Modeling and Analysis of Biochemical pathways of Glucose Metabolism and Cell cycle

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"APPLICATION OF CONTROL THEORY AND OPTIMIZATION TECHNIQUES IN BIOCHEMICAL PATHWAYS"
ICM 2010, Hyderabad

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Overview

- Introduction
- Mathematical Modeling in Cancer
- Cell cycle events
- Intracellular pathways
- Sensitivity analysis
- Conclusions

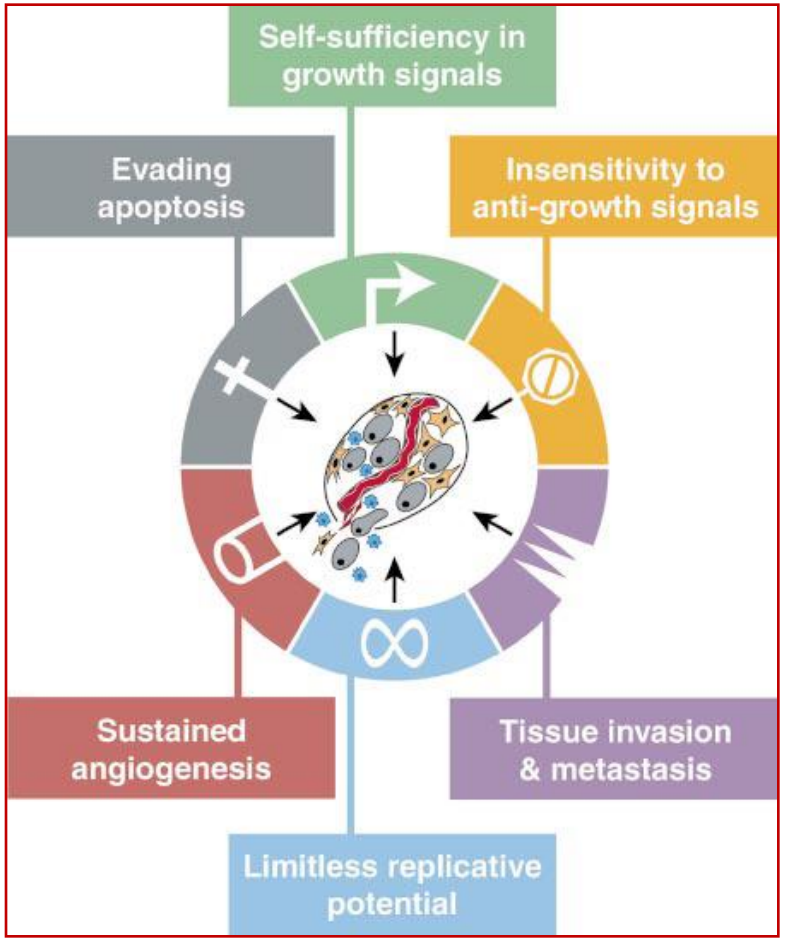
War between human community and cancer

What is Cancer ?

- Uncontrolled and unregulated growth of cells in the body.
- Normal cell undergoes series of mutations to form a cancer cell
- Cancer cell shows its power of invulnerability and eternity.
- Presently 100 types of cancer are found

• According to WHO*, 7.6 million died of cancer out of 58 million deaths in 2007

• It may increase to 18% and 50% by 2015 and 2030 respectively



Douglas Hanahan and Robert A. Weinberg, *Cell, Vol. 100, 57–70, January 7, 2000*

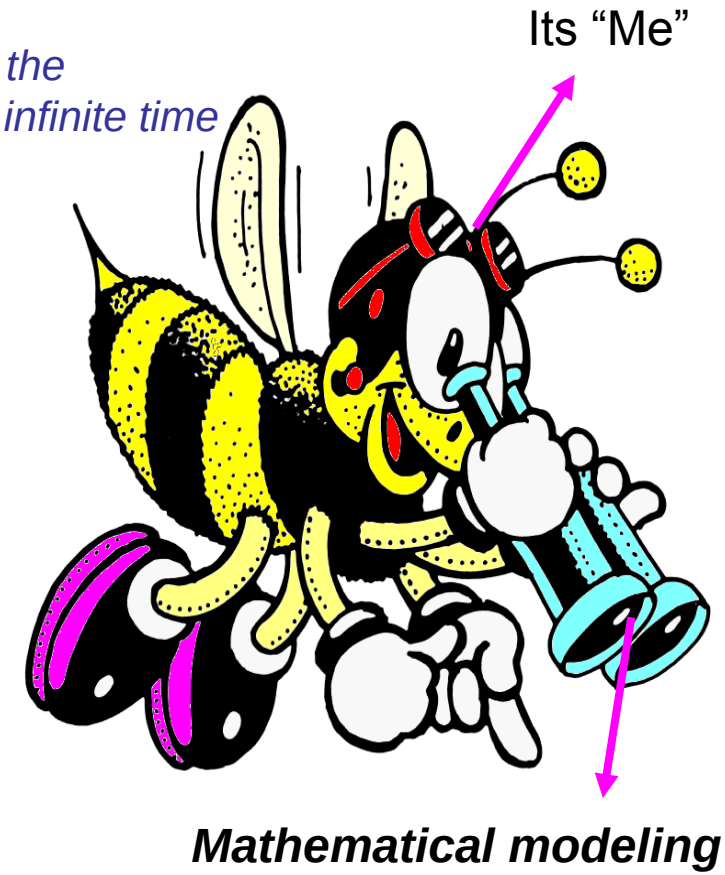
Bryne (1999) , *"effective and efficient treatment modalities can be developed by identifying the mechanisms which control the cancer growth."*

Laboratory experiments (in vitro or in vivo) can unravel all the mechanisms for all types of cancer , but at the cost of infinite time and numerous replications.

Tool to hasten comprehension of cancer ?

Mathematical modeling

- *Verification of hypotheses*
- *Prediction of outcomes of intuitive ideas*
- *Design experiments*



Murray (2002) states that " the goal is to develop models which capture the essence of various interactions allowing their outcome to be more fully understood."

Gatenby and Maini (2003) states that "clinical oncologists and tumor biologists possess virtually no comprehensive theoretical model to serve as a framework for understanding, organizing and applying data.

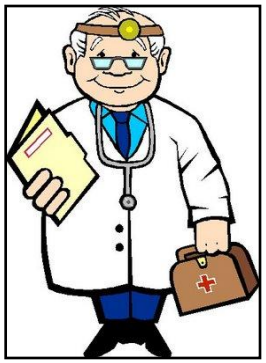
"Mechanistic models that provide real insights into critical parameters that control system dynamics" are needed.

Tiina et al., (2007) presents – out of 1.5 million papers in the area of cancer research, approximately 5% are related to mathematical modeling.

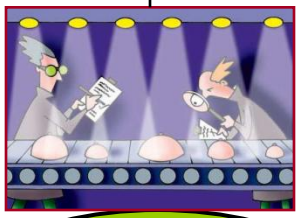
Chemical engineers work at the interface between mathematics and biology

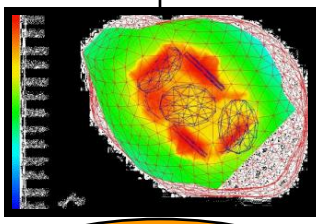
"Tumor Growth Computer Model Sets Stage For Customized Cancer Treatment" (Vito Quaranta & group – www.sciencedaily.com)

Informatics / Data analysis



Process Modeling

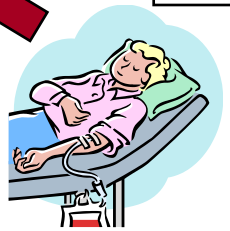




Diagnosis

1. Is cancer there ?
2. What type ?
3. Which stage ?

Screening techniques



Prognosis

1. How is it growing ?
2. Is it treatable ?

Growth mechanisms

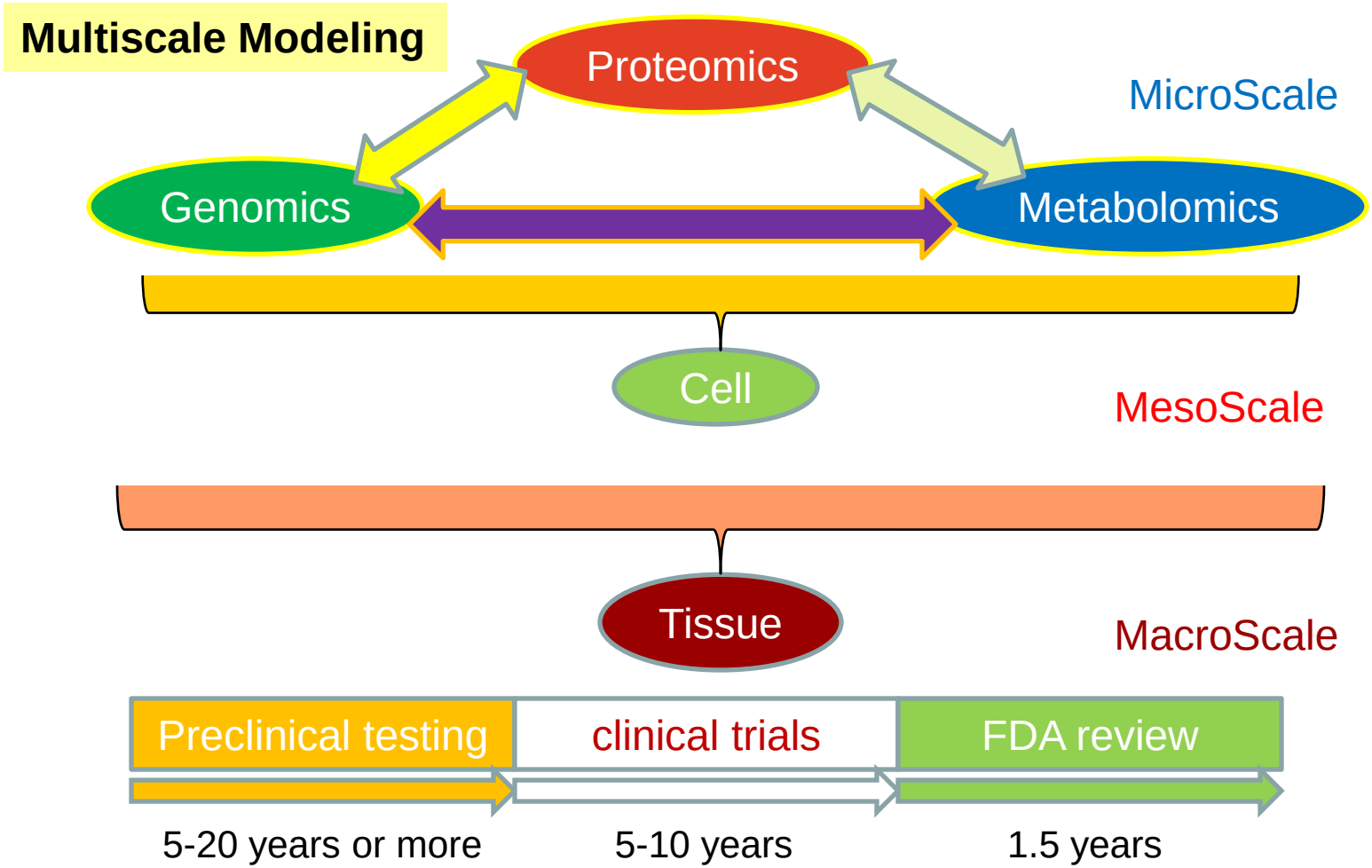
Therapy

1. Which therapy ?
2. When and How much ?

Pharmacokinetics & Pharmacodynamics

Control / Optimization

Preventive-Predictive-Personalized Therapy

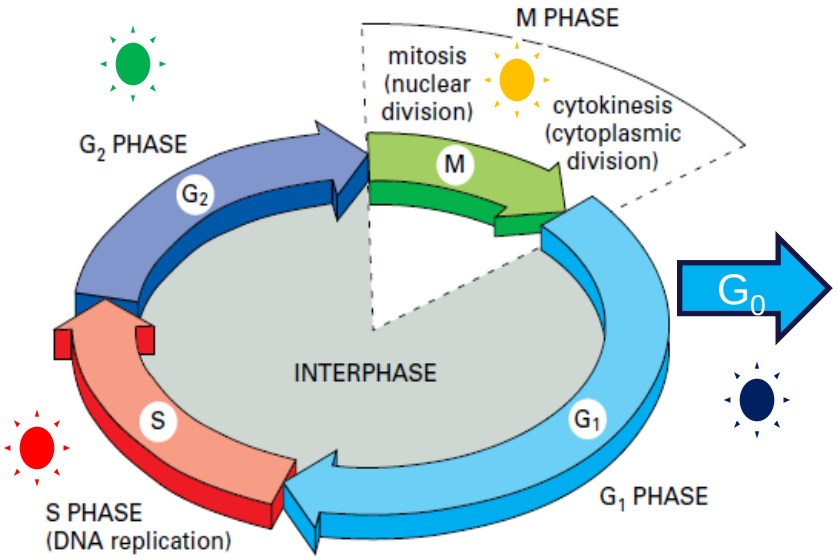


Martins et al., (2007) *Physics of Life Reviews*, **4**, 128-156
Kleinsmith LJ. 2005. Principles of cancer biology: Addison-Wesley.
Alarcon et al., (2006), computers and mathematical methods in medicine, 7, 85-119

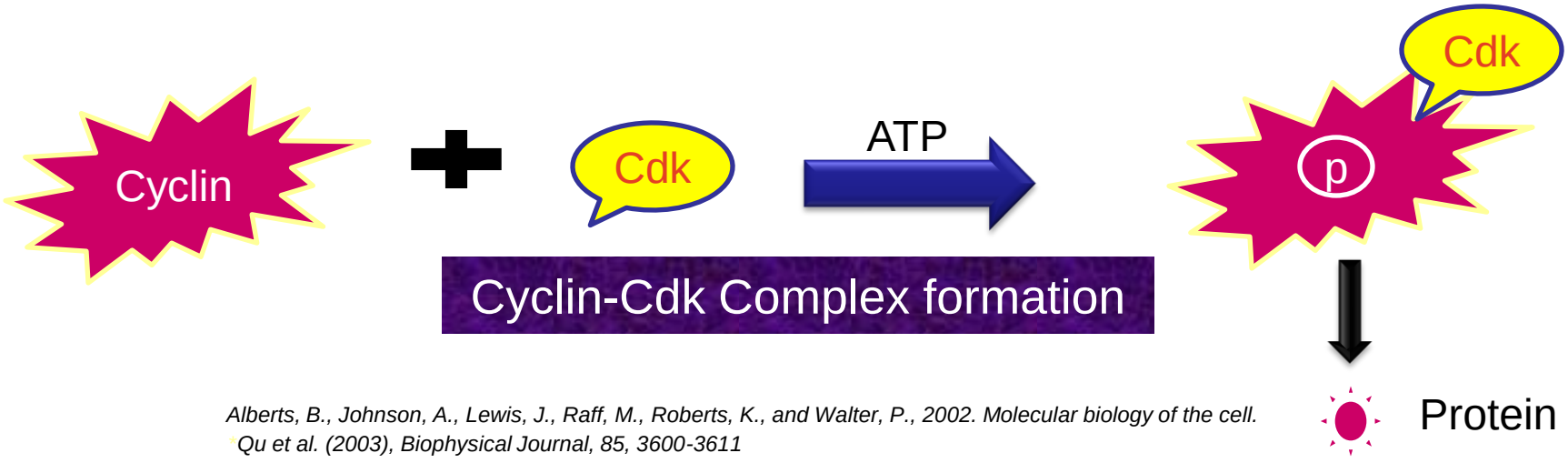
Objectives

1. Glycolysis pathway (9 Eq., 17 parameters)
2. Glycolysis + TCA + Oxidative phosphorylation pathway (12 Eq., 37 parameters)
3. Cell Cycle model (13 Eq., 90 parameters)
4. p53 pathway (4 Eq., 10 parameters)

Cell cycle Events

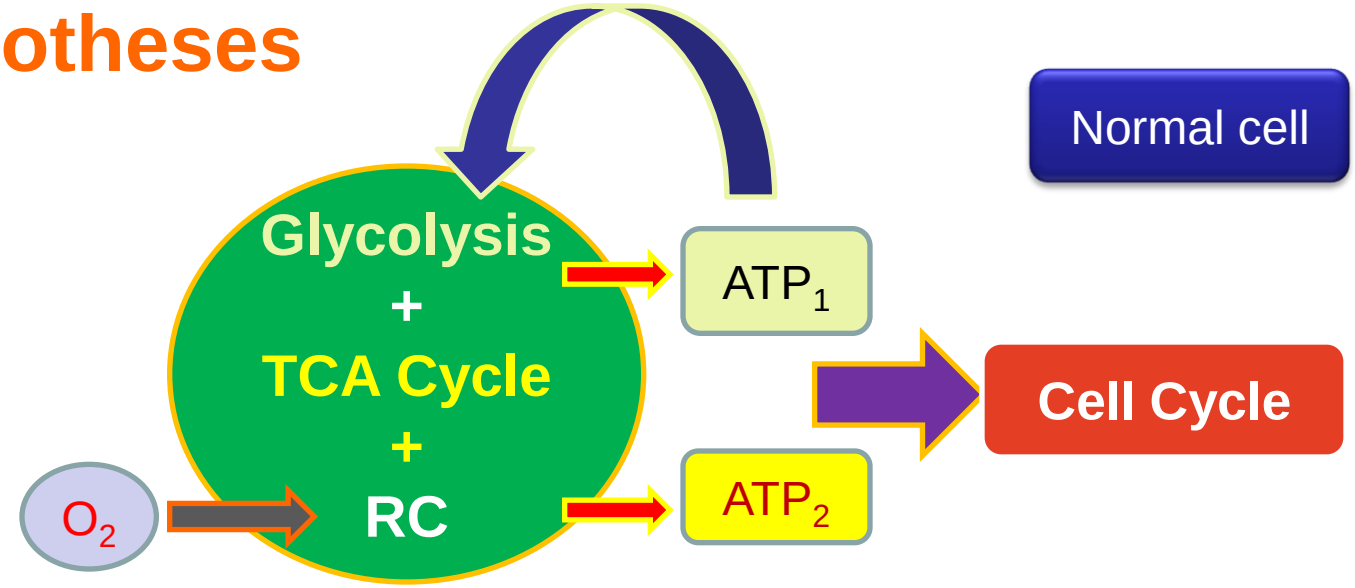


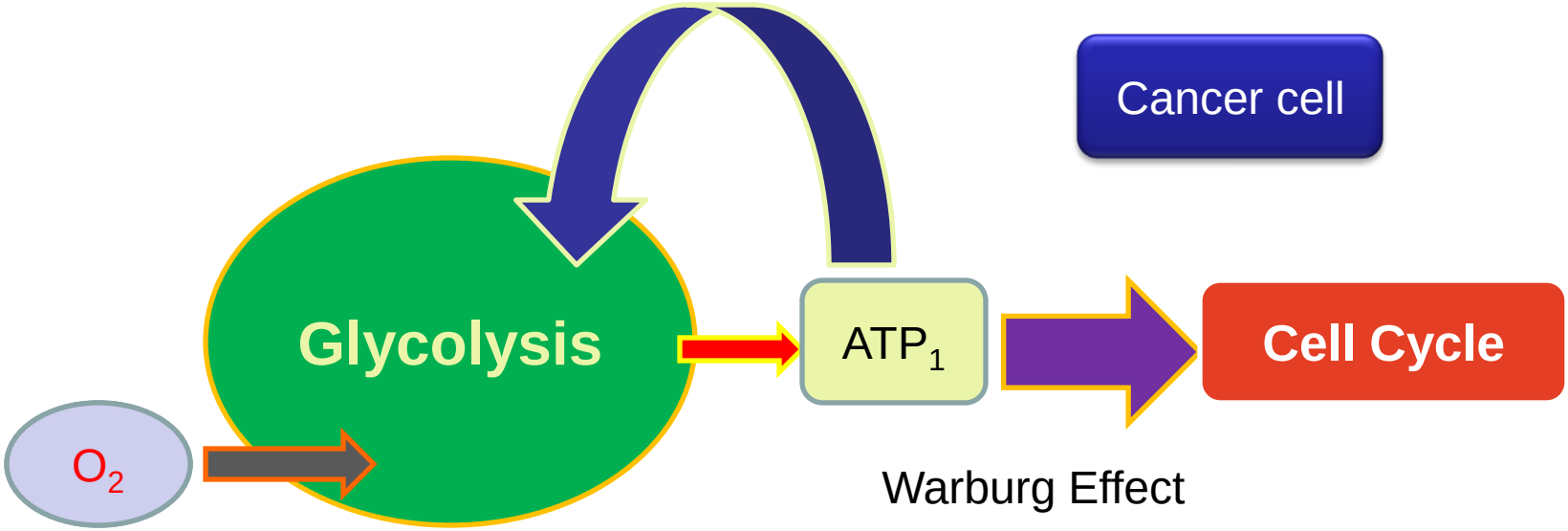
Cyclin-Cdk complex	Cyclin	Cdk Partner
G1-Cdk	Cyclin D	Cdk4, Cdk6
G1/S-Cdk	Cyclin E	Cdk2
S-Cdk	Cyclin A	Cdk2
M-Cdk	Cyclin B	Cdk1



Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., and Walter, P., 2002. Molecular biology of the cell.
Qu et al. (2003), Biophysical Journal, 85, 3600-3611
Alarcon et al., (2004, Journal of Theoretical biology, 229, 395-411

Hypotheses





Warburg Effect

*Moreno-Sanchez et al. (2007), FEBS Journal, 274, 1393-1418

Ralph et al. (2008),Cell Metabolism. 7, 11-20

Classification of Sensitivity Analysis Methods

Local sensitivity analysis

1. Varying of parameters one at a time while fixing others at their nominal values
2. Variation of parameters is within a small range about the nominal values
3. Differential analysis

Global sensitivity analysis

1. Sampling based methods -Monte-Carlo regression and correlation analysis Pearson Coefficient (PC), Standard Regression Coefficient (SRC), Partial Rank Regression Coefficient (PRCC)
2. Variance based methods - Sobol technique, EFAST
3. HDMR- High Dimensional Model Reduction

RS-HDMR

The mapping between the input variables $x_1, x_2, \ldots x_n$ and the output variables $f(x)$ in the domain R^n can be represented as follows

$$f(x) = f_0 + \sum_{i=1}^{n} f_i(x_i) + \sum_{1 \le i < j \le n} f_{ij}(x_i, x_j) + \ldots\ldots + f_{12\ldots n}(x_1, x_2, \ldots x_n)$$

Criteria :
- Accuracy
- Sensitivity indices

Here, f_0 denotes the mean effect (zeroth order), which is a constant, function $f_i(x_i)$ is a first order term giving the effect of variable x_i, Similarly others take care of interaction effects

The determination of the higher order component functions is based on the approximation of the component functions by orthonormal basis functions

$$f_i(x_i) \approx \sum_{r=1}^{k} \alpha_r^i \varphi_r(x_i)$$

$$f_{ij}(x_i, x_j) \approx \sum_{p=1}^{l} \sum_{q=1}^{l'} \beta_{pq}^{ij} \varphi_p(x_i) \varphi_q(x_j)$$

Orthogonal condition

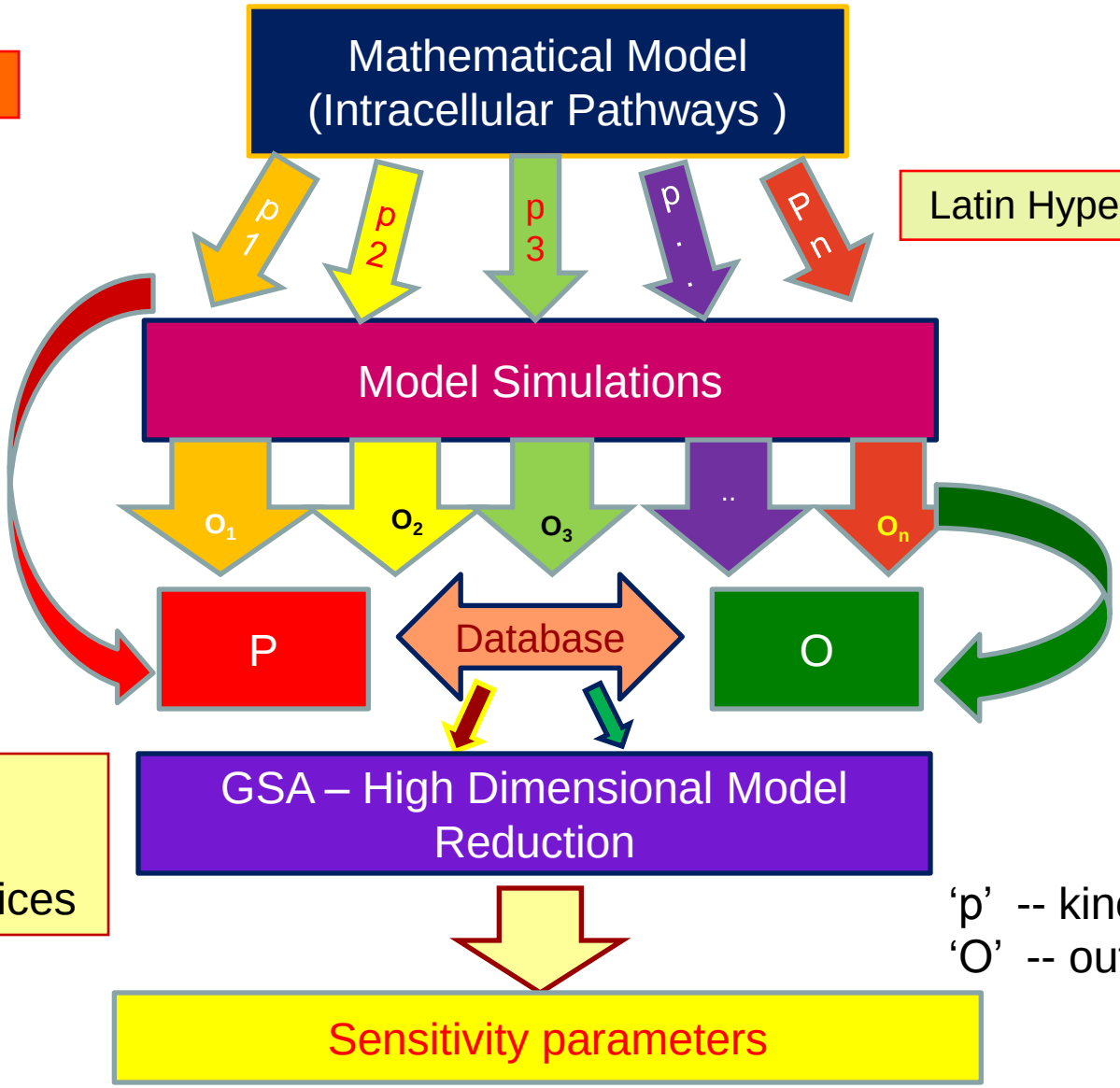
$$\int_a^b \varphi_k(x) dx = 0$$

$$\int_a^b \varphi_k^2(x) dx = 1$$

$$\int_a^b \varphi_k(x) \varphi_l(x) dx = 0 \quad (k \neq l)$$

Li et al., 2002, *Chemical Engineering Science* 57, 4445-4460.

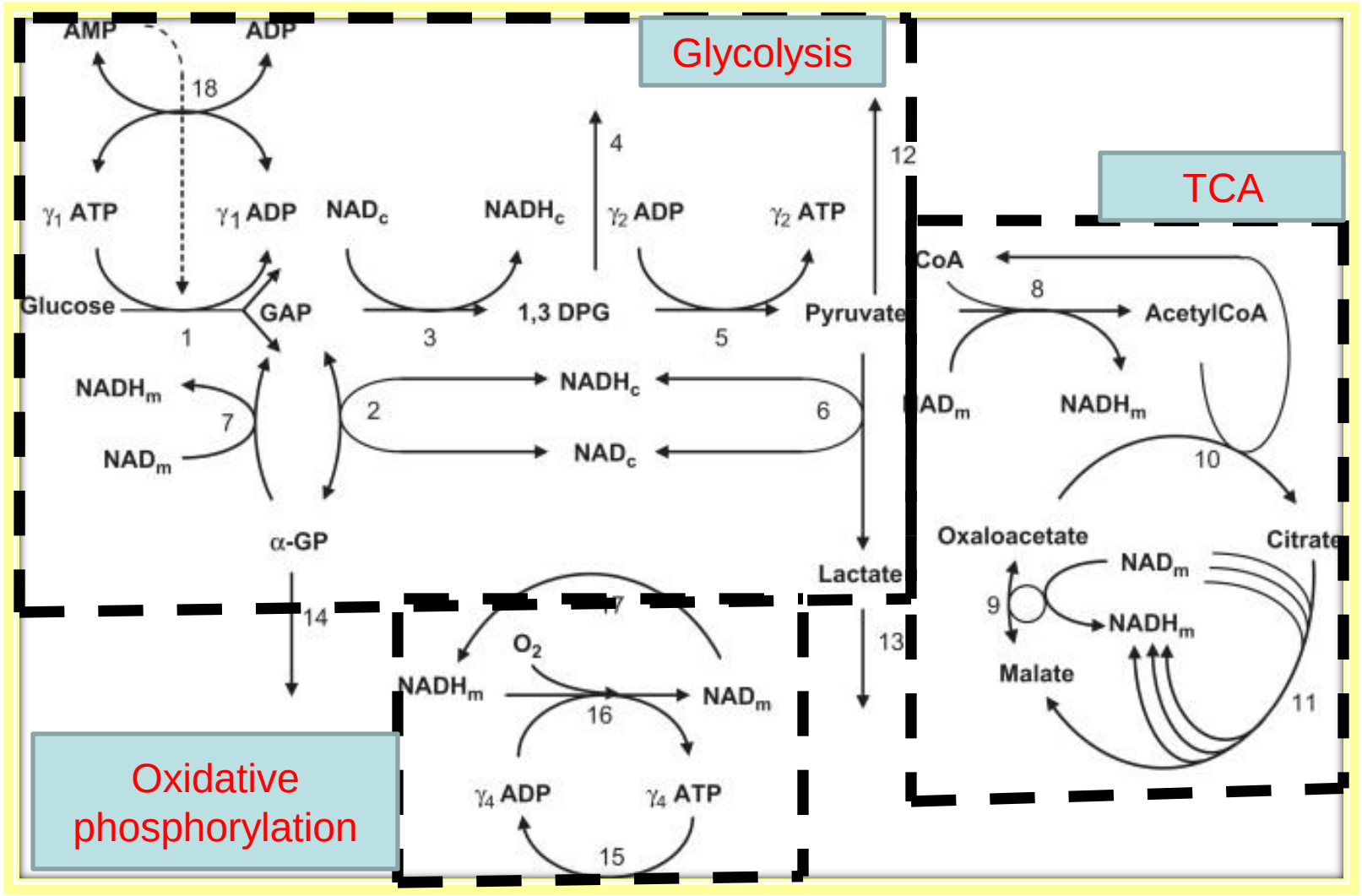
FLOW CHART



Criteria :
- Accuracy
- Sensitivity indices

'p' -- kinetic parameters
'O' -- output

Glucose metabolism



Nazaret, C., Mazat, J.P., Journal of theoretical biology 252 (2008) 520-529

Glucose metabolism – Full Pathway

Accuracy

Output 1

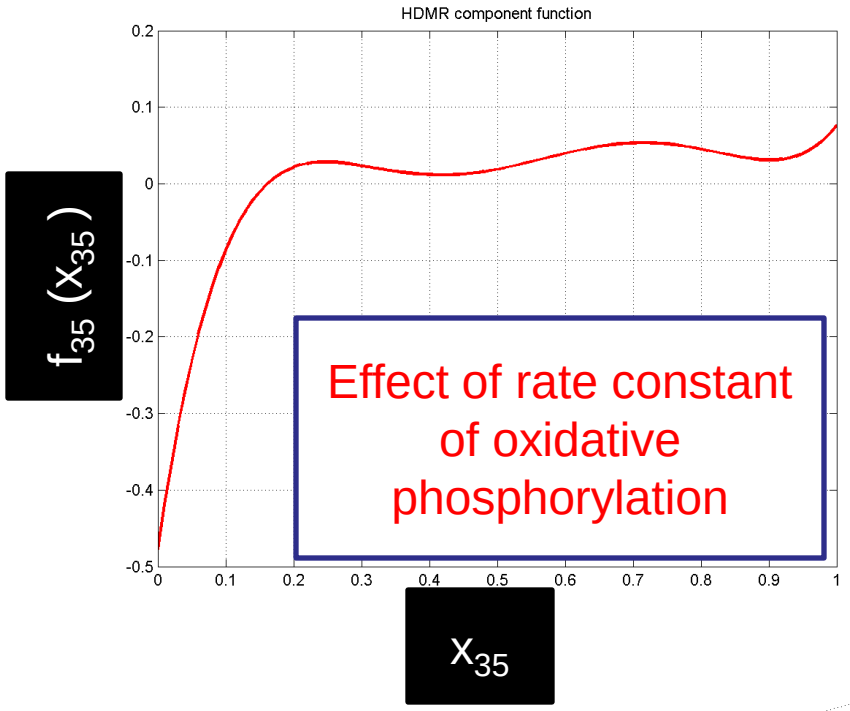
$$\int_{o}^{T_f} (ATP)\, dt$$

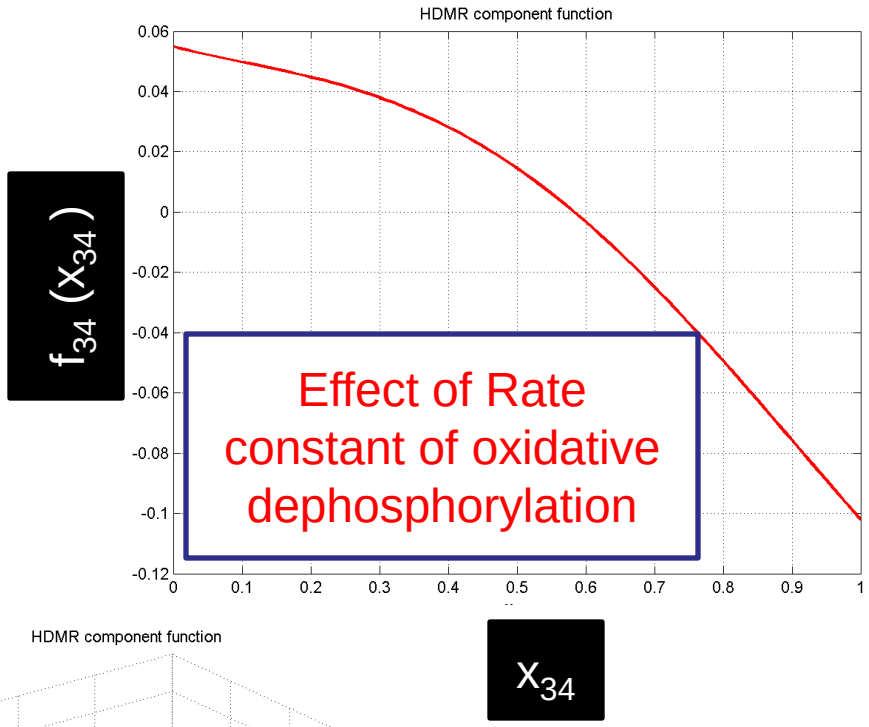
Output 1	1% RE	5% RE	10% RE	20% RE
1st order	17.12	66.96	88.48	93.36
2nd order	18.56	75.28	90.36	94.88

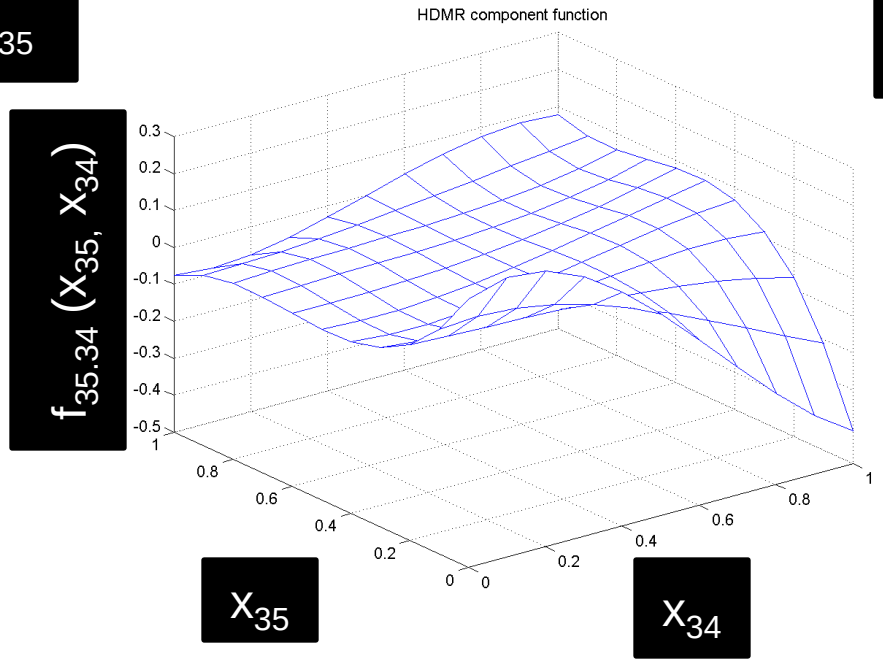
Sensitivity (Output 1)

Rank	1	2	3	4	5
Par. no.	35	34	4	10	5
S_i	0.3289	0.0853	0.0161	0.0015	0.0015

Rank	1	2	3	4	5
Par. no.	35,34	4, 35	4, 34	1, 18	3, 19
S_{ij}	0.1557	0.0107	0.007	0.0029	0.0014


HDMR component function
$f_{35}(x_{35})$
Effect of rate constant of oxidative phosphorylation
x_{35}


HDMR component function
$f_{34}(x_{34})$
Effect of Rate constant of oxidative dephosphorylation
x_{34}


HDMR component function
$f_{35.34}(x_{35}, x_{34})$
x_{35}
x_{34}

Glucose metabolism – only Glycolysis

Output 2

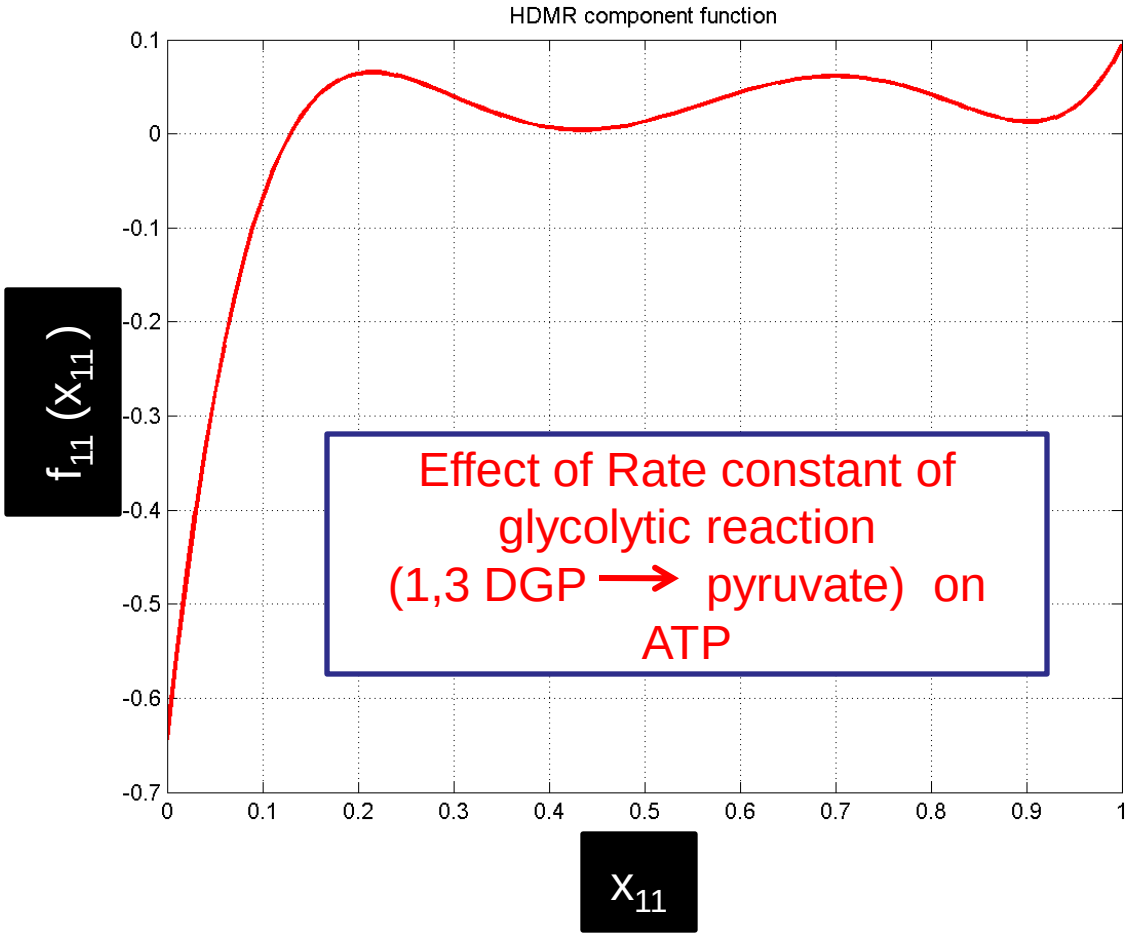
$$\int_{o}^{T_f} (ATP)\, dt$$

Accuracy

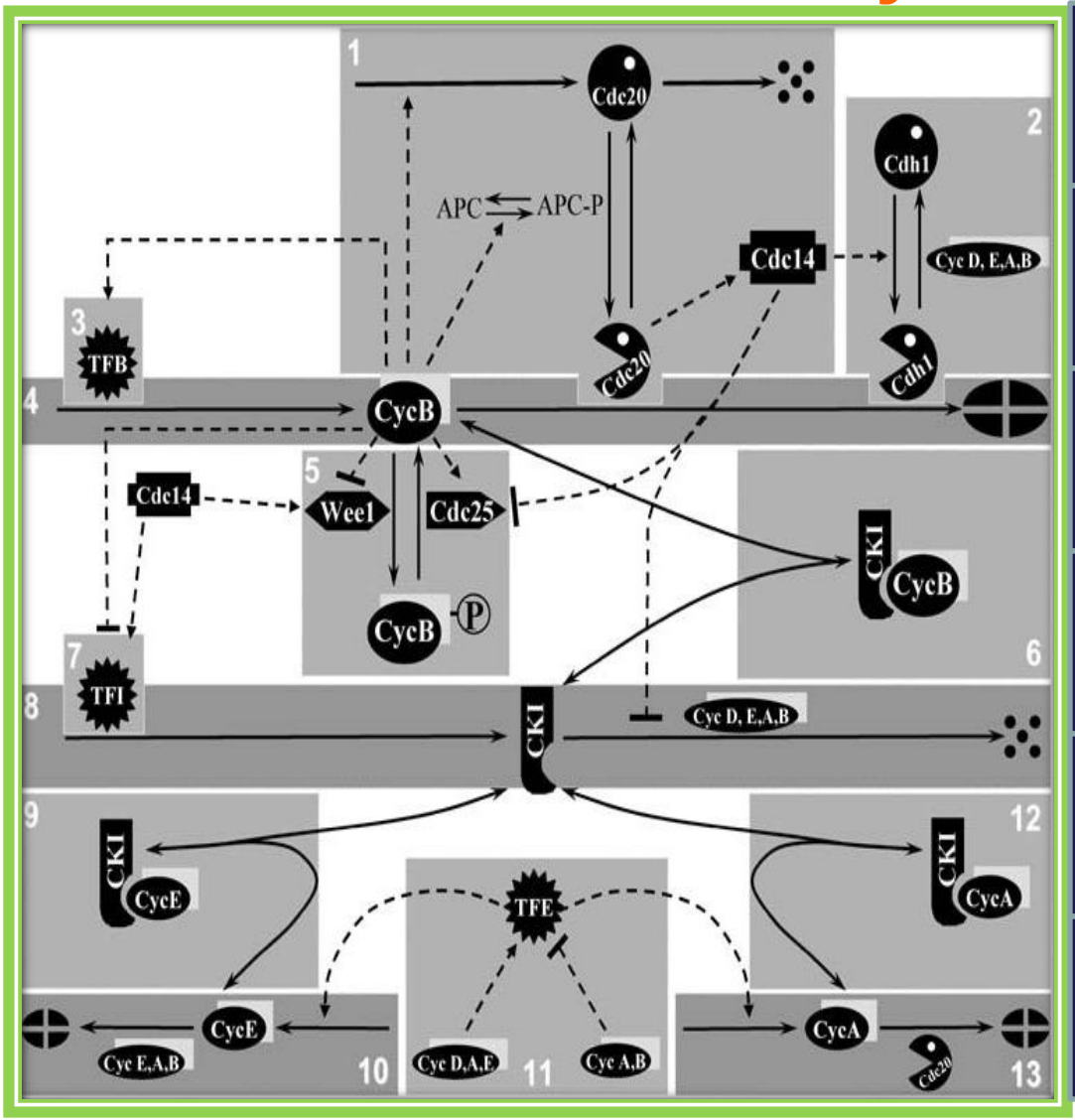
Output 2	1% RE	5% RE	10% RE	20% RE
1st order	19.84	76.72	90.88	94.24
2nd order	17.36	74.24	90.48	94.4

Sensitivity (Output 2)

Rank	1	2	3	4	5
Par. no.	11	10	15	14	6
S_i	0.4647	0.0091	0.0064	0.0038	0.0033


HDMR component function
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
$f_{11}(x_{11})$
x_{11}
Effect of Rate constant of glycolytic reaction (1,3 DGP → pyruvate) on ATP

Cell cycle model



Modules 4, 10,13 : synthesis and degradation of cyclins B, E and A

Modules 1,2: Regulation of Anaphase

Modules 8: Synthesis and degradation of CKI

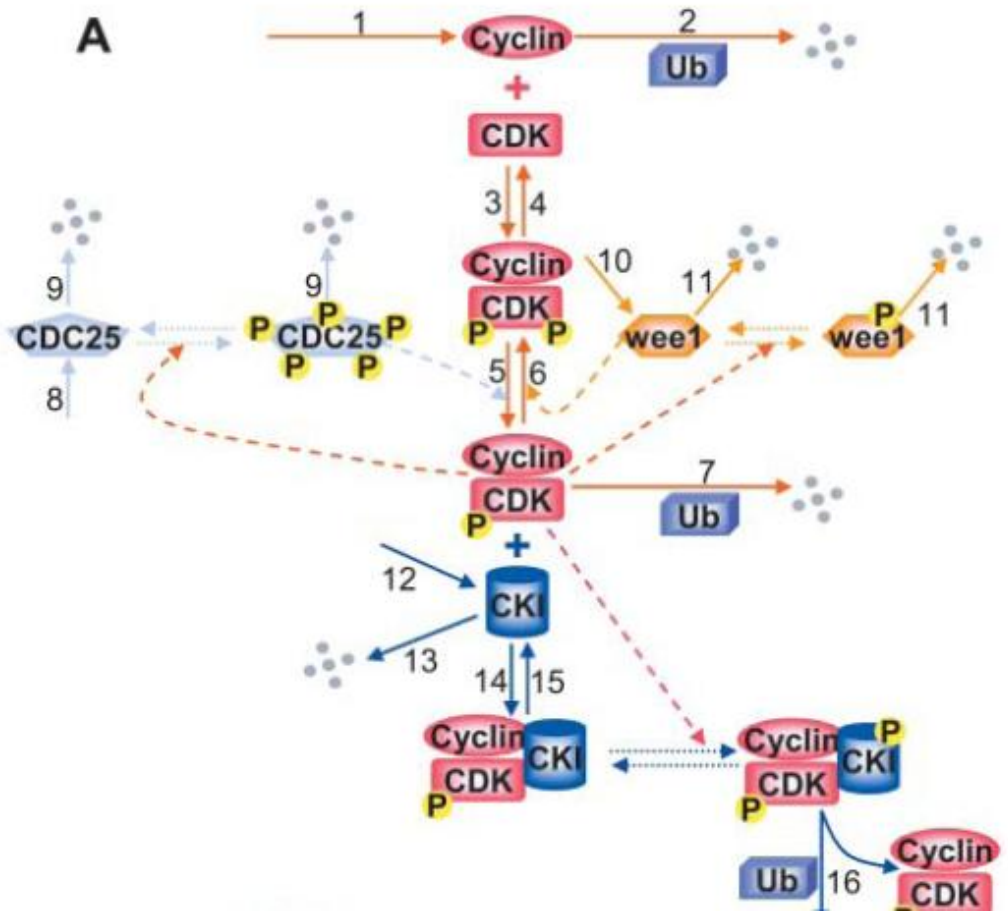
Modules 6, 9,12 : reversible binding of CKI to cyclin/Cdk dimers

Modules 3, 7, 11: Regulation of transcription factors that drive the expression of cyclins

Modules 5: Regulation of cyclin B dependent kinase (wee1 and Cdc25)

Csikasz-Nagy, Biophysical Journal, 90(2006) 4361-4379

Cyclin-Cdk Complex



Qu et.al, (2003), Biophysical Journal, 85, 3600-3611

CycA*

Rank	1	2	3	4	5
Par. no.	89	14	12	1	67
S_i	0.6141	0.0112	0.0105	0.0082	0.0055

CycB*

Rank	1	2	3	4	5
Par. no.	89	90	67	70	59
S_i	0.4975	0.0198	0.0062	0.0034	0.0034

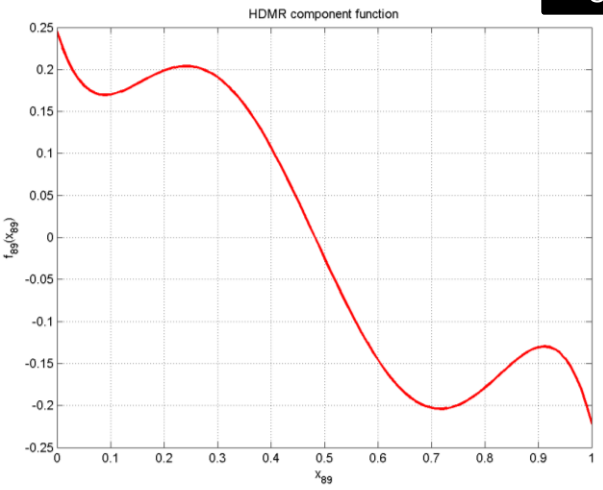
CycE*

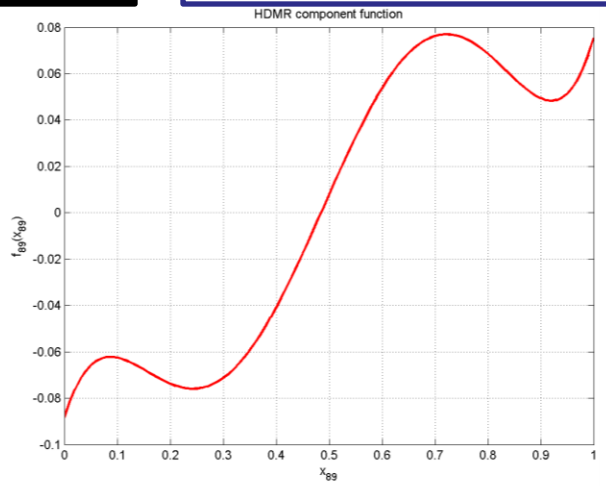
Rank	1	2	3	4	5
Par. no.	89	3	90	5	35
S_i	0.3867	0.1322	0.0488	0.0446	0.0265

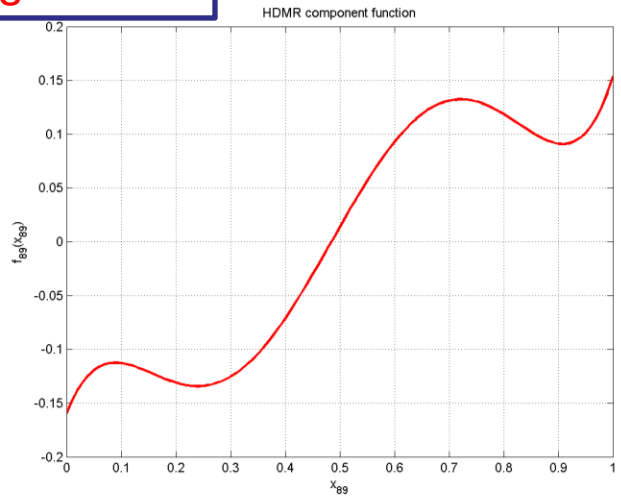
* activated

$f_{89}(x_{89})$

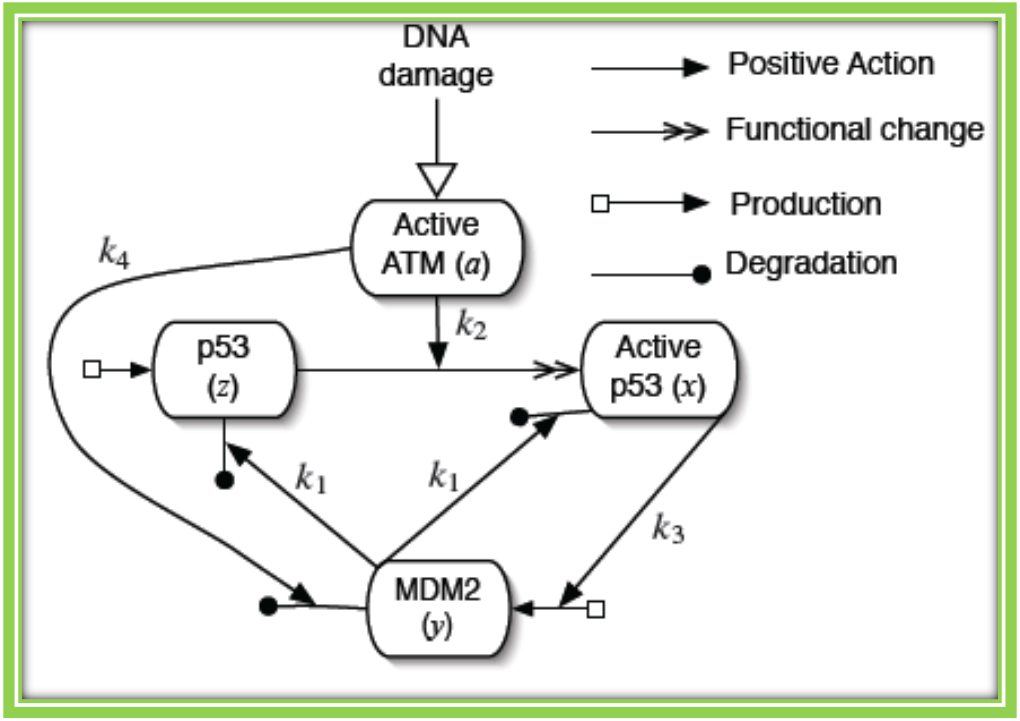
Effect of Cdh1 is significant







Kinetic model of p53



$$\frac{d[a]}{dt} = -D_a[a]$$

$$\frac{d[z]}{dt} = P_{p53} - D_{p53}[z] - k_1[y][z] - k_2[a][z]$$

$$\frac{d[x]}{dt} = -D_{p53}[x] - k_1[y][x] + k_2[a][z]$$

$$\frac{d[y]}{dt} = P_{Mdm2} + k_3[x] - D_{Mdm2}[y] - k_4[a][y]$$

P53 – Tumor suppressor

- “Guardian of the genome" and controls the cell cycle to enable the repair of damaged DNA.

D.S. Brewer, Modeling the p53 gene regulatory network. Doctor of Philosophy Thesis, University of London, London, UK, 2006

Output 1

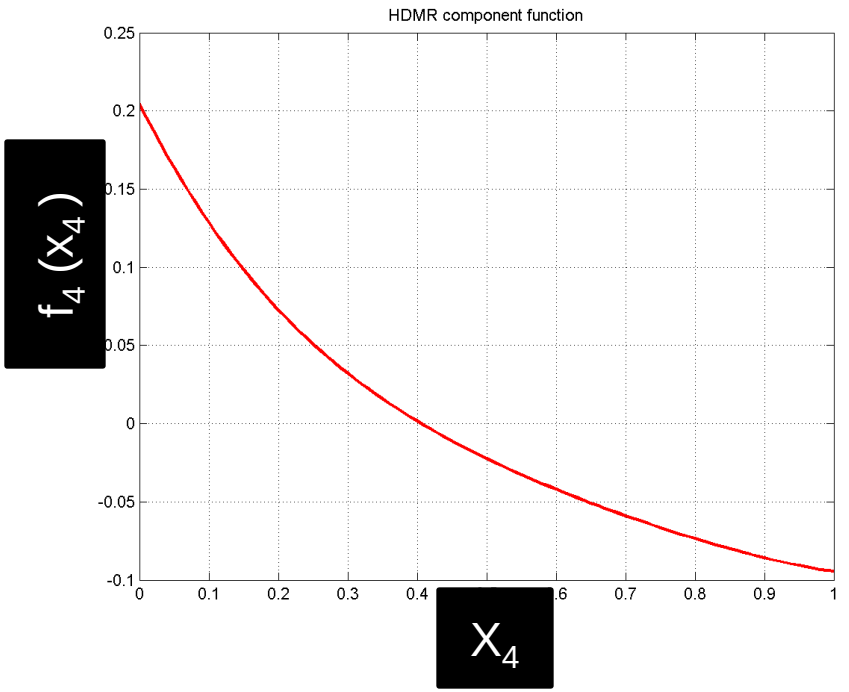
$$\int_{o}^{T_f} p53\,dt$$

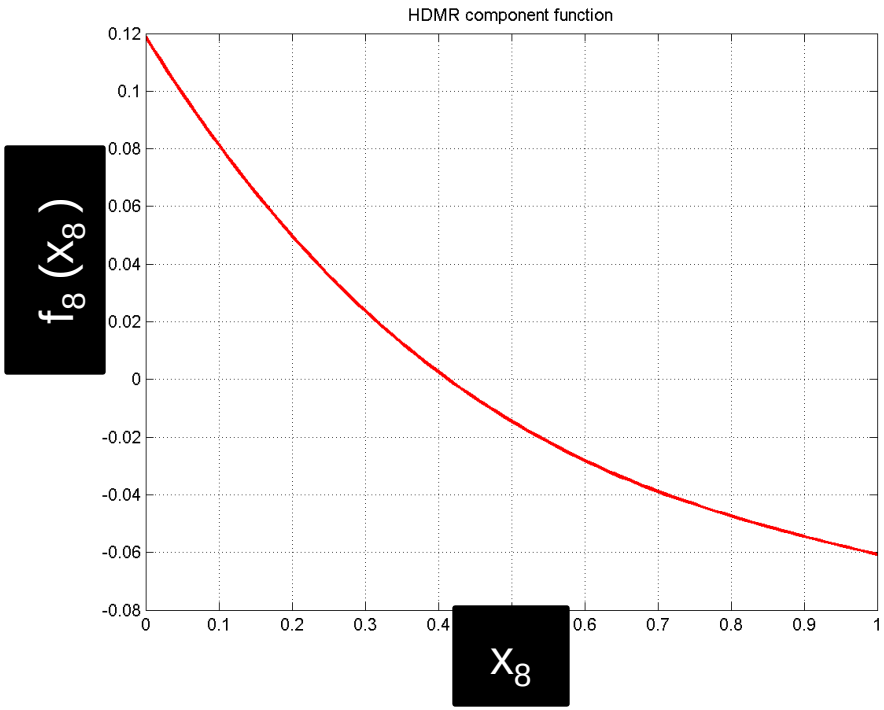
Accuracy

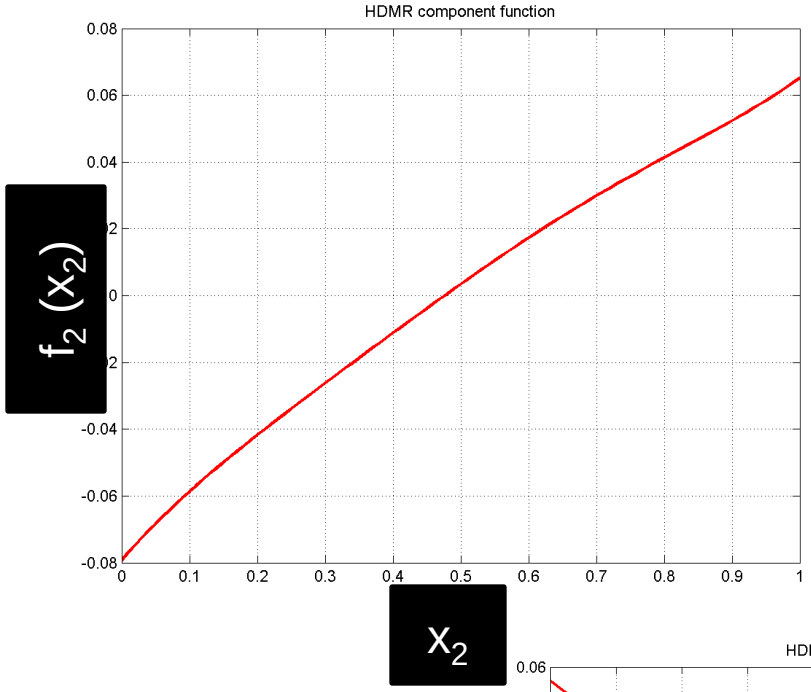
Output 1	1% RE	5% RE	10% RE	20% RE
1st order	6.64	28.32	52.8	81.2
2nd order	10.88	46.96	73.52	89.36

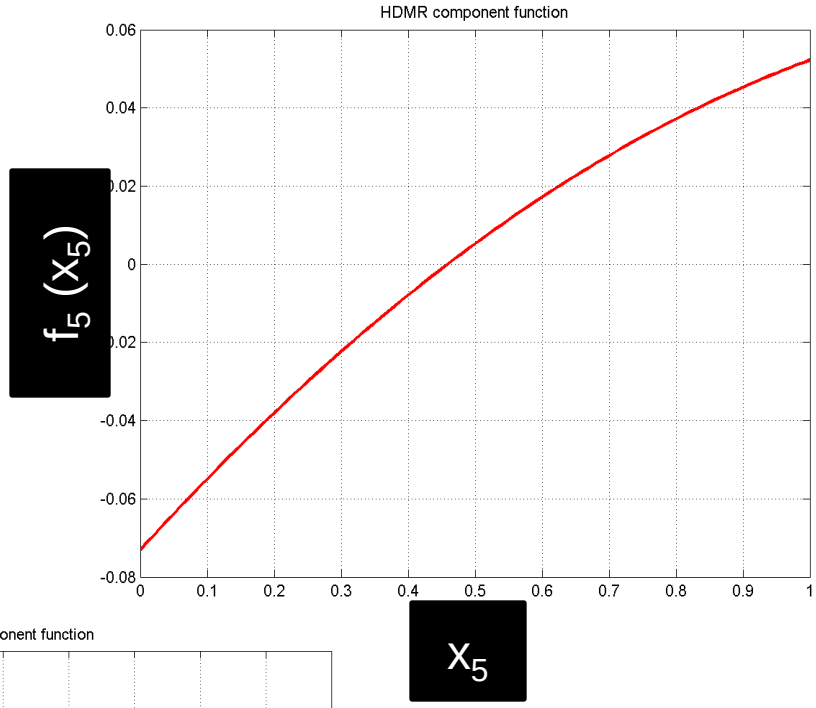
Sensitivity (Output)

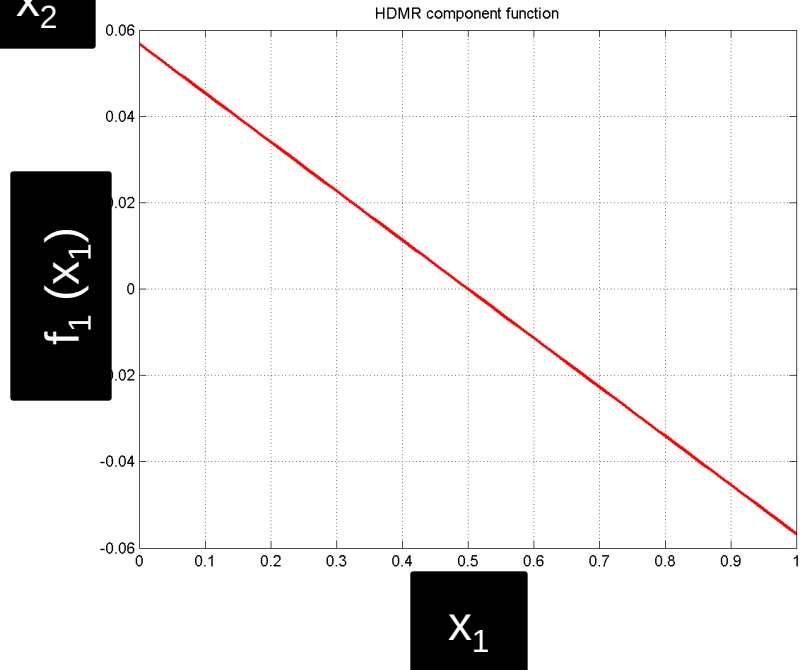
Rank	1	2	3	4	5
Par. no.	4	8	2	5	1
S_i	0.4046	0.1617	0.1046	0.0846	0.0757






HDMR component function
$f_2(x_2)$
x_2


HDMR component function
$f_5(x_5)$
x_5


HDMR component function
$f_1(x_1)$
x_1

Implications

- Key parameters affecting the output of interest
- Parameter identifiability
- Practically, it directs which protein (or gene) is responsible.
- Specific gene identification for specific type of cancer may be useful for drug discovery .

Conclusions

- Application of sensitivity analysis on Glycolysis, TCA cycle, Cyclin-CDKs, p53 pathway, cell cycle is considered
- Effect of rate constant of ADP to ATP reaction is significant
- Activated complex concentration is very much dependent on Cdh1
- In our future work, we will integrate the intracellular pathways and study the cancerous features.
- As a whole, this analysis will help in reducing experimental effort in order to implement novel diagnostic procedures for diabetes.

Key Contributions

- Kiran, K.L., Lakshminarayanan, S. and Jayachandran, D. Mathematical modeling of avascular tumor growth based on diffusion of nutrients and its validation, The Canadian Journal of Chemical Engineering, 2009, 87, 732-740.

- Kiran, K. L.; Lakshminarayanan, S. Treatment planning of cancer dendritic cell therapy using multi-objective optimization, ADCHEM, Turkey, 2009 (Keynote paper).

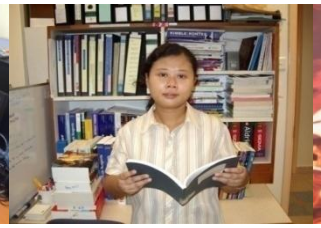
- Kiran, K.L., Lakshminarayanan, S., Global Sensitivity Analysis and Model-based Reactive Scheduling of Targeted Cancer Immunotherapy, BioSystems, 2010 (Accepted)

- Kiran, K.L., Lakshminarayanan, S. Sequential Scheduling of Cancer Immunotherapy and Chemotherapy using Multi-Objective Optimization, BioSystems, 2010 (Submitted).

Our Group - IPC

A/Prof. Lakshminarayanan S

Anesthesia



Diabetes

Epidemics

Kidney dialysis

Pathway analysis

Process monitoring

Process intensification

Diabetes

Image analysis

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