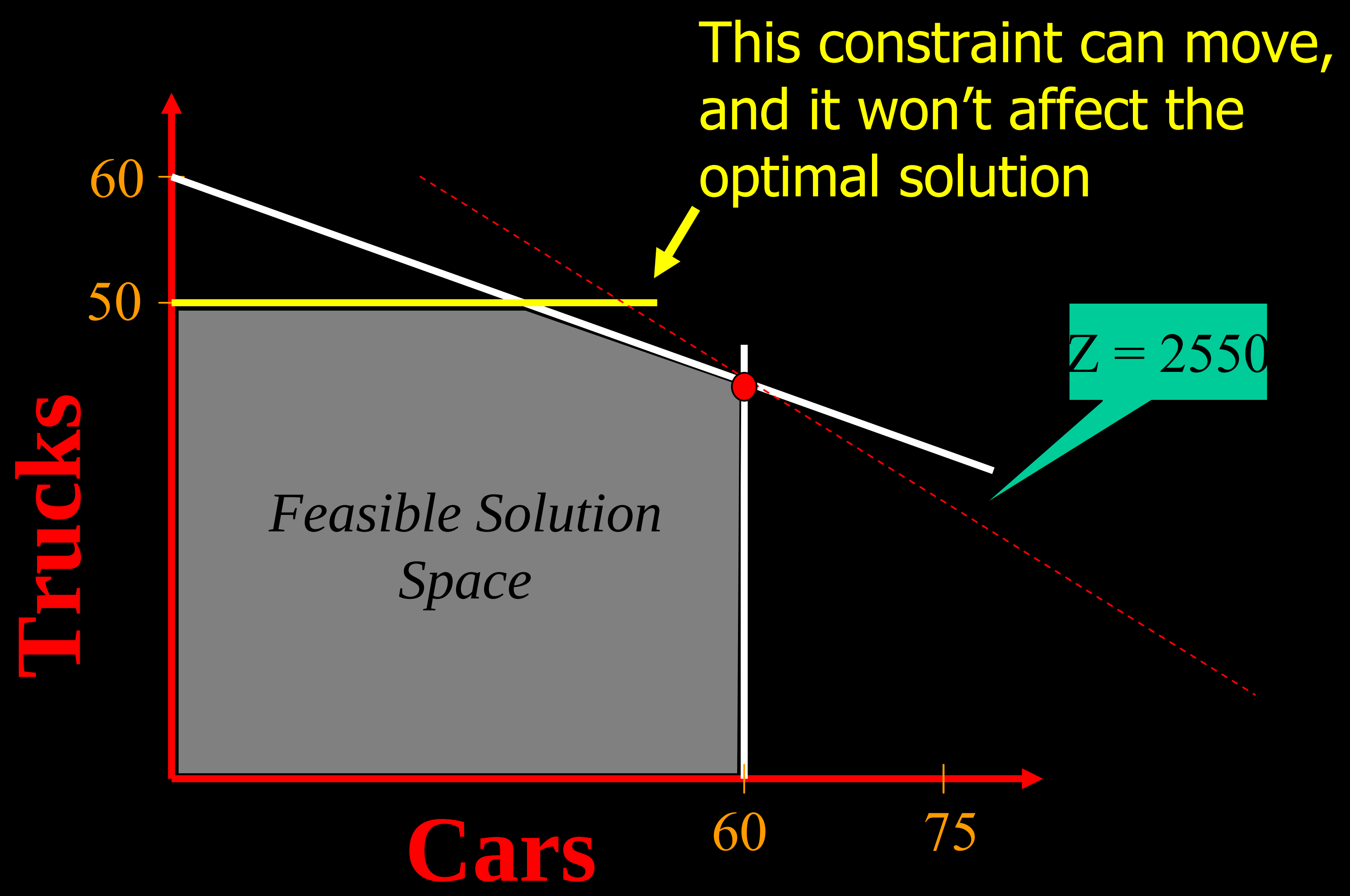
$SP_1 = 5$ → This means if we lower b_1 from 60 to 59, the profit would go down to $2550+(59-60)*SP_1$ and the solution would change (cars & trucks).

$SP_2 = 0$ → 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.

	LOWER	LEVEL	UPPER	MARGINAL
---- EQU constrain~	-INF	60.000	60.000	5.000
---- EQU constrain~	-INF	45.000	50.000	.
---- EQU constrain~	-INF	150.000	150.000	15.000
---- EQU earnings	.	.	.	1.000

	LOWER	LEVEL	UPPER	MARGINAL
---- VAR cars	.	60.000	+INF	.
---- VAR trucks	.	45.000	+INF	.
---- VAR profit	-INF	2550.000	+INF	.

Graphical Representation of the Objective Function: Z=20A+30B



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)

	LOWER	LEVEL	UPPER	MARGINAL
---- EQU constrain~	-INF	60.000	60.000	5.000
---- EQU constrain~	-INF	45.000	50.000	.
---- EQU constrain~	-INF	150.000	150.000	15.000
---- EQU earnings	.	.	.	1.000

	LOWER	LEVEL	UPPER	MARGINAL
---- VAR cars	.	60.000	+INF	.
---- VAR trucks	.	45.000	+INF	.
---- VAR profit	-INF	2550.000	+INF	.

Metabolic Network Example

Reaction List

v_1: A → B

v_2: A → C

b_1: → A

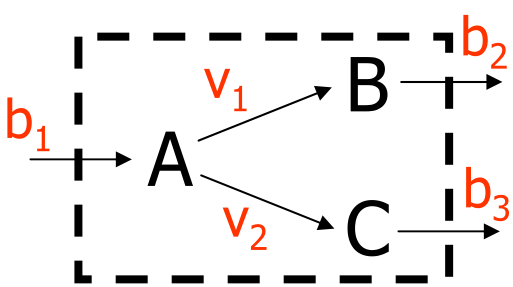
b_2: B →

b_3: C →

S Matrix

$$
\begin{array}{c} \\ A \\ B \\ C \end{array}
\begin{array}{c}
\begin{array}{ccccc} v_1 & v_2 & b_1 & b_2 & b_3 \end{array} \\
\begin{pmatrix} -1 & -1 & 1 & 0 & 0 \\ 1 & 0 & 0 & -1 & 0 \\ 0 & 1 & 0 & 0 & -1 \end{pmatrix}
\end{array}
$$

Metabolic Map



Maximize $Z = c \cdot v = v_1$

Such that $S \cdot v = 0$

$0 \leq v \leq 10$

```
sets
metabolites /A,B,C,D/
reactions /v1,v2,b1,b2,b3/;

parameters
c(reactions)
S(metabolites,reactions)
/A.v1 -1
B.v1 1
A.v2 -1
C.v2 1
A.b1 1
B.b2 -1
C.b3 -1/;

variables
v(reactions)
Z;

equations
massbalance(metabolites)
objectivefunction;

massbalance(metabolites).. sum(reactions, S(metabolites,reactions)*v(reactions))=e=0;
objectivefunction.. Z=e=sum(reactions,c(reactions)*v(reactions));

v.lo(reactions)=0;
v.up(reactions)=10;

c('v1')=1;

model FBA /all/;
solve FBA using lp maximizing Z;
```

Define S

Define Equations (Z=c·v and S·v=0)

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

Define C, ie. pick flux to optimize

Before Solve Summary in LST File: Equation Listing

```
G e n e r a l   A l g e b r a i c   M o d e l i n g   S y s t e m
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

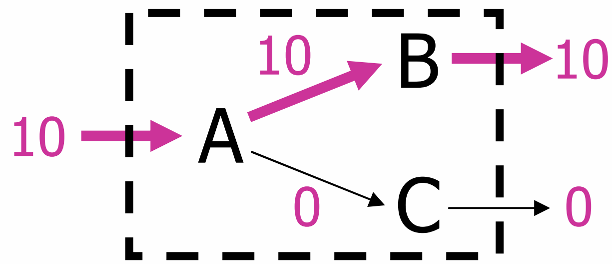
```
---- EQU massbalance

          LOWER     LEVEL     UPPER    MARGINAL

A           .         .         .       -1.000
B           .         .         .         EPS
C           .         .         .         EPS

                    LOWER     LEVEL     UPPER    MARGINAL

---- EQU objective~   .         .         .       1.000
```

S·v = level

Z-c·v = level

```
---- VAR v

          LOWER     LEVEL     UPPER    MARGINAL

v1          .      10.000    10.000      .
v2          .        .       10.000    -1.000
b1          .      10.000    10.000     1.000
b2          .      10.000    10.000      .
b3          .        .       10.000      .

                    LOWER     LEVEL     UPPER    MARGINAL

---- VAR Z          -INF     10.000     +INF       .
```

Flux Map

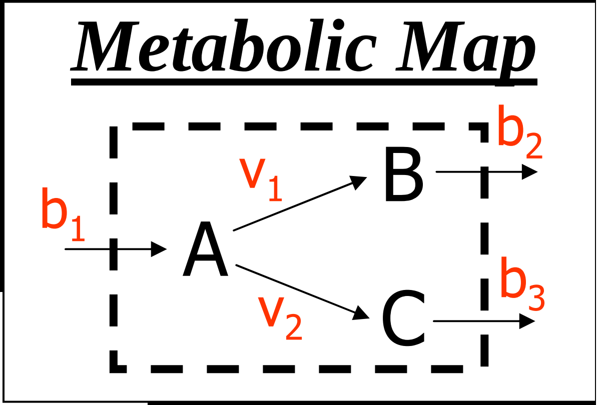


Shadow Prices (1 per constraint)

$SP_A = -1$ →

- 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·v=production-consumption).
- A lower consumption of A means that the flux through v1 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) → This is because if you added B or C to the network they wouldn't allow for higher flux through v_1.



---- EQU massbalance

	LOWER	LEVEL	UPPER	MARGINAL
A	.	.	.	-1.000
B	.	.	.	EPS
C	.	.	.	EPS

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 (v1=10)

Reduced Cost b_2 = 0, because b_2 is non-zero (b2=10)

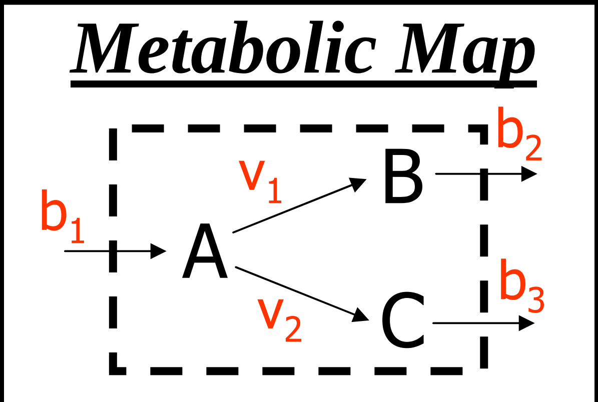
Exception: if the non-zero flux is at is simple upper bound ($b_1 \leq 10$) then the shadow price for is reported (shadow price for A is -1)

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.

---- VAR v

	LOWER	LEVEL	UPPER	MARGINAL
v1	.	10.000	10.000	.
v2	.	.	10.000	-1.000
b1	.	10.000	10.000	1.000
b2	.	10.000	10.000	.
b3	.	.	10.000	.



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

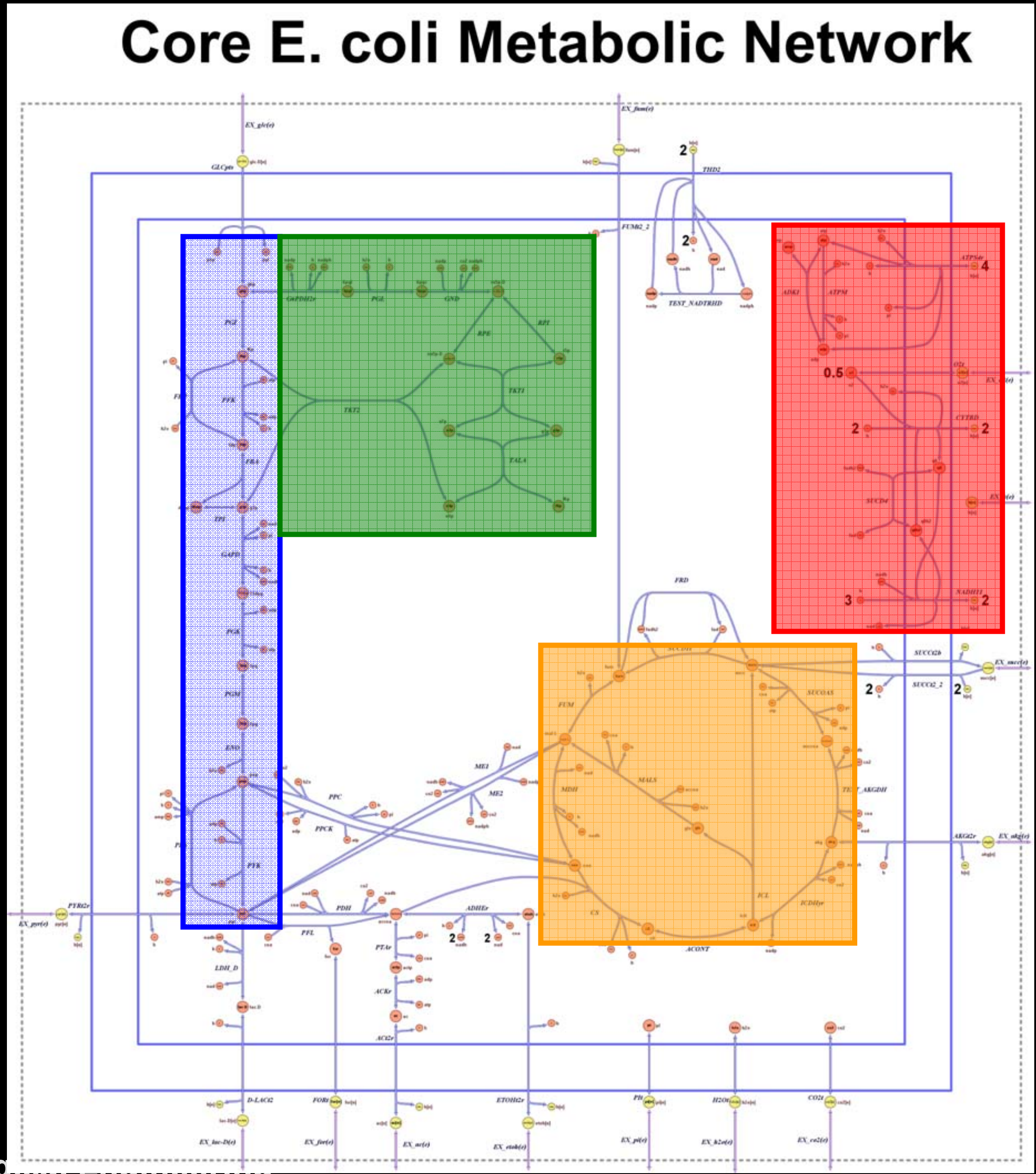
TCA Cycle

Oxididative 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 <u>negative</u> value indicates <u>uptake</u> and

a <u>positive</u> value indicates <u>secretion</u>

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File Edit Search Windows Help

result2

fba.gms | coretextbookmodel.gms

```
**THIS CODE WAS WRITTEN FOR SYSTEMS BIOLOGY SHORT COURSE BY J.REED (7/2005)

*Read in the appropriate S matrix
$include CoreTextbookModel.gms

*Place limits on the exchange fluxes based on the minimal media
*for a negative flux through the exchange reactions implies that
*the metabolites are being taken up or consumed by the cell.
*By default the upperlimits of the exchange fluxes are all set to
*the Vmax, indicating that the cell can secrete any of the extracellular
*metabolites
UpperLimits(j)=Vmax;
...ver limits for exchange flux
LowerLimits('EX_glc_e')=-1;
UpperLimits('EX_glc_e')=-1;
...up by the cell
LowerLimits('EX_co2_e')=-Vmax;
LowerLimits('EX_h2o_e')=-Vmax;
LowerLimits('EX_o2_e')=-Vmax;

Parameter
c(j) used to define the objective function for FBA;

Variables
v(j) flux values through reaction in network
Obj  this is the value of the objective function for the FBA solutions;

Equations
massbalance(i) mass balance equations for each metabolite
calcobj calculates the dot product of the c vector the flux vector;
massbalance(i).. sum( j,S(i,j)*v(j) )=e=0;
calcobj.. Obj=e=sum( j,c(j)*v(j) );

Model FBA /massbalance, calcobj/;


v.lo(j)=LowerLimits(j);
c('Biomass')=1;
```

Define Carbon Source and Uptake Rate

Define LowerLimits on Oxygen Uptake Rate

Define Objective Function

GAMS Results: LST File

Non-Zero Fluxes

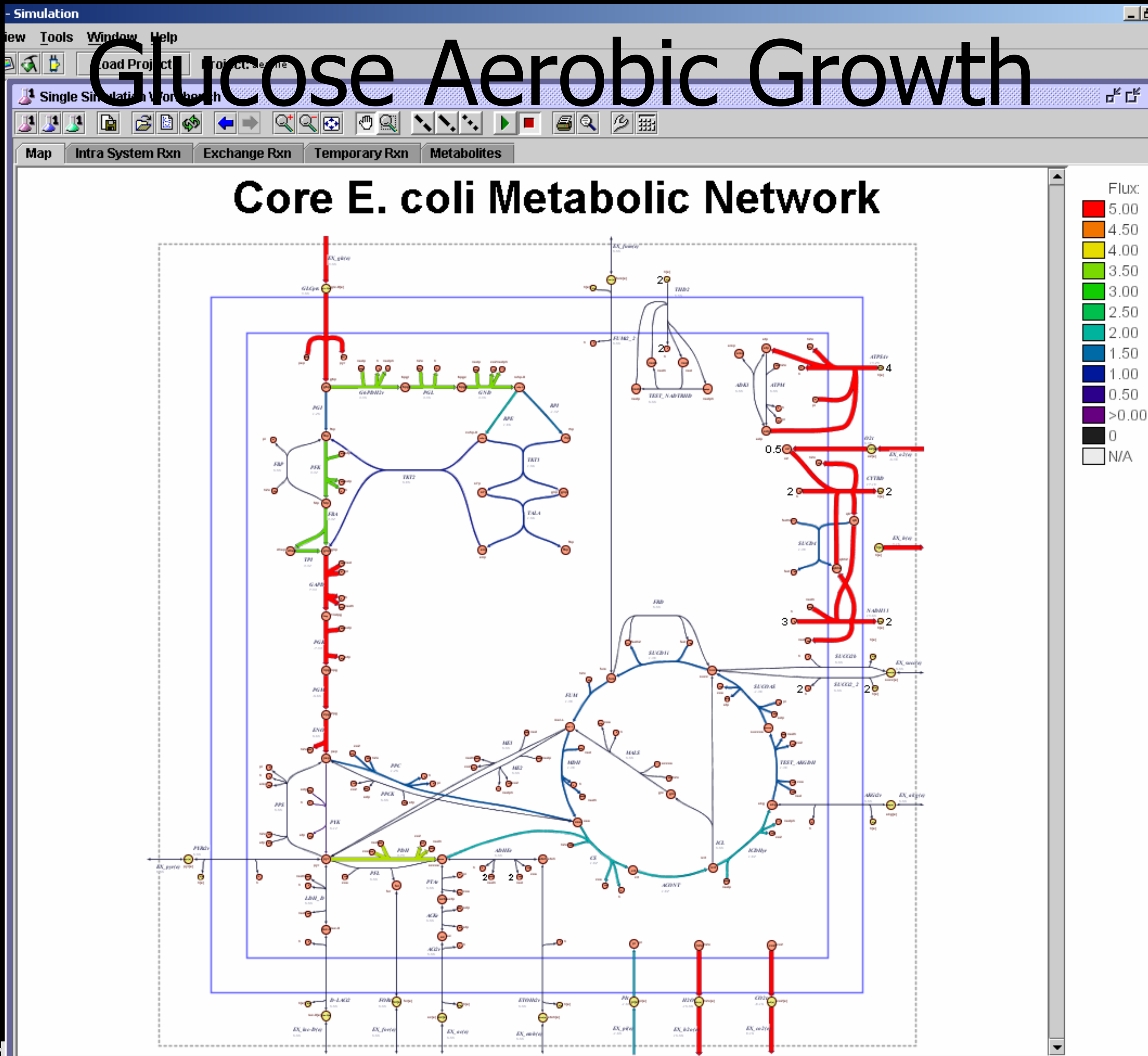
```
----     370 VARIABLE v.L  flux values through reaction in network

EX_co2_e    9.160,     EX_glc_e  -5.000,     EX_h_e       5.181,     EX_h2o_e  10.057
EX_o2_e    -8.594,     EX_pi_e   -1.802,     ACONT        1.917,     ATPS4r    15.198
Biomass     0.490,     CO2t      -9.160,     CS           1.917,     CYTBD     17.188
ENO         6.798,     FBA        3.345,     FUM          1.389,     G6PDH2r    3.504
GAPD        7.530,     GLCpts     5.000,     GND          3.504,     H2Ot     -10.057
ICDHyr      1.917,     MDH        1.389,     NADH11      15.798,     O2t        8.594
PDH         3.753,     PFK        3.345,     PGI          1.396,     PGK       -7.530
PGL         3.504,     PGM       -6.798,     PIt         -1.802,     PPC        1.403
PYK         0.140,     RPE        1.984,     RPI         -1.520,     SUCD1i     1.389
SUCD4       1.389,     SUCOAS    -1.389,     TALA         1.080,     AKGDH      1.389
TKT1        1.080,     TKT2       0.904,     TPI          3.345

        370 VARIABLE Obj.L                 =        0.490  this is the value of
                                                           the objective functio
                                                           n for the FBA solutio
                                                           ns
```

Growth Rate

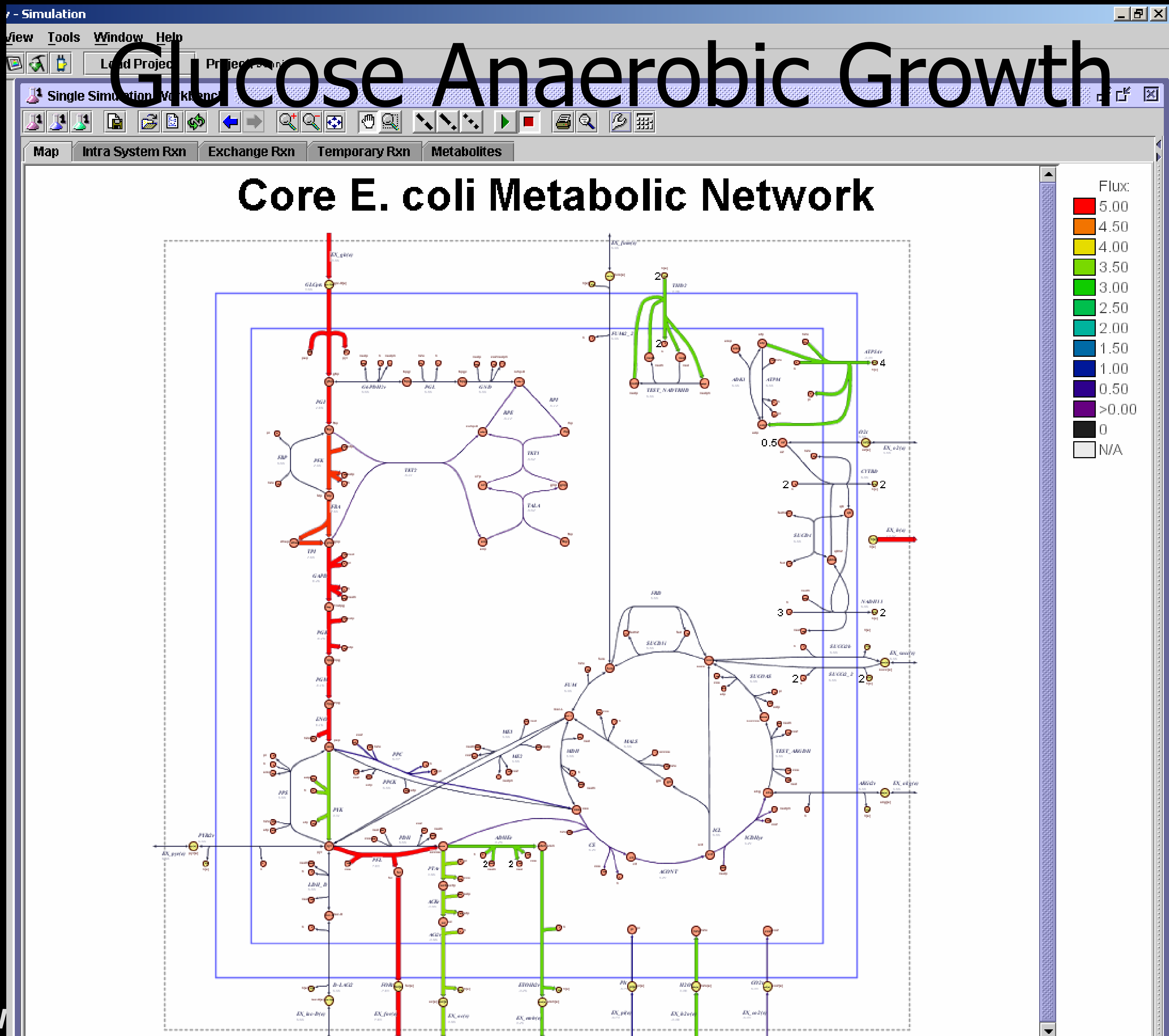
FBA Calculations

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



Glucose Anaerobic Growth



UW

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