# Mathematical modelling for studying the allosteric regulation of Phosphofructokinase 1

KAJAL GUPTA

# OVERVIEW

- BACKGROUND - MOTIVATION TO IMPROVE MODEL
- METHOD - MODEL CANDIDATES
- RESULT
- CONCLUSION - BIOLOGICAL INTERPRETATION

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# WHAT CAN BE MODIFIED?

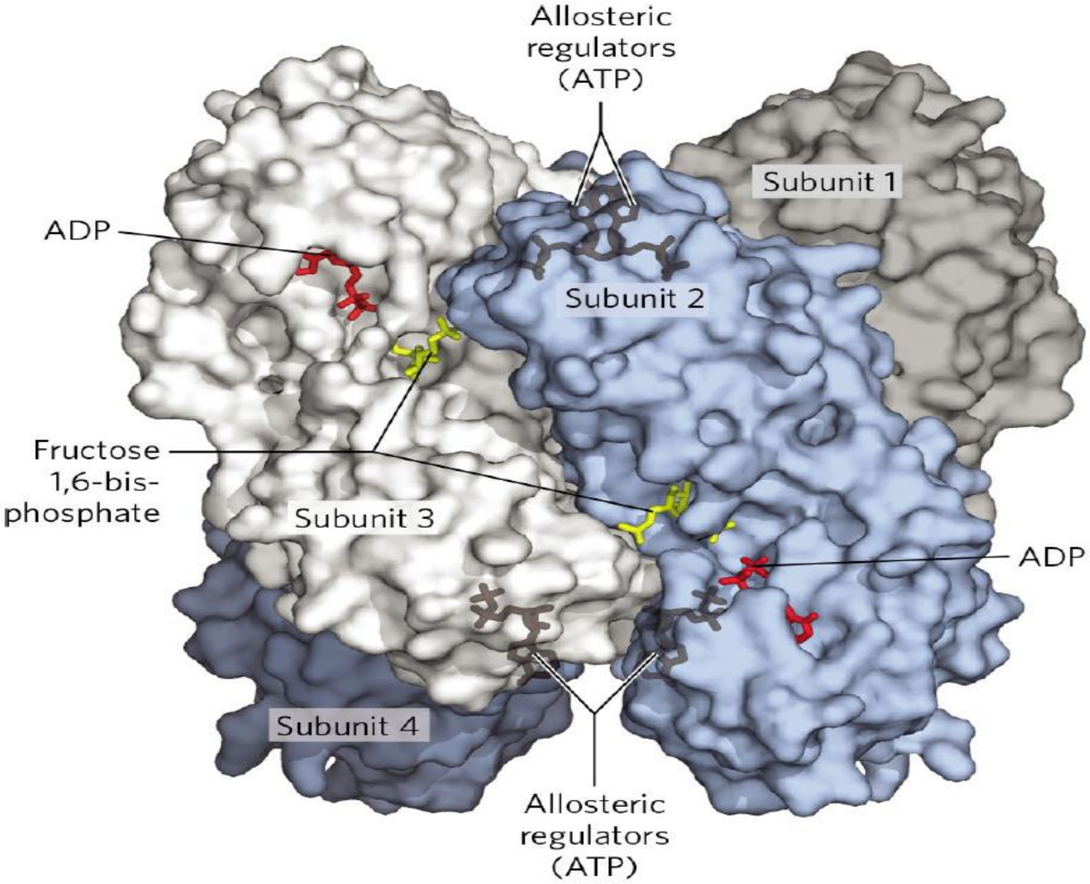
1. VARIABLE
2. REACTION KINETICS

# 1. Variable selection

- Simple model does not take in account regulation(except by pS6k)

- PFKL reaction regulated by many known allosteric regulators.

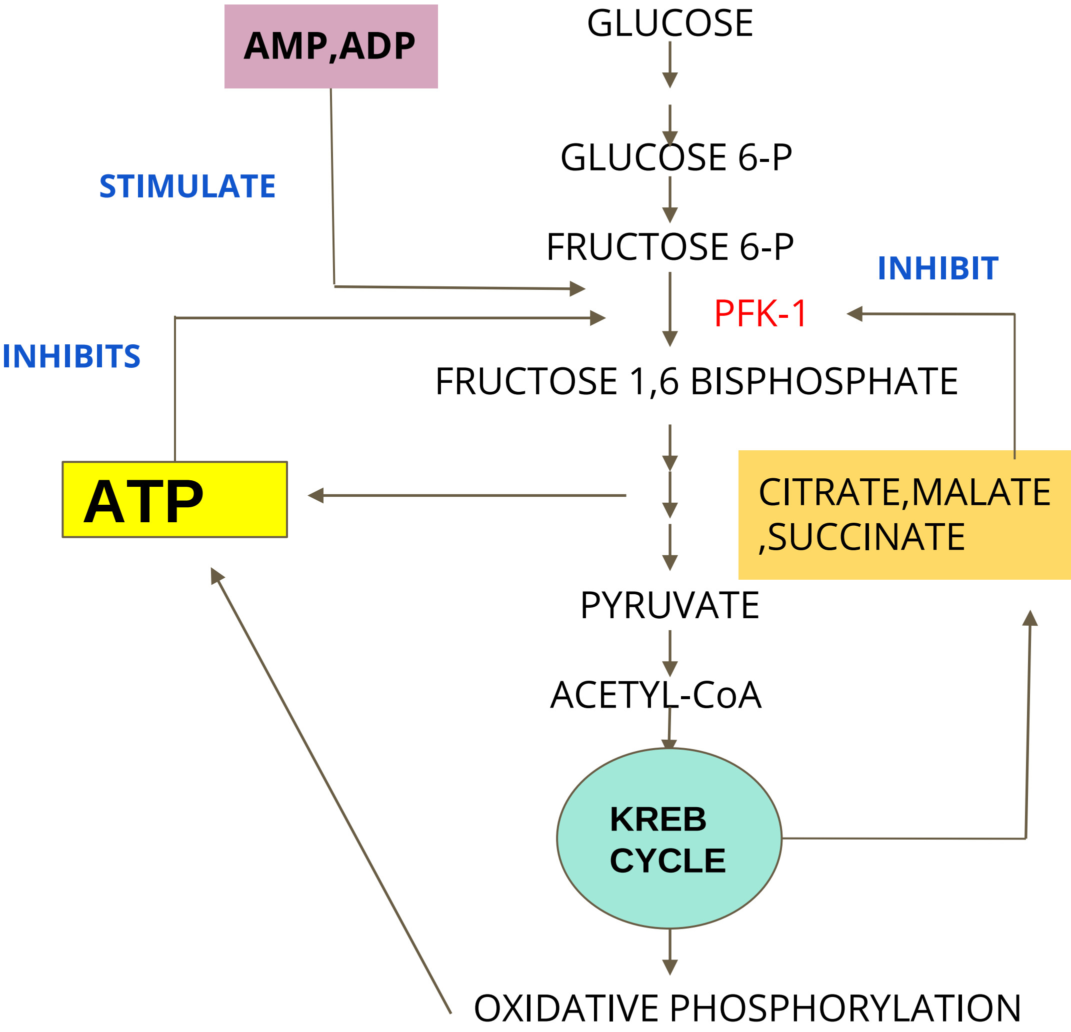
# 1. Variable selection



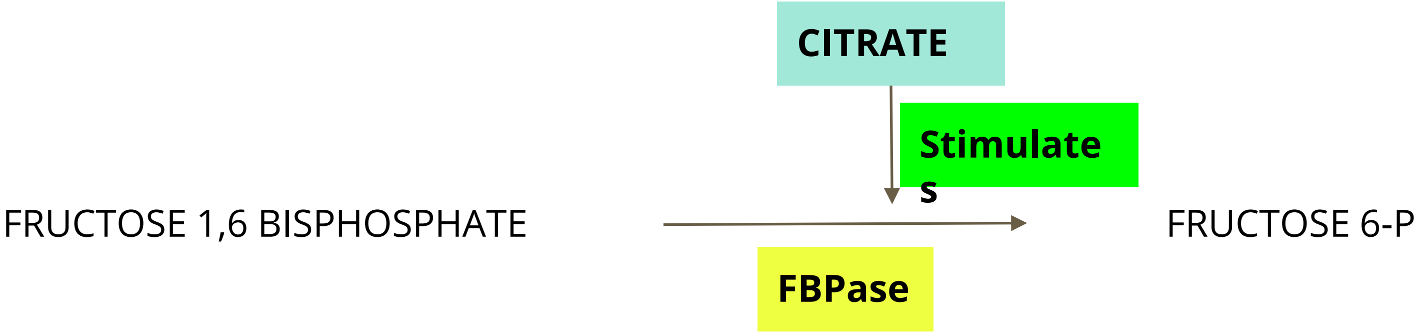

Lehninger:Principles of Biochemistry by David Nelson and Michael Cox(7th edition) (

# 1. Variable selection

- Variables selected from literature review



# 1. Variable selection



# 2. REACTION KINETICS

Reaction equation for mass-action: $v = k[\text{Substrate}]$

- Modular rate law model

$$v = \left\{\prod_i \left(\frac{[A]_i}{K_{A_i} + [A]_i}\right)\right\}\left\{\prod_j \left(\frac{K_{I_j}}{K_{I_j} + [I]_j}\right)\right\}\left(\frac{V_{max}[S]}{K_m + [S]}\right)$$

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# MODEL CANDIDATES

| MODEL | VARIABLE SELECTION for PFKL regulation | Variable selection for FBPase |
|---|---|---|
| ORIGINAL | NO | NO |
| MODEL 1 | ATP,ADP,AMP,CITRATE,SUCCINATE,MALATE | CITRATE |
| MODEL 2 | ATP,CITRATE,SUCCINATE,MALATE | CITRATE |
| MODEL 3 | CITRATE,SUCCINATE,MALATE | CITRATE |
| MODEL 4 | SUCCINATE,MALATE | NO |
| MODEL 5 | CITRATE,MALATE | CITRATE |
| MODEL 6 | CITRATE,SUCCINATE | CITRATE |
| MODEL 7 | ATP,AMP,ADP | NO |

# ORIGINAL MODEL

$$\frac{d[\mathrm{F1,6BP}]}{dt} = v_{\mathrm{PFKL}} - v_{\mathrm{FBPase}} - v_{\mathrm{ALDO}}$$

$$v_{\mathrm{PFKL}} = k_{\mathrm{PFKL}}[\mathrm{F6P}][\mathrm{pS6K}]$$
$$v_{\mathrm{FBPase}} = k_{\mathrm{FBPase}}[\mathrm{F1,6BP}]$$
$$v_{\mathrm{ALDO}} = k_{\mathrm{ALDO}}[\mathrm{F1,6BP}]$$

# MODEL 1

$$\boldsymbol{\nu}_{pfkl} = (K_{Cit}/ K_{Cit} + [Cit]) (K_{ATP}/ K_{ATP} + [ATP])(K_{Suc}/ K_{Suc} + [Suc])(K_{Mal}/ K_{Mal} + [Mal] ([ADP]/K_{ADP} + [ADP])([AMP]/K_{AMP} + [AMP])(V_{max}[F6P] / K_{F6P} + [F6P])$$

$$\boldsymbol{\nu}_{fbpase} = ([Cit]/K_{Cit} + [Cit])(V_{max}[F1,6P] / K_{F1,6P} + [F1,6P])$$

$$\boldsymbol{\nu}_{aldo} = k_{aldo} [F1,6P]$$

# MODEL 2

$\boldsymbol{\nu}_{pfkl}$ = $(K_{Cit}/\ K_{Cit}\ + [Cit])\ (K_{ATP}/\ K_{ATP} + [ATP])(K_{Suc}/\ K_{Suc} + [Suc])(K_{Mal}/\ K_{Mal}\ + [Mal]$
$(V_{max}[F6P]\ /\ K_{F6P} + [F6P])$

$\boldsymbol{\nu}_{fbpase}$ = $([Cit]/K_{Cit}\ + [Cit])(V_{max}[F1,6P]\ /\ K_{F1,6P} + [F1,6P])$

$\boldsymbol{\nu}_{aldo}$ = $k_{aldo}\ [F1,6P]$

# MODEL 3

$\boldsymbol{\nu}_{pfkl} = (K_{Cit}/ K_{Cit} + [Cit]) (K_{Suc}/ K_{Suc} + [Suc])(K_{Mal}/ K_{Mal} + [Mal]$
$(V_{max}[F6P] / K_{F6P} + [F6P])$

$\boldsymbol{\nu}_{fbpase} = ([Cit]/K_{Cit} + [Cit])(V_{max}[F1,6P] / K_{F1,6P} + [F1,6P])$

$\boldsymbol{\nu}_{aldo} = k_{aldo} [F1,6P]$

# MODEL 4

$\boldsymbol{\nu}_{pfkl}$ = $(K_{Suc}/ K_{Suc} + [Suc])(K_{Mal}/ K_{Mal} + [Mal](V_{max}[F6P] / K_{F6P} + [F6P])$

$\boldsymbol{\nu}_{fbpase}$ = $(V_{max}[F1,6P] / K_{F1,6P} + [F1,6P])$

$\boldsymbol{\nu}_{aldo}$ = $k_{aldo} [F1,6P]$

# MODEL 5

$\boldsymbol{\nu}_{pfkl}$ = (K$_{Cit}$/ K$_{Cit}$ + [Cit]) (K$_{Mal}$/ K$_{Mal}$ + [Mal](V$_{max}$[F6P] / K$_{F6P}$ + [F6P])

$\boldsymbol{\nu}_{fbpase}$ = ([Cit]/K$_{Cit}$ + [Cit])(V$_{max}$[F1,6P] / K$_{F1,6P}$ + [F1,6P])

$\boldsymbol{\nu}_{aldo}$ = k$_{aldo}$ [F1,6P]

# MODEL 6

$\boldsymbol{\nu}_{pfkl} = (K_{Cit}/ K_{Cit} + [Cit])(K_{Suc}/ K_{Suc} + [Suc])(V_{max}[F6P] / K_{F6P} + [F6P])$

$\boldsymbol{\nu}_{fbpase} = ([Cit]/K_{Cit} + [Cit])(V_{max}[F1,6P] / K_{F1,6P} + [F1,6P])$

$\boldsymbol{\nu}_{aldo} = k_{aldo} [F1,6P]$

# MODEL 7

$\boldsymbol{\nu}_{pfkl}$ = $(K_{ATP}/\ K_{ATP} + [ATP])([ADP]/K_{ADP}\ + [ADP])([AMP]/K_{AMP}\ + [AMP])$
$(V_{max}[F6P]\ /\ K_{F6P} + [F6P])$

$\boldsymbol{\nu}_{fbpase}$ = $(V_{max}[F1,6P]\ /\ K_{F1,6P} + [F1,6P])$

$\boldsymbol{\nu}_{aldo}$ = $k_{aldo}\,[F1,6P]$

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# Parameter estimation

- Process of computing a model's parameter values from measured data.
- If experimental data is available for one or more species in the system, the values of these parameters can be estimated

# Residual sum of squares(RSS)

- Sum of the squares of residuals (deviations predicted from actual empirical values of data).
- Measure the discrepancy between the data and an estimation model.
- A small RSS indicates a tight fit of the model to the data.

○residuals $y_i - f(\boldsymbol{k}, t_i)$

Data (experiment)

Model output (estimation)

$\boldsymbol{k}$: parameter、t: time

The difference between observed data and model output (simulated trajectories)

$$\mathbf{RSS} = \sum_{i=1}^{N} \left(y_i - f(\boldsymbol{k}, t_i)\right)^2$$

N= The number of data points

# Akaike information criterion(AIC)

- Estimator of prediction error and thereby relative quality of statistical models for a given set of data.

$$AIC = -2\log L + 2(k+2)$$

**L: likelihood**
**k: number of parameters**

$$AIC = n\ln RSS + n\ln 2\pi - n\ln n - n + 2(k+2)$$

$n$: number of samples

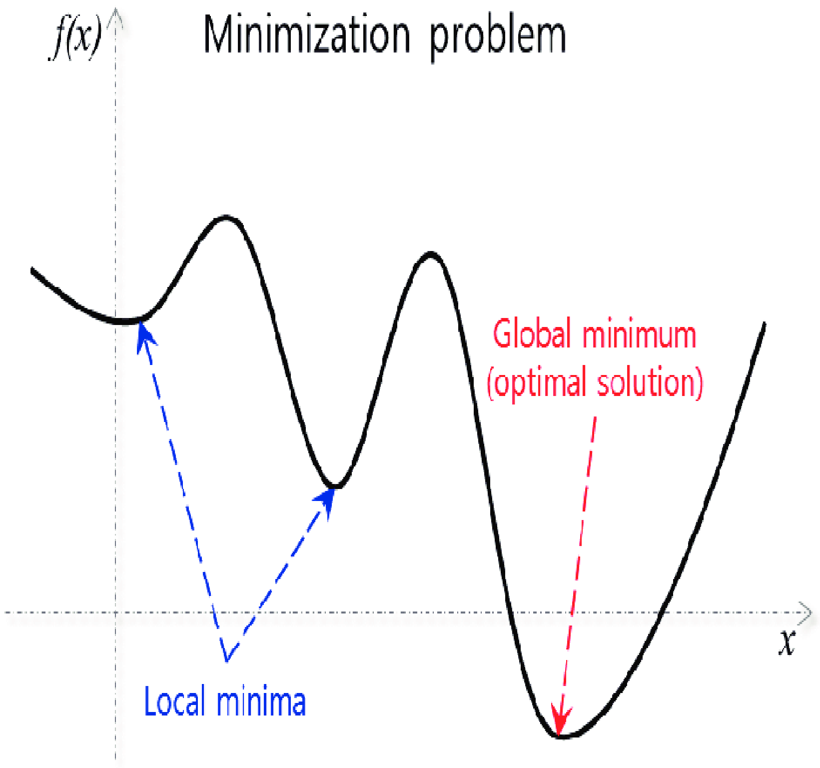
# PARAMETER ESTIMATION

1. Global optimization - Evolutionary programming (EP)

Objective function : RSS

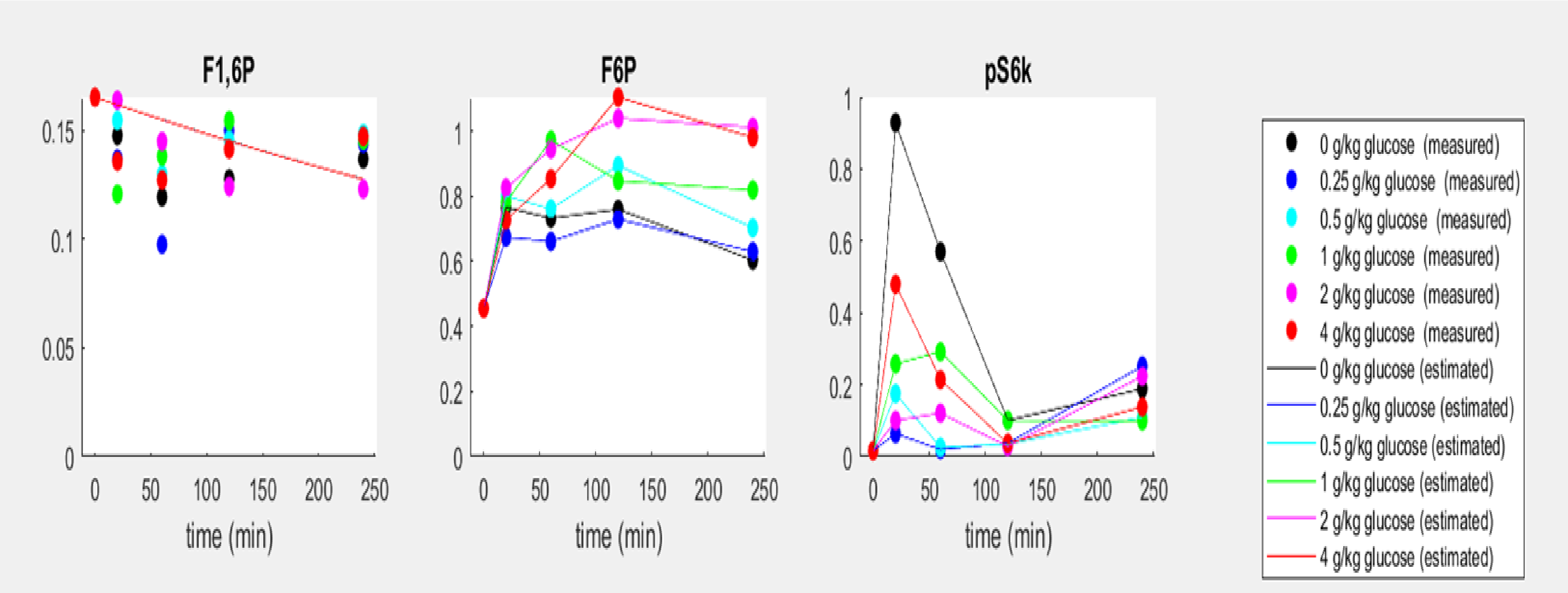
#Parents = 10

1. Local optimization - MATLAB function (lsqnonlin)
2. Parameter set with smallest RSS is selected




Jeon et al., *JRPR* (2017)

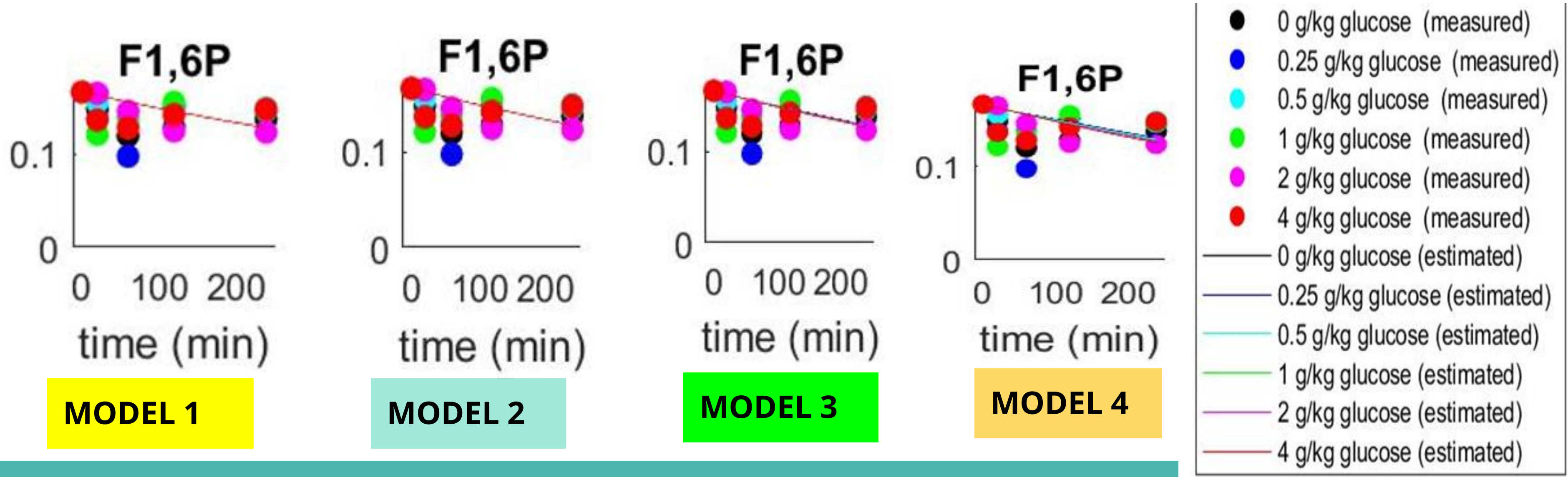
# Simulation results of original model




**RSS : 0.43749**
**AIC : -13.8409**

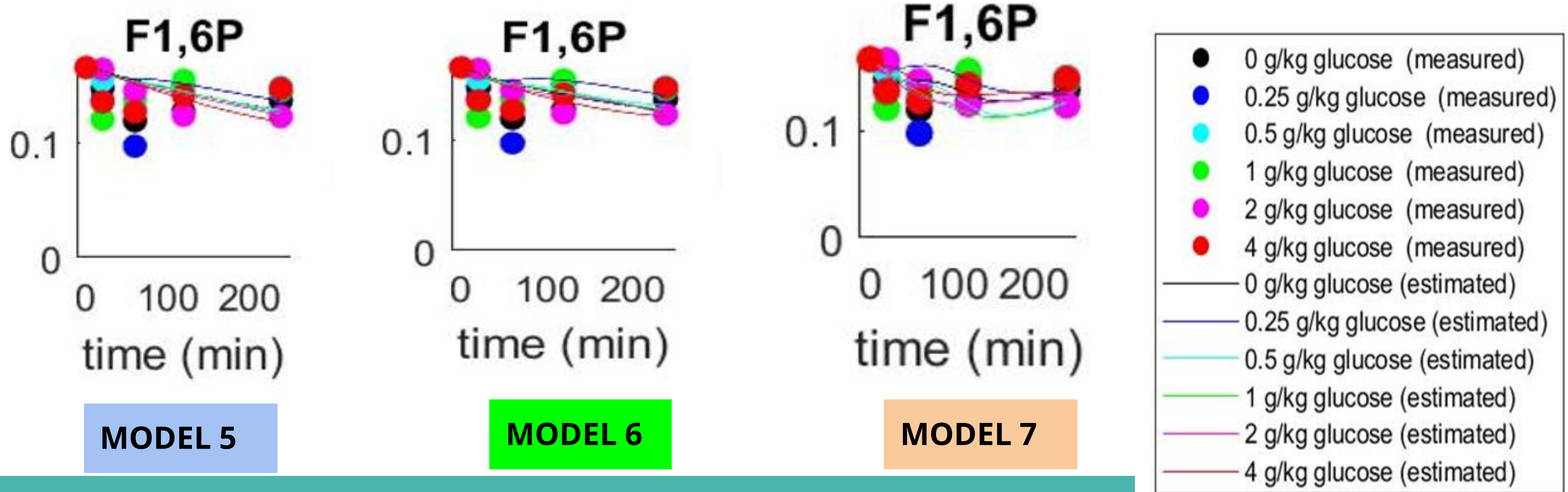
# Simulation results of model 1-4

| Models | Allosteric Molecules of PFKL | Allosteric molecules of FBPase | RSS | AIC |
|---|---|---|---|---|
| Original Model | No | NO | 0.43749 | -13.8409 |
| Model 1 | ATP,ADP,AMP,CITRATE,SUCCINATE,MALATE | CITRATE | 0.43743 | 4.1559 |
| Model 2 | ATP,CITRATE,SUCCINATE,MALATE | CITRATE | 0.43744 | 0.15657 |
| Model 3 | CITRATE,SUCCINATE,MALATE | CITRATE | 0.43576 | -1.9359 |
| Model 4 | SUCCINATE,MALATE | NO | 0.43552 | -5.9494 |

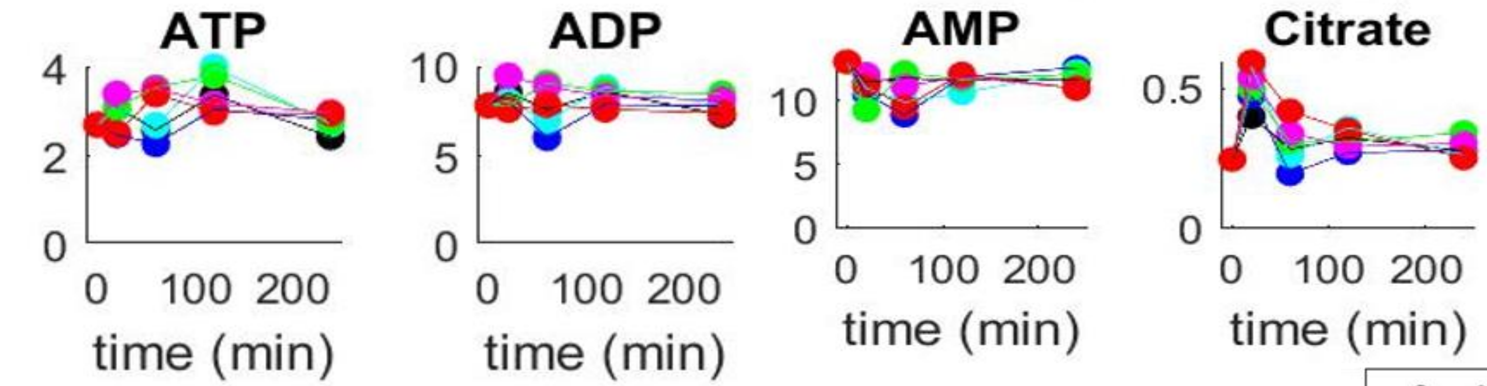


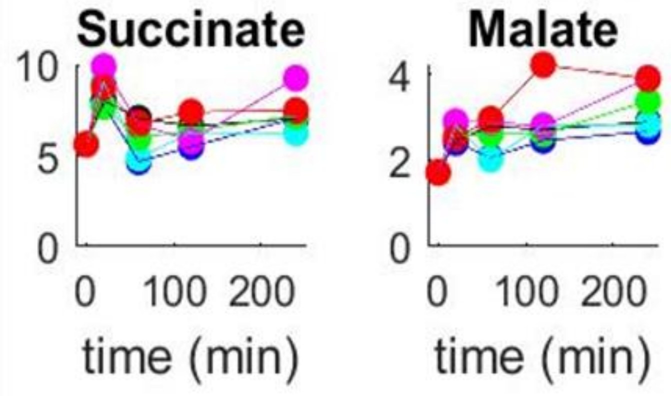
# Simulation result of model 5-7

| Models | Allosteric Molecules of PFKL | Allosteric molecules of FBPase | RSS | AIC |
|---|---|---|---|---|
| Original Model | No | NO | 0.43749 | -13.8409 |
| model 5 | CITRATE,MALATE | CITRATE | 0.42772 | -4.3831 |
| Model 6 | CITRATE,SUCCINATE | CITRATE | 0.36739 | -8.032 |
| Model 7 | ATP,AMP,ADP | NO | 0.3911 | -6.5312 |

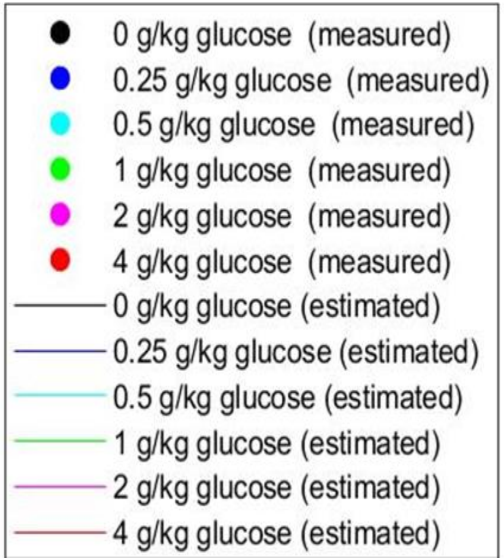


# Simulation results of allosteric regulators




**y-axis : metabolite concentration(μmol/g-protein)**
**x-axis : time(min)**



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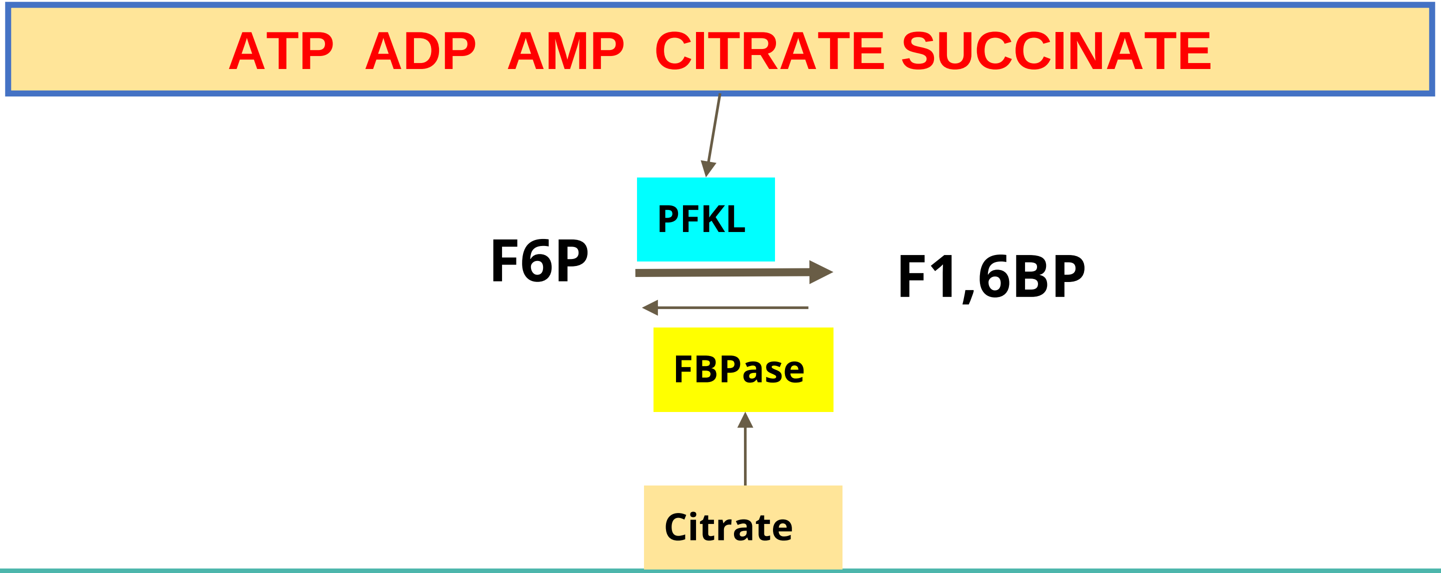
# AICs of all the models

| Models | Allosteric Molecules | RSS | AIC |
| --- | --- | --- | --- |
| Original model | NO | 0.43749 | -13.8409 |
| Model 1 | ATP,ADP,AMP,CITRATE,SUCCINATE,MALATE | 0.43743 | 4.1559 |
| Model 2 | ATP,CITRATE,SUCCINATE,MALATE | 0.43744 | 0.15657 |
| Model 3 | CITRATE,SUCCINATE,MALATE | 0.43576 | -1.9359 |
| Model 4 | SUCCINATE,MALATE | 0.43552 | -5.9494 |
| model 5 | CITRATE,MALATE | 0.42772 | -4.3831 |
| Model 6 | CITRATE,SUCCINATE | 0.36739 | -8.032 |
| Model 7 | ATP,AMP,ADP | 0.3911 | -6.5312 |

# Possible reaction mechanism

- Model 6 showed the minimum AIC value.
- Malate have mild inhibitory regulation according to the current data.
- Citrate and Succinate can significantly regulate PFKL.
- ATP,ADP AND AMP together had significant effect on PFKL regulation.



# THANK YOU