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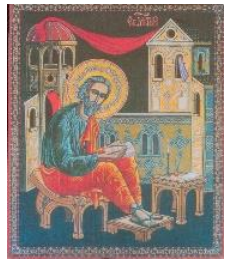
Почетен член на "Съвета на Европейската научна и културна общност”



Contemporary methods for modeling and adaptive control of bioprocesses embedded in the software system InSEMCoBio

Velislava Lyubenova, Prof. DSc

24 October 2024
Craiova, Roumania

Project working team

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Model-based adaptive control algorithms of bioreactors – a brief review

1. General Dynamical Model Approach

2. Developments of General Dynamical Model Approach

- ✓ New formalization of biotechnological processes' kinetics
- ✓ Derivation and tuning of the general software sensor of the full kinetics of biotechnological processes
- ✓ General algorithm for fully adaptive linearizing control with software sensors

3. Applications of proposed theoretical solutions

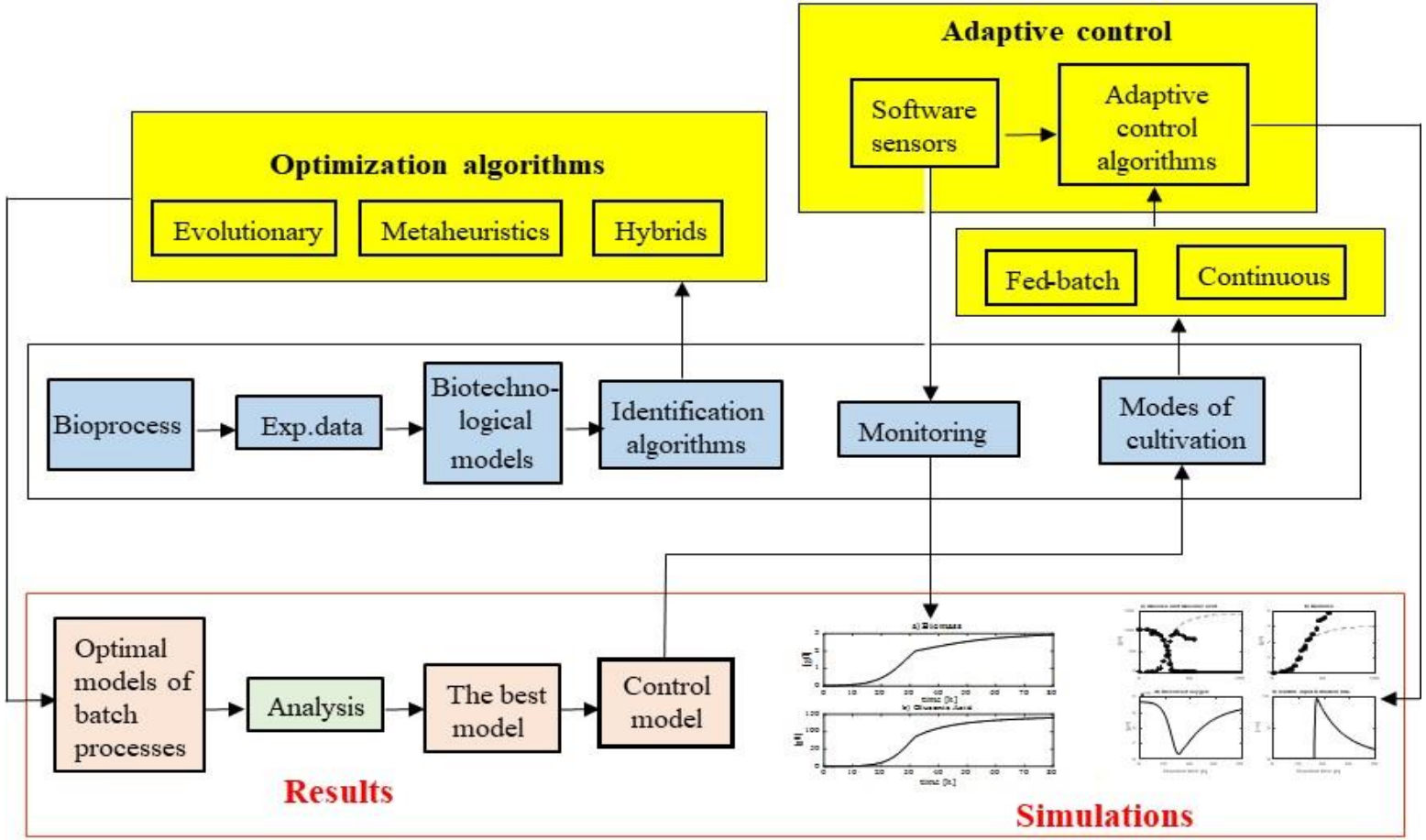
Three control strategies:

- ✓ fully adaptive control of the main substrate
- ✓ partially adaptive control of intermediate metabolite
- ✓ stabilization of the desired physiological state

4. Disscusion

Development of a Interactive System for Education in Modelling and Control of Biotehnological Processes (InSEMCoBio)

1. Modules and functions of InSEMCoBio
2. Demonstration of results for concrete processes



Scheme of the interactive system InSEMCoBio

Model-based adaptive control algorithms of bioreactors – a brief review

1. General Dynamical Model Approach

Bastin, G., D. Dochain. On-line estimation and adaptive control of bioreactors. Amsterdam, Oxford, New York, Tokyo: Elsevier, 1990, p.378.

$$S + O_2 \xrightarrow{\varphi_1} X$$
$$S \xrightarrow{\varphi_2} X + E$$
$$E + O_2 \xrightarrow{\varphi_3} X$$

$$\frac{d\xi}{dt} = \sum_{j \approx i} (\pm) k_{ij} \varphi_j - D\xi + F_i - Q_i$$

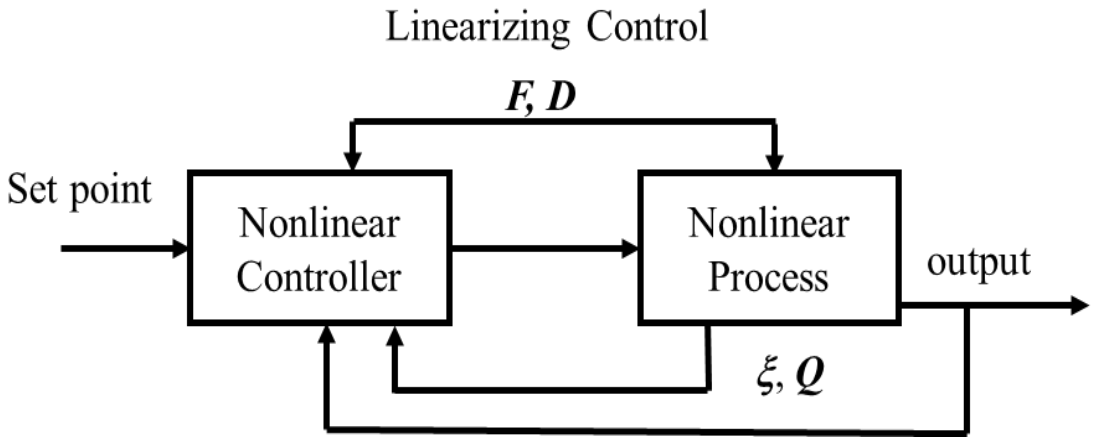
ξ - component *i* in the liquid phase in the reactor;
k - yield coefficient: (+) if the component is a *product* ; (-) if the component is a *substrate;*
φ - reaction rate *j;*
F - the mass feed rate in the reactor of the component ξ_i ;
Q - the rate of mass outflow of the component ξ_i from the reactor in gaseous form.

1. General Dynamical Model Approach

Process kinetics

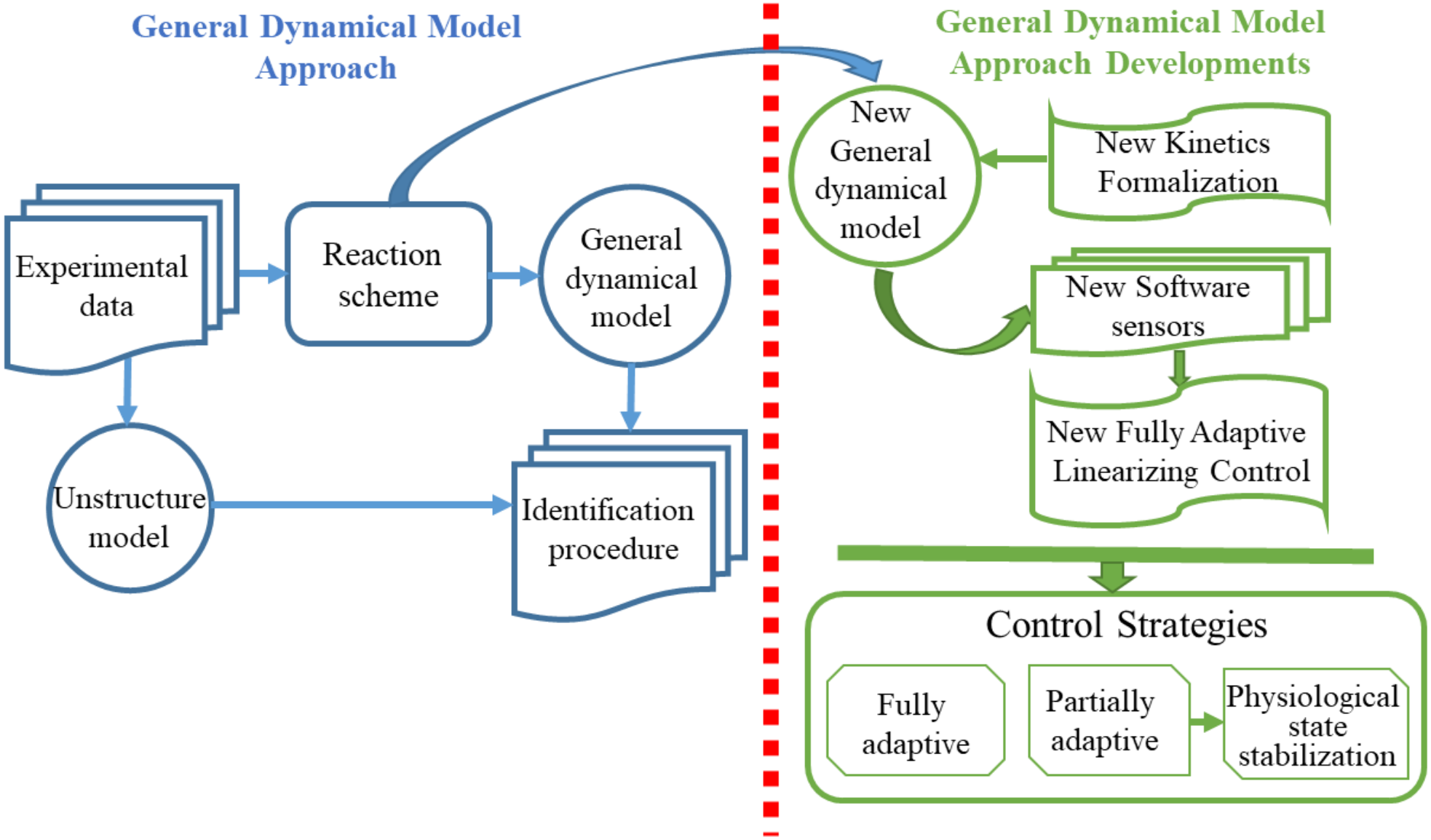
Transport dynamics

$$d\xi/dt = K\varphi - D\xi + F - Q$$



Scheme of linearizing control

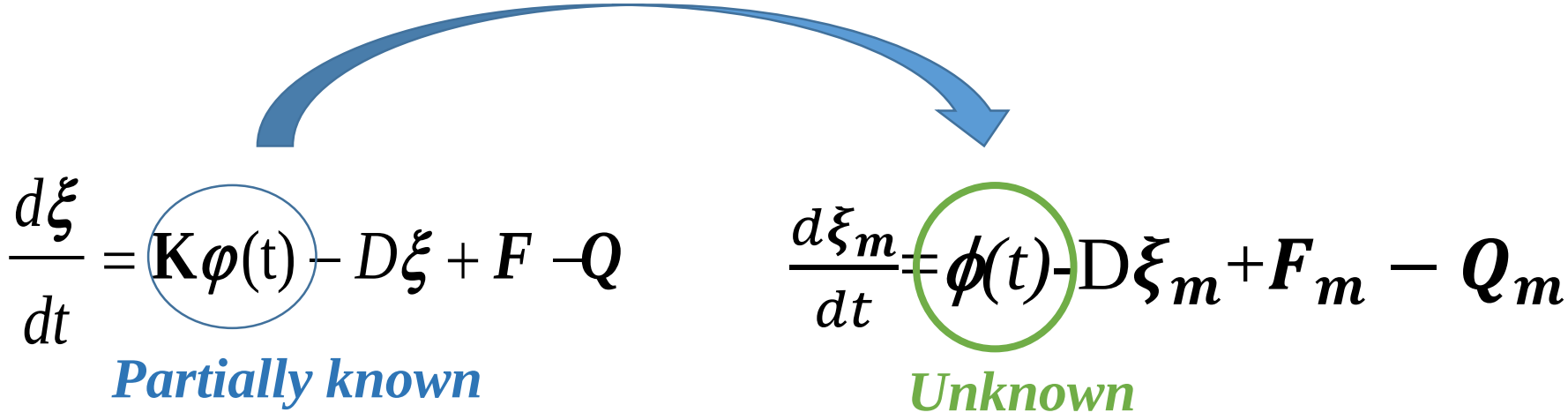
2. Developments of General Dynamical Model Approach



Classic GDM approach and the proposed developments – a comparison.

2. Developments of General Dynamical Model Approach

- ✓ New formalization of biotechnological processes' kinetics



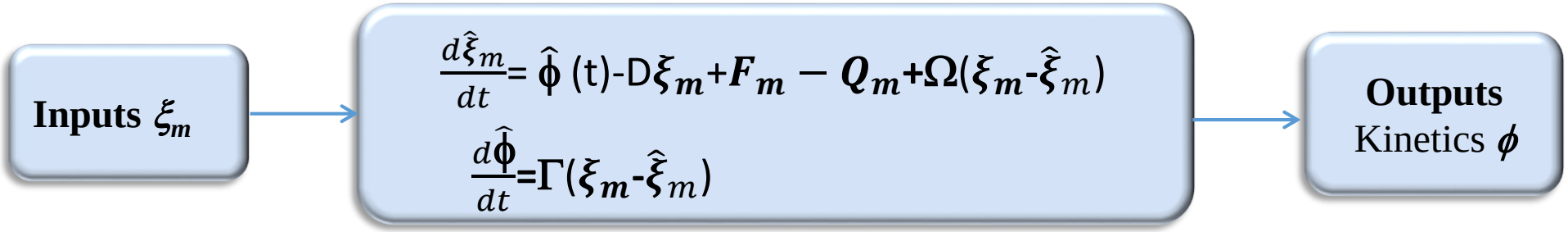
K – constant yield coefficient matrix

***φ(t)* –** reaction rate vector

***ϕ(t)* – unknown time-varying parameters vector**

2. Developments of General Dynamical Model Approach

✓ Derivation and tuning of the general software sensor of the full kinetics of biotechnological processes



Ω and $\Gamma \in \mathbb{R}_{nmxnm}$ - matrices with tuning estimator parameters

***Theorem**: Under* admissible limitations of the kinetics and measurements noises, *estimation errors are* are asymptotically bounded for all *t* as follows*:*

$$\limsup_{t\to\infty} \left|\tilde{\xi}_1(t)\right| \le \frac{2m_{21}\delta\beta_{11}}{\sqrt{\omega_1^2 - 4\gamma_1}} + \frac{\beta_{21}}{\gamma_1}$$

$$\limsup_{t\to\infty} \left|\tilde{\phi}_1(t)\right| \le m_{21}\beta_{11} + \omega_1 \frac{\beta_{21}}{\gamma_1}$$

where $\beta_{11} = D + \omega_1$ and $\beta_{21} = m_{21}\gamma_1 + m_{11}$ $\qquad \delta = \left(\frac{\lambda_1}{\lambda_2}\right)^{\lambda_1/\lambda_1-\lambda_2} - \left(\frac{\lambda_1}{\lambda_2}\right)^{\lambda_2/\lambda_1-\lambda_2}$

2. Developments of General Dynamical Model Approach

✓ Derivation and tuning of the general software sensor of the full kinetics of biotechnological processes

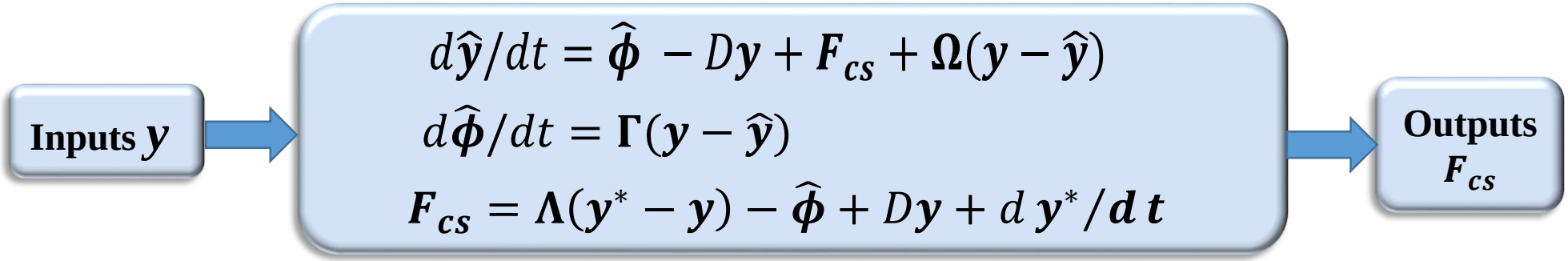
$$\omega_{opt} = \arg\min_{\omega}\left(\limsup_{t\to\infty}\left|\tilde{\phi}_u(t)\right|\right)$$

$$\omega_{opt} = 2\zeta\sqrt{\frac{m_1}{2m_2}} \qquad \gamma_{opt} = \frac{\omega_{opt}^2}{4\zeta^2}$$

m_1 and m_2 are upper bounds of kinetics derivative and measurement noise

2. Developments of General Dynamical Model Approach

✓ General algorithm for fully adaptive linearizing control with software sensors



$$d\xi_{cs}/dt = \mathbf{K_{cs}}\varphi_{cs}(\xi) - D\xi_{cs} + F_{cs}$$

$y = \xi_{cs}$ - vector y is assumed to be the vector ξ_{cs} of concentrations of the controlled measured substrates

where $\Lambda \in \mathbb{R}^{cs\times cs}$[1/h] is a diagonal matrix containing the control design parameters, $\xi_{cs} \in \mathbb{R}^{cs\times 1}$ [g/l] is a vector of the concentrations of the controlled feeding substrates (c_s indicates their number); $\mathbf{K_{cs}} \in \mathbb{R}^{cs\times n_{cs}}$ [g/g] represents the yield coefficient matrix, related to the kinetics of ξ_{cs} (n_{cs} indicates the number of the reaction rates), $\varphi_{cs} \in \mathbb{R}^{n_{cs}\times 1}$ [g/lh] stands for the reaction rates vector and $F_{cs} \in \mathbb{R}^{cs\times 1}$ [g/lh] is the mass feed rate of the substrate ξ_{cs} in the bioreactor.

2. Developments of General Dynamical Model Approach

- ✓ General algorithm for fully adaptive linearizing control with software sensors

Theorem: Under assumptions A1 – A9, the estimation errors of y and ϕ_1 are bounded for all t and asymptotically bounded as follows:

$$\lim_{t\to\infty} sup\,|\tilde{y}_1(t)| \leqq \frac{2m_{21}\delta\beta_{11}}{\sqrt{\omega_1^2 - 4\gamma_1}} + \frac{\beta_{21}}{\gamma_1}$$

$$\lim_{t\to\infty} sup\,\left|\tilde{\phi}_1(t)\right| \leqq m_{21}\beta_{11} + \omega_1\frac{\beta_{21}}{\gamma_1}$$

and then the error between the state (y) and the reference is bounded as follows:

$$\lim_{t\to\infty} sup\,|y - y^*| \leqq \frac{m_{21}\beta_{11} + \omega_1\dfrac{\beta_{21}}{\gamma_1} + (D+\gamma_1)m_{21}}{\gamma_1}$$

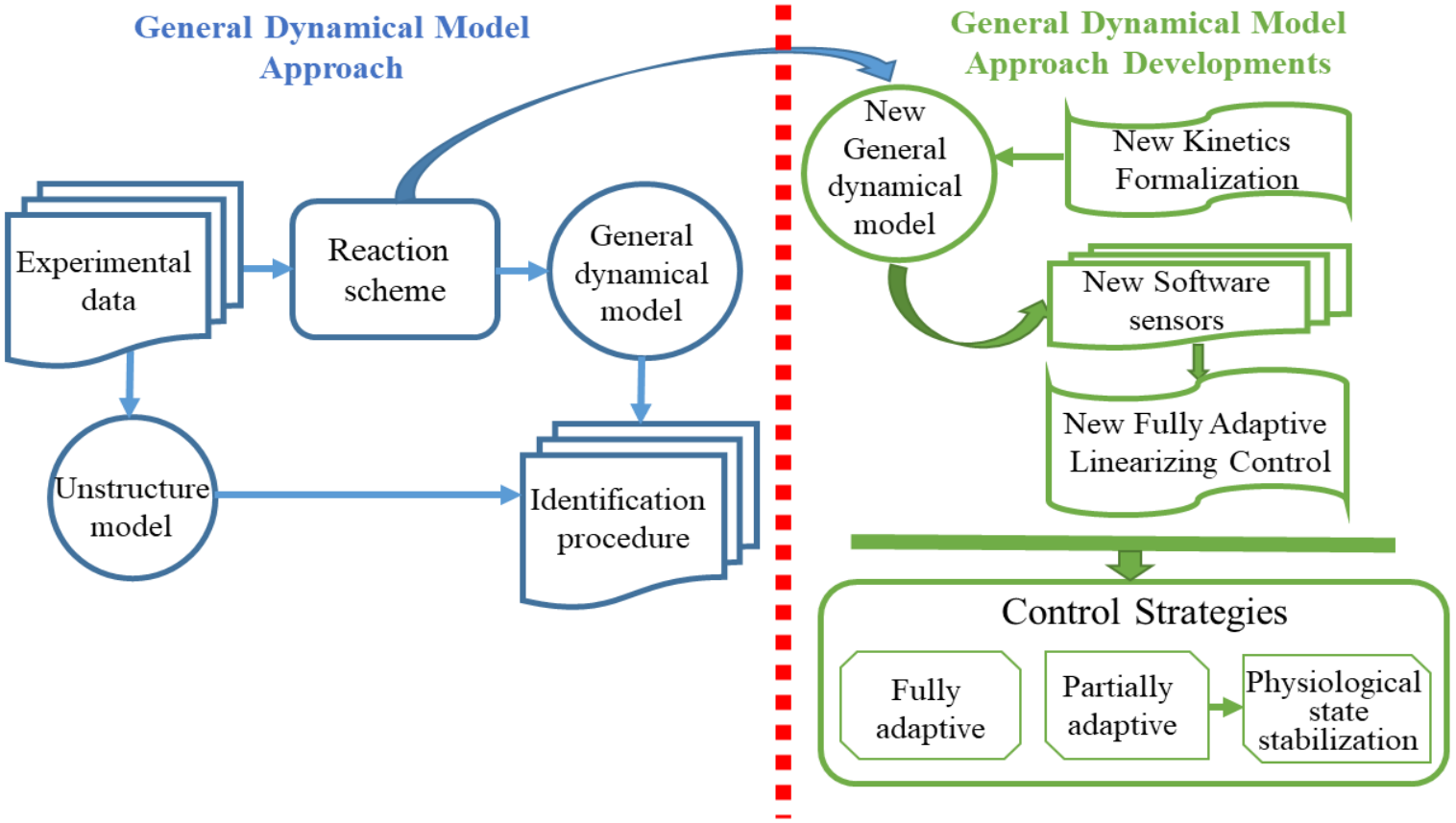
$\beta_{11} = D+\omega_1$ and $\beta_{21} = m_{21}\,\gamma_1 + m_{11}$

$$\delta = \left(\frac{\lambda_1}{\lambda_2}\right)^{\lambda_1/(\lambda_1-\lambda_2)} - \left(\frac{\lambda_1}{\lambda_2}\right)^{\lambda_2/(\lambda_1-\lambda_2)}$$

3. Applications of proposed theoretical solutions

Three control strategies:

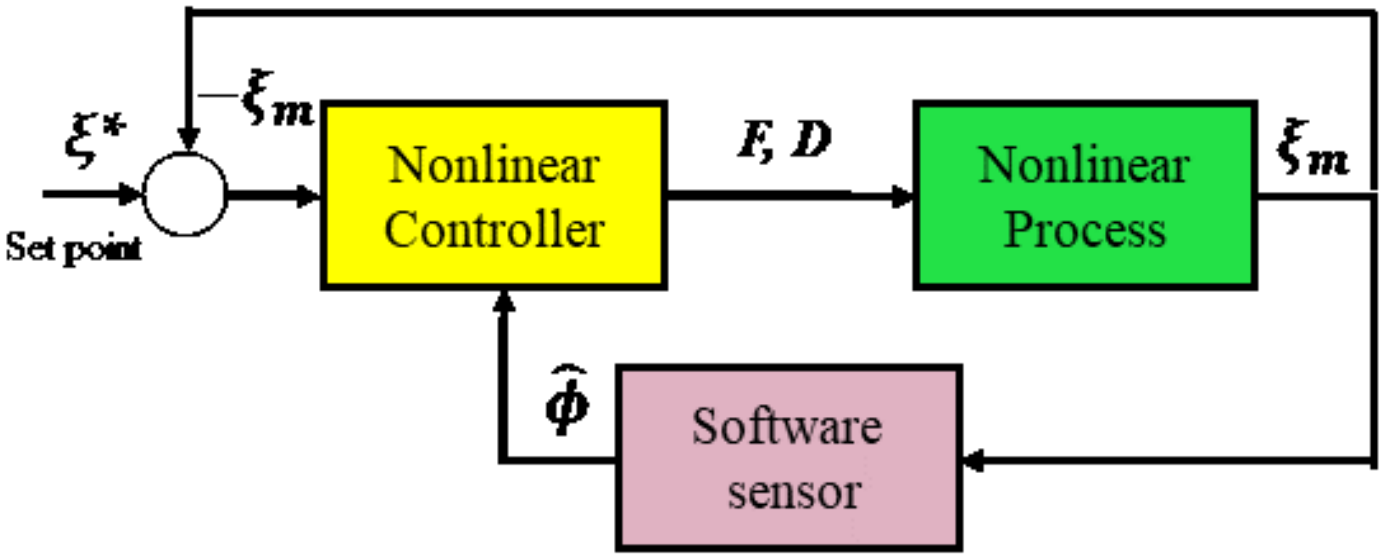
- ✓ fully adaptive control of the main substrate
- ✓ partially adaptive control of intermediate metabolite recognition
- ✓ stabilization of the desired physiological state



3. Applications of proposed theoretical solution

- ✓ fully adaptive control of the main substrate

Fully adaptive control of main substrate



Case studies:

1.Control of gluconic acid production by *Aspergillus niger*

2.Control of Alpha-amylase production by *Bacillus subtilis*

Advantages: The process kinetics, $\phi(t)$, is presented as a fully unknown time-varying parameter. Optimal SS tuning is done. The SS included in the control law makes it fully adaptive in terms of kinetics.

Limitation: It is mainly applied for the stabilization of the limiting substrate

3. Applications of proposed theoretical solution

- ✓ partially adaptive control of intermediate metabolite recognition

Control Marker

$$\Delta = \hat{\Phi}_1 - \hat{\Phi}_2$$

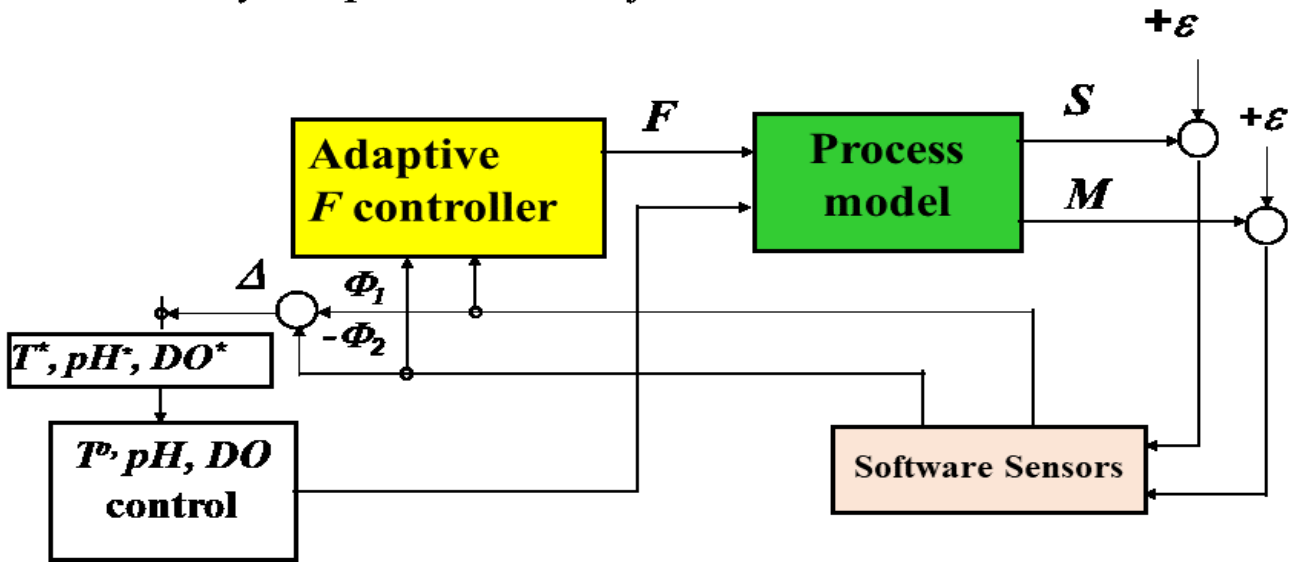
$\hat{\Phi}_1$ Intermediate metabolite production rate

$\hat{\Phi}_2$ Intermediate metabolite consumption rate

3. Applications of proposed theoretical solution

- ✓ partially adaptive control of intermediate metabolite recognition

Partially adaptive control of an intermediate metabolite



Case studies:

1. Impulse control of simultaneous saccharification and fermentation of starch to ethanol (SSFSE)
2. Impulse Adaptive Control of Biopolymer Production by Mixed Culture

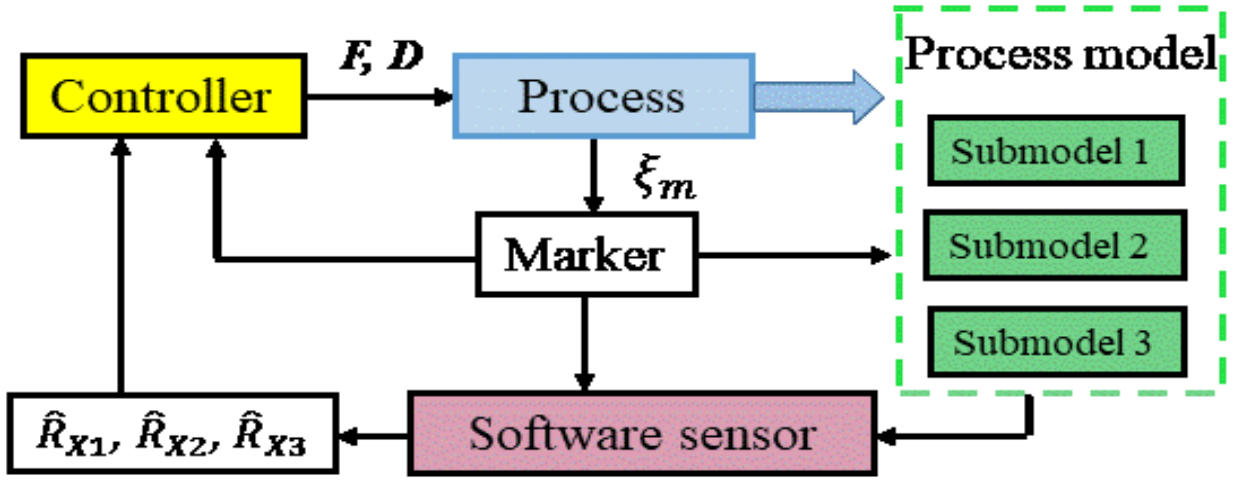
Advantages: The control stabilizes an intermediate metabolite at an optimal value using a marker as the difference between consumption and production of that metabolite

Limitation: The SS included in the control law makes it partially adaptive in terms of kinetics.

3. Applications of proposed theoretical solution

- ✓ stabilization of the desired physiological state

Recognition and stabilization of desired physiological state



Advantages: Monitoring of physiological states in multi-rate processes by a marker of the kinetics of an intermediate metabolite. Recognition and stabilization of the desired physiological state.

Limitation: The SS included in the control law makes it partially adaptive in terms of kinetics.

3. Applications of proposed theoretical solution

✓ stabilization of the desired physiological state

Case study: fed-batch fermentation of *E. coli*

boundary conditions for changing the regime of glucose from oxidative to oxidative-fermentative:

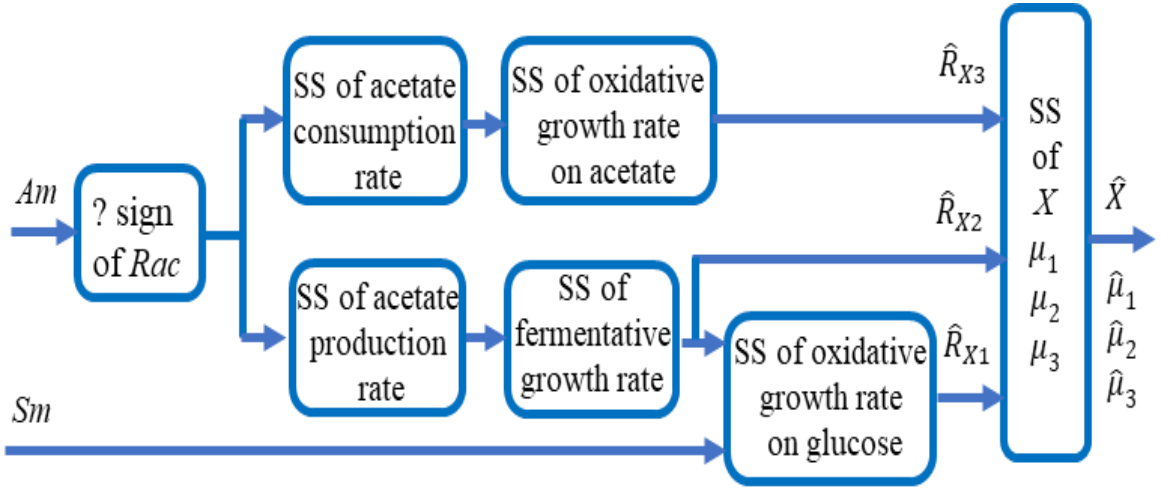
$Rac = 0$, $G \neq 0$ oxidative growth on glucose

$Rac > 0$, $G \neq 0$ oxidative-fermentative growth on glucose

boundary conditions for changing the regime of acetate production depending on the presence of glucose

$Rac < 0$, $G \neq 0$ oxidative growth on acetate and glucose

$Rac < 0$, $G = 0$ oxidative growth on acetate



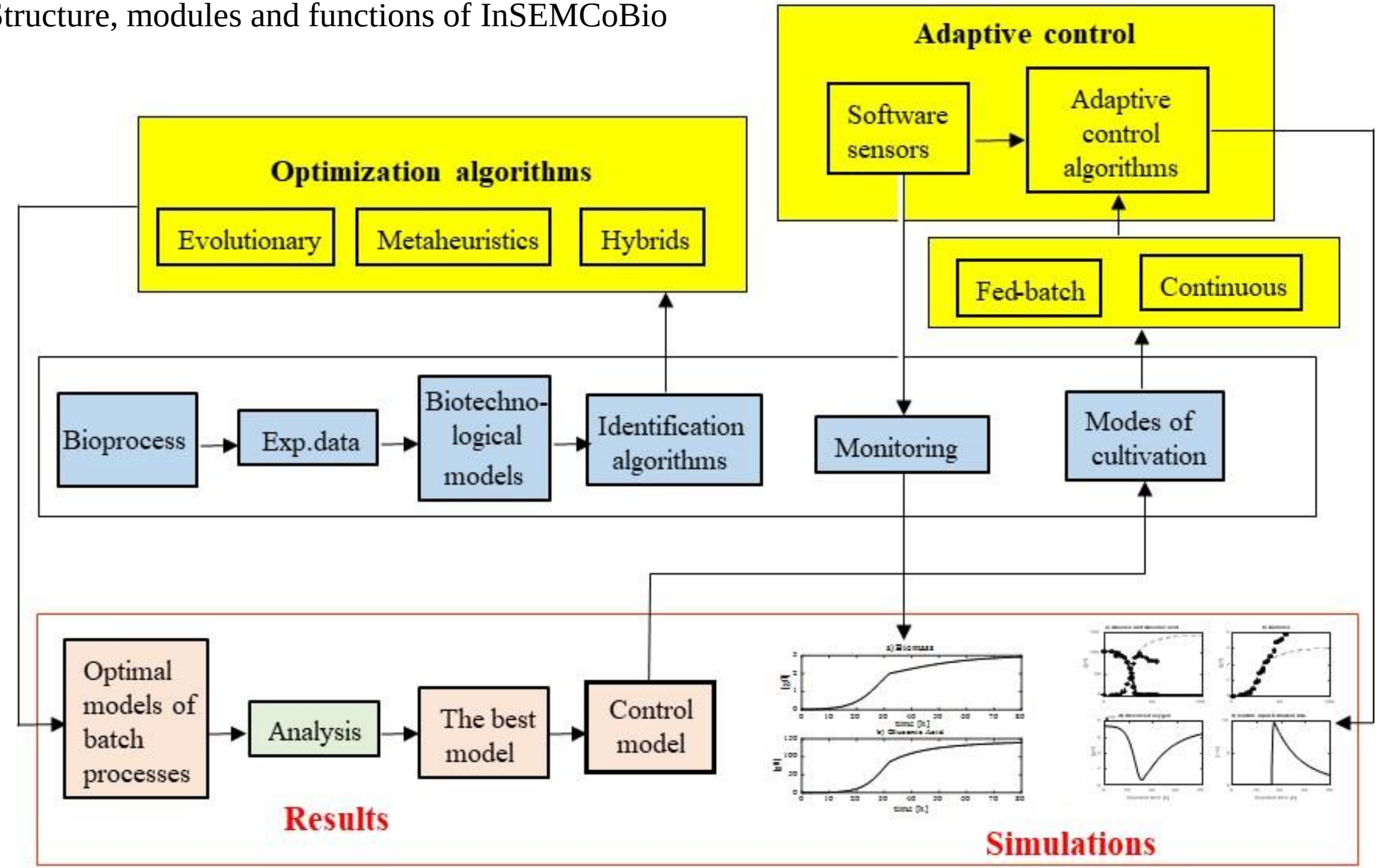
Scheme of software sensors designed for monitoring of the physiological states

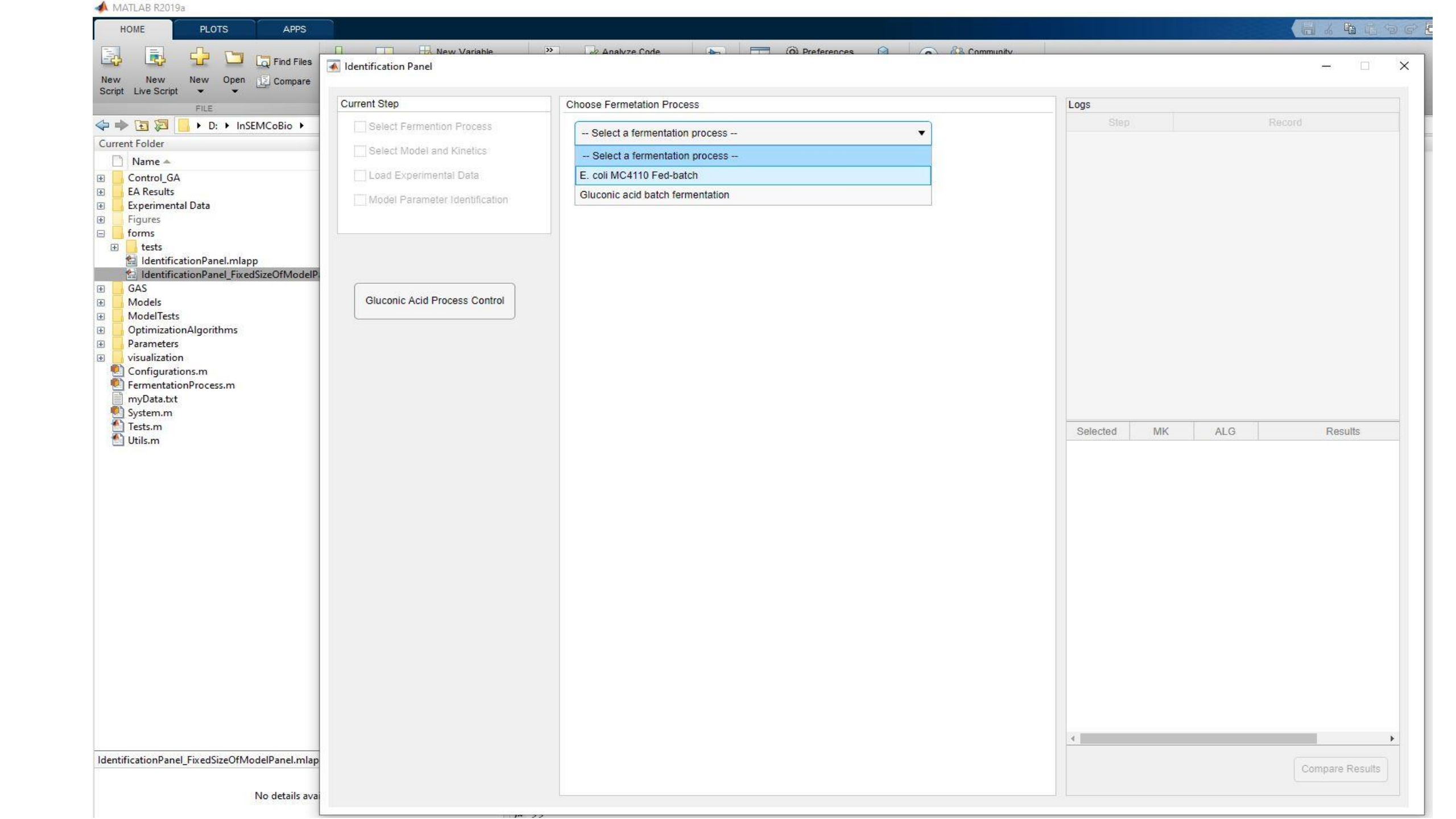
$$F = (W(-\Lambda_1(\mathrm{G}^* - G_m) + \mathrm{k}_1\hat{R}_{X1} + \mathrm{k}_2\hat{R}_{X2})/(G_{in} - G_m)$$

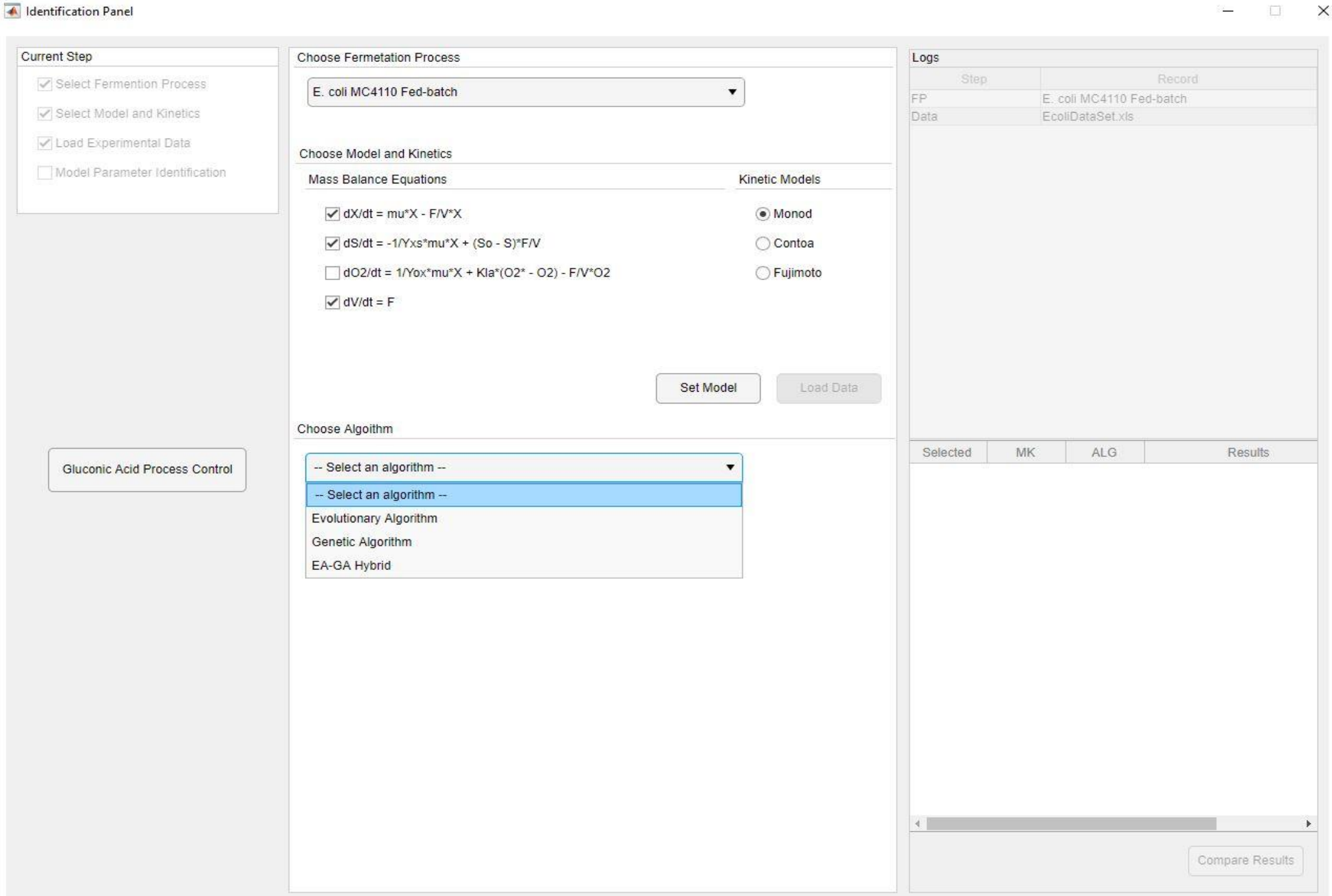
Adaptive Control algorithm

Development of a Interactive System for Education in Modelling and Control of Biotehnological Processes (InSEMCoBio)

1. Structure, modules and functions of InSEMCoBio




MATLAB R2019a
HOME
PLOTS
APPS
New Script
New Live Script
New
Open
Find Files
Compare
FILE
New Variable
Analyze Code
Preferences
Community
D: ▸ InSEMCoBio ▸
Current Folder
Name
Control_GA
EA Results
Experimental Data
Figures
forms
tests
IdentificationPanel.mlapp
IdentificationPanel_FixedSizeOfModelP
GAS
Models
ModelTests
OptimizationAlgorithms
Parameters
visualization
Configurations.m
FermentationProcess.m
myData.txt
System.m
Tests.m
Utils.m
IdentificationPanel_FixedSizeOfModelPanel.mlap
No details ava
Identification Panel
Current Step
Select Fermention Process
Select Model and Kinetics
Load Experimental Data
Model Parameter Identification
Gluconic Acid Process Control
Choose Fermetation Process
-- Select a fermentation process --
-- Select a fermentation process --
E. coli MC4110 Fed-batch
Gluconic acid batch fermentation
Logs
Step
Record
Selected
MK
ALG
Results
Compare Results


Identification Panel
Current Step
Select Fermention Process
Select Model and Kinetics
Load Experimental Data
Model Parameter Identification
Gluconic Acid Process Control
Choose Fermetation Process
E. coli MC4110 Fed-batch
Choose Model and Kinetics
Mass Balance Equations
dX/dt = mu*X - F/V*X
dS/dt = -1/Yxs*mu*X + (So - S)*F/V
dO2/dt = 1/Yox*mu*X + Kla*(O2* - O2) - F/V*O2
dV/dt = F
Kinetic Models
Monod
Contoa
Fujimoto
Set Model
Load Data
Choose Algoithm
-- Select an algorithm --
-- Select an algorithm --
Evolutionary Algorithm
Genetic Algorithm
EA-GA Hybrid
Logs
Step
Record
FP
E. coli MC4110 Fed-batch
Data
EcoliDataSet.xls
Selected
MK
ALG
Results
Compare Results

Identification Panel

Current Step

- Select Fermention Process
- Select Model and Kinetics
- Load Experimental Data
- Model Parameter Identification

Gluconic Acid Process Control

Choose Fermetation Process

Gluconic acid batch fermentation

Choose Model and Kinetics

Mass Balance Equations

- dX/dt = Rx
- dGA/dt = Rga
- dS/dt = -1/Yxs*Rx -1/Ysga*Rga
- dO2/dt = 1/Yox*Rga+Kla*(O2*-O2)

Kinetic Models

- Monod

Set Model | Load Data

Choose Algoithm

Evolutionary Algorithm

Set Algorithm Parameters

Max Iter	5	(1, 5)
Step	2	(0, 5)

Set Problem Parameters

Mumax	0.15	(0.15, 0.2)
K	8.031	(6.5, 9)
Muga	0.335	(0.3, 0.4)
Kga	107.1	(90, 120)
1/Yxs	6.262	(5, 7)
1/Ysga	0.028	(0.02, 0.03)
1/Yox	0.81	(0.7, 0.9)

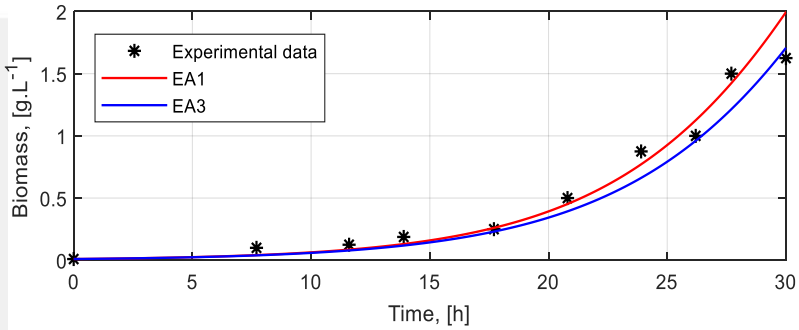
Run

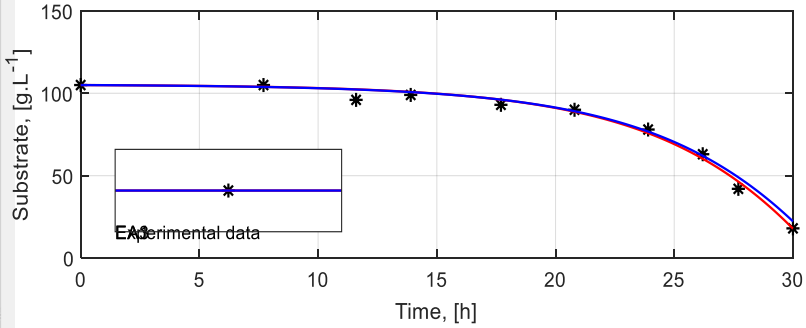
Logs

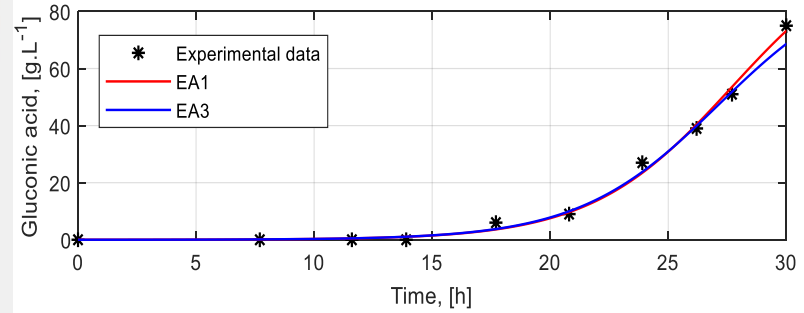
Step	Record
FP	Gluconic acid batch fermentation
Data	GADataSet.xlsx

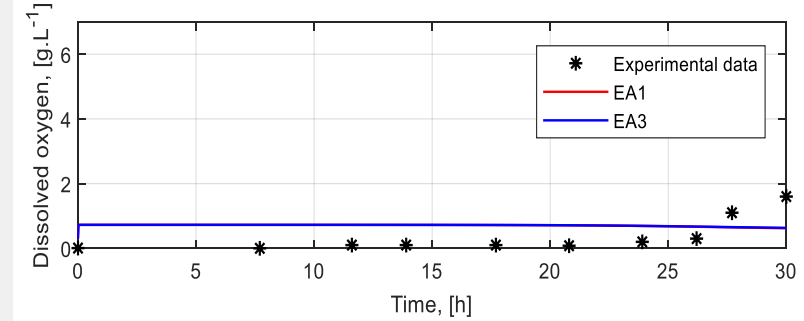
Selected	MK	ALG	Results
☑	GAB, Monod	EA1	J = 123.34 Mumax = 0.19 K =
☐	GAB, Monod	EA2	J = 123.34 Mumax = 0.19 K =
☑	GAB, Monod	EA3	J = 1768.02 Mumax = 0.18 K =

Compare Results









Identification Panel

Current Step

Select Fermention Process

Choose Fermetation Process

Gluconic acid batch fermentation

e Model and Kinetics

Balance Equations

dX/dt = Rx

dGA/dt = Rga

dS/dt = -1/Yxs*Rx -1/Ysga*Rga

dO2/dt = 1/Yox*Rga+Kla*(O2*-O2)

Kinetic Models

Monod

Set Model

Load Data

e Algoithm

Evolutionary Algorithm

Set Algorithm Parameters

Max Iter	5	(1, 5)
Step	0.5	(0, 5)

Set Problem Parameters

Mumax	0.16	(0.15, 0.2)
K	7	(6.5, 9)
Muga	0.35	(0.3, 0.4)
Kga	110	(90, 120)
1/Yxs	6	(5, 7)
1/Ysga	0.025	(0.02, 0.03)
1/Yox	0.8	(0.7, 0.9)

Run

Figure 2

File Edit View Insert Tools Desktop Window Help

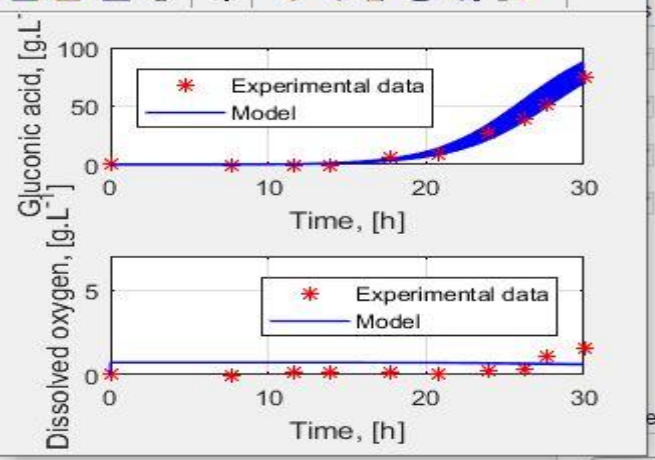


Figure 1

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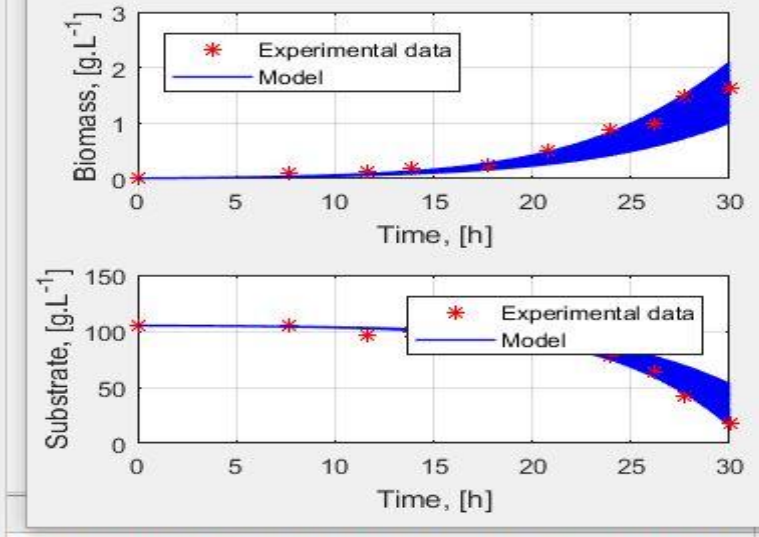


0.33 Kga = 112.44 K1 = 6.12 K2 = 0.03 K3 = 0.79, meanJ = 1075.1...

Figure 4: Best solution

File Edit View Insert Tools Desktop Window Help

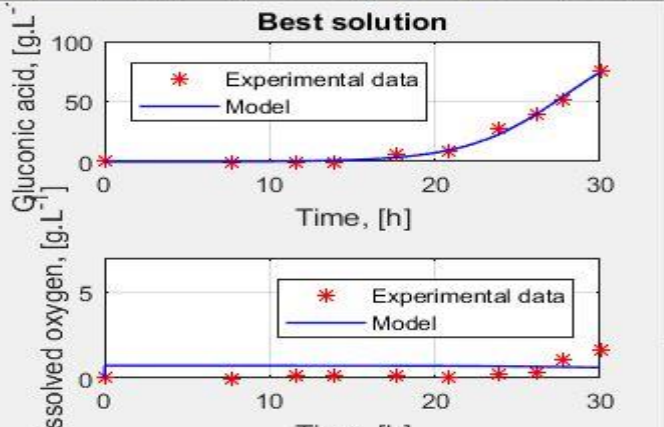
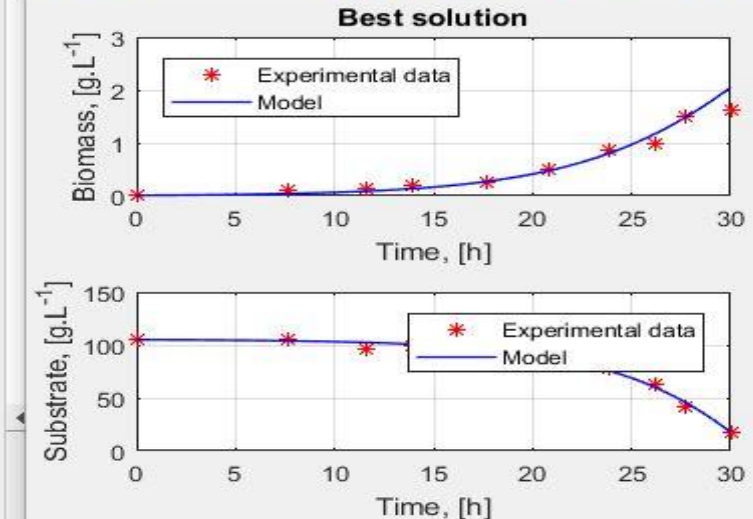


Figure 3: Best solution

File Edit View Insert Tools Desktop Window Help



Identification Panel

Current Step

- Select Fermention Process
- Select Model and Kinetics
- Load Experimental Data
- Model Parameter Identification

Choose Fermetation Process

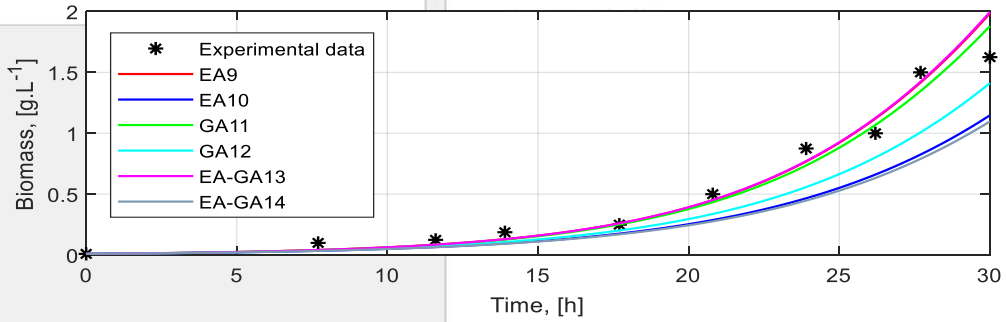
Gluconic acid batch fermentation

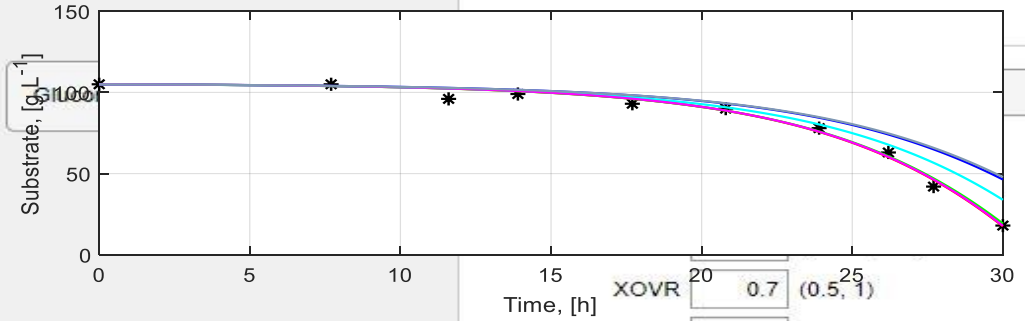
Choose Model and Kinetics

Mass Balance Equations

Kinetic Models

Monod





Set Model

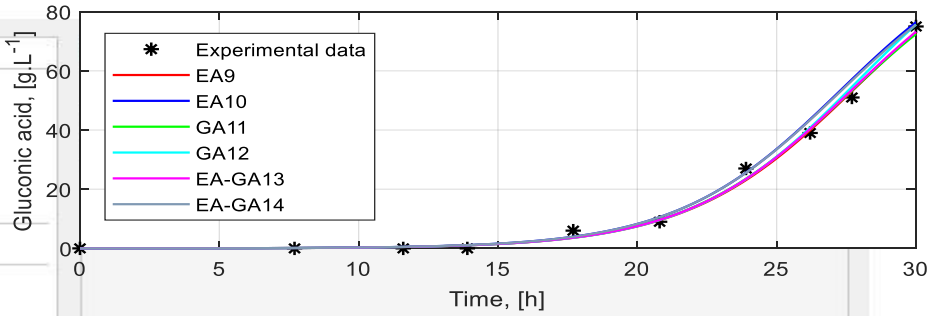
Load Data

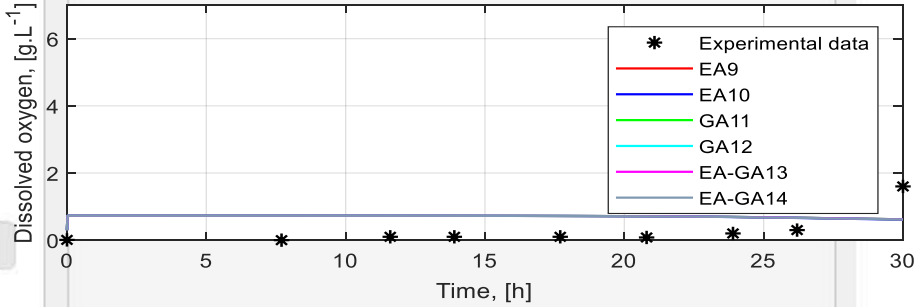
Set Problem Parameters

XOVR	0.7	(0.5, 1)
NIND	10	(1, 50)
MAXGEN	5	(1, 50)
GGAP	0.97	(0.5, 1)
NRUN	3	(1, 10)
Max Iter	5	(1, 5)
Step	0.5	(0, 5)

Mumax	0.15	(0.15, 0.2)
K	8.031	(6.5, 9)
Muga	0.335	(0.3, 0.4)
Kga	107.1	(90, 120)
1/Yxs	6.262	(5, 7)
1/Ysga	0.028	(0.02, 0.03)
1/Yox	0.81	(0.7, 0.9)

Run



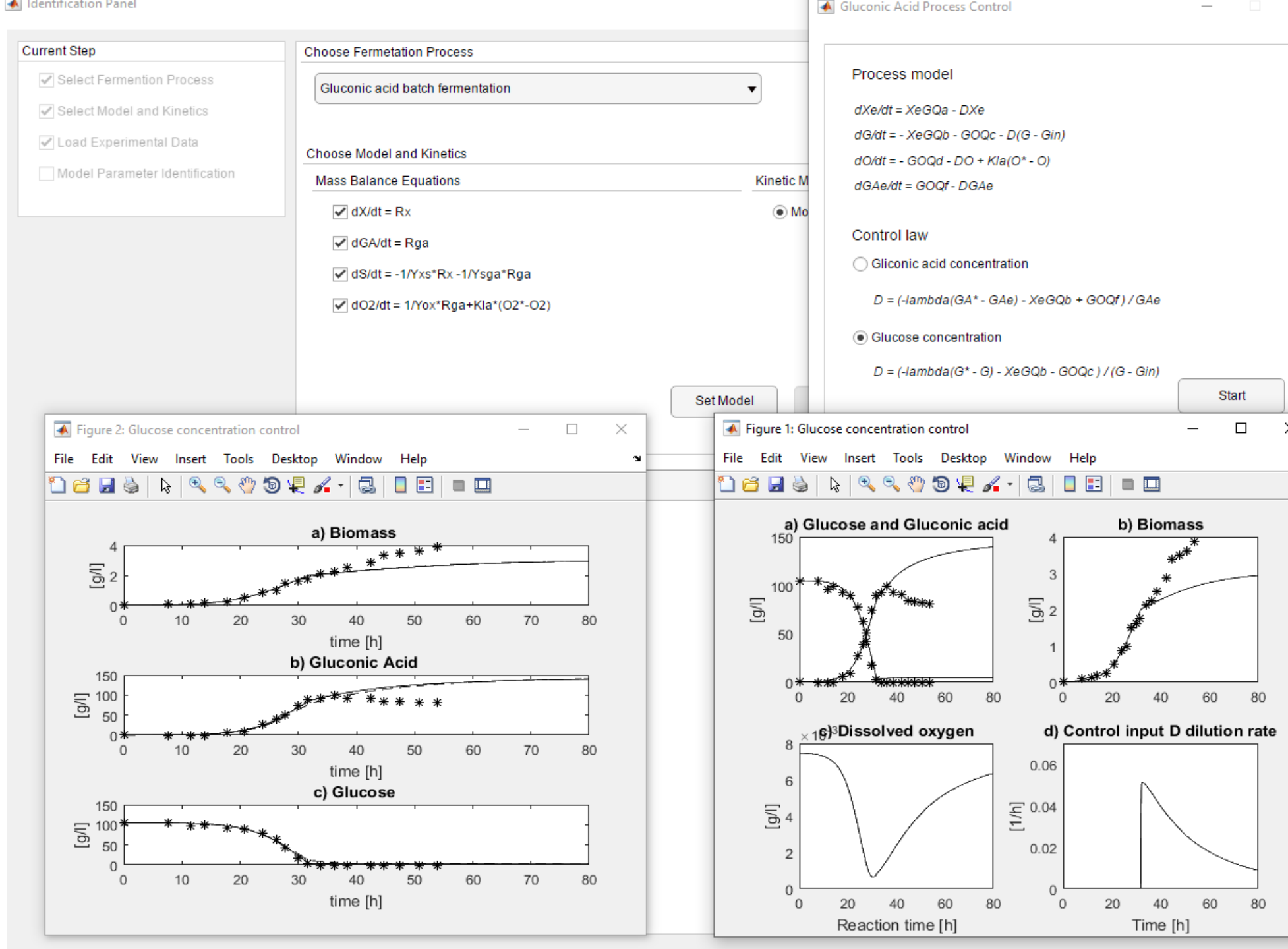


Selected	MK	ALG	Results
✓	GAB, Monod	EA9	J = 123.20 Mumax = 0.19 K =
✓	GAB, Monod	EA10	J = 2510.91 Mumax = 0.16 K =
✓	GAB, Monod	GA11	J = 128.81 Mumax = 0.18 K =
✓	GAB, Monod	GA12	J = 643.25 Mumax = 0.17 K =
✓	GAB, Monod	EA-GA13	J = 123.34 Mumax = 0.19 K =
✓	GAB, Monod	EA-GA14	J = 1804.15 Mumax = 0.16 K =

Compare Results

Continous Control of Glucose concentration

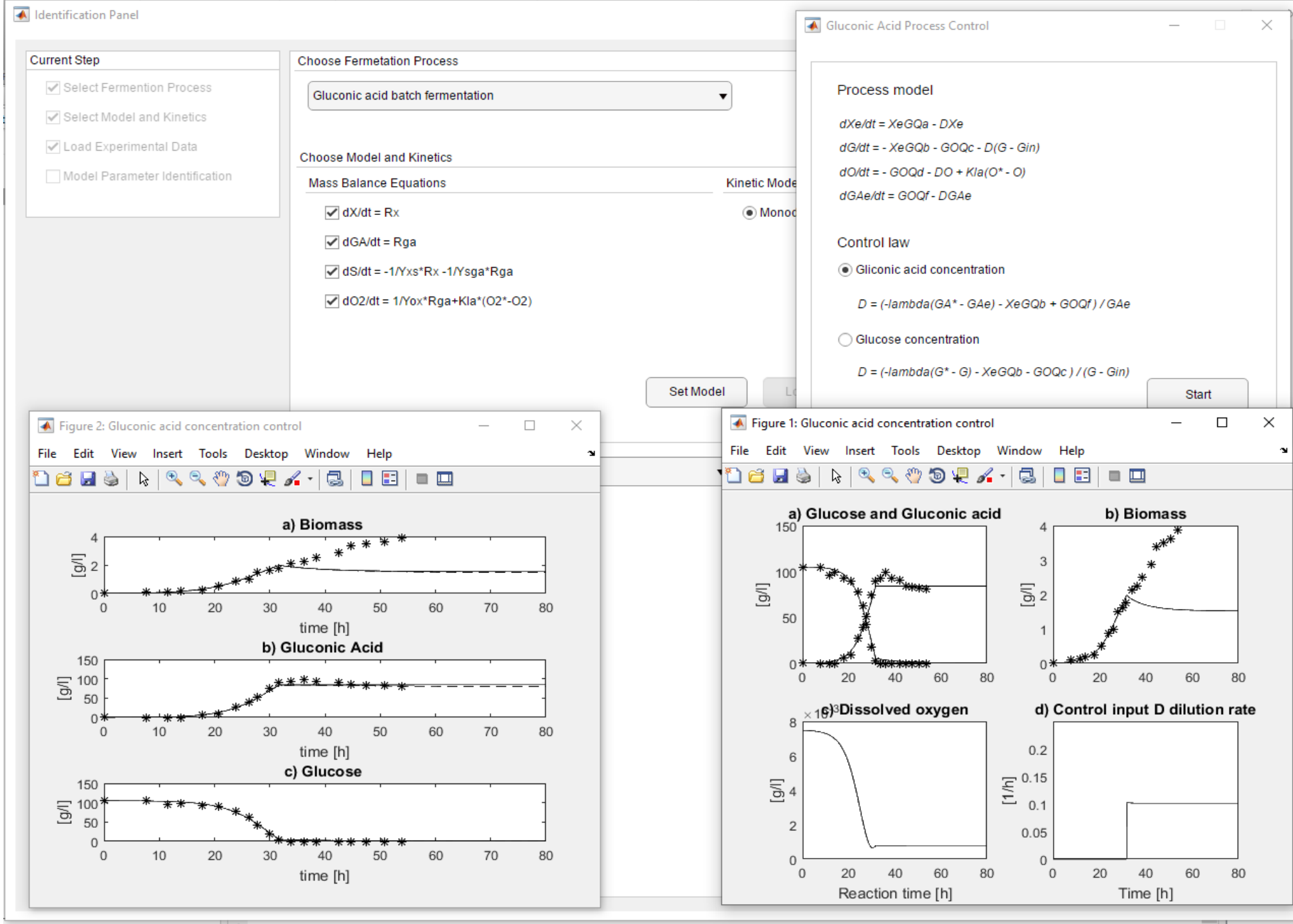
$$D = \frac{-\lambda(G^* - G) - X_e G\theta_2 - GO_2\theta_3}{G - G_{in}}$$



Continous Control

of Gluconic Acid Concentration

$$D = \frac{-\lambda(GA^* - GA_e) + GO_2\theta_5}{GA_e}$$



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THANKS FOR YOUR ATTENTION