Dezvoltarea de strategii de control avansat și optimizare pentru procese din industria farmaceutica prin integrarea conceptelor de digital twin și machine learning

Ioana Nascu

Departamentul de Automatica, Universitatea Tehnica din Cluj Napoca, Romania

provocări în dezvoltarea modelelor de proces predictive pentru procesele bazate pe solide

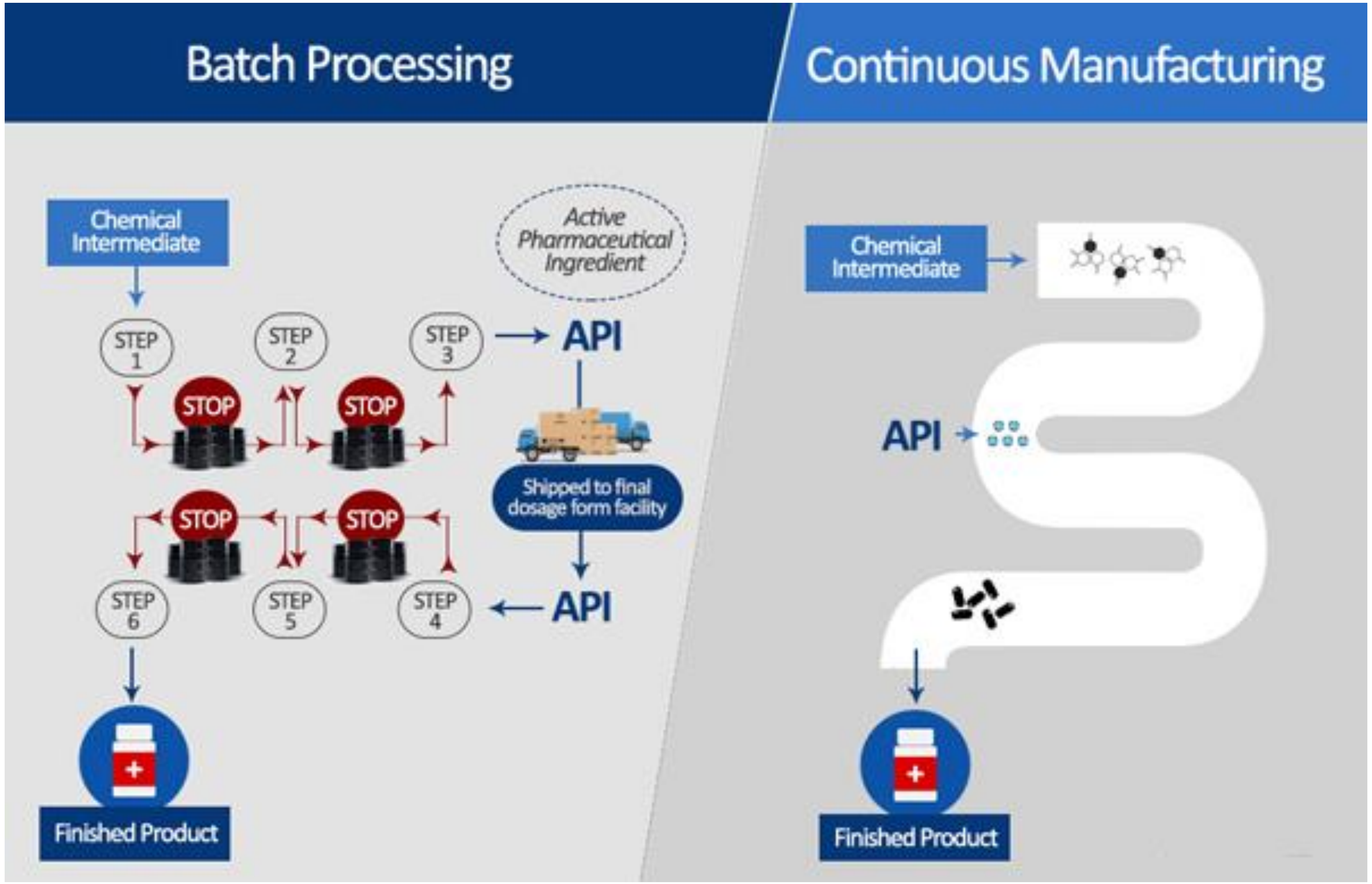
un mediu economic și de reglementare unic

controlul strict al calității produselor

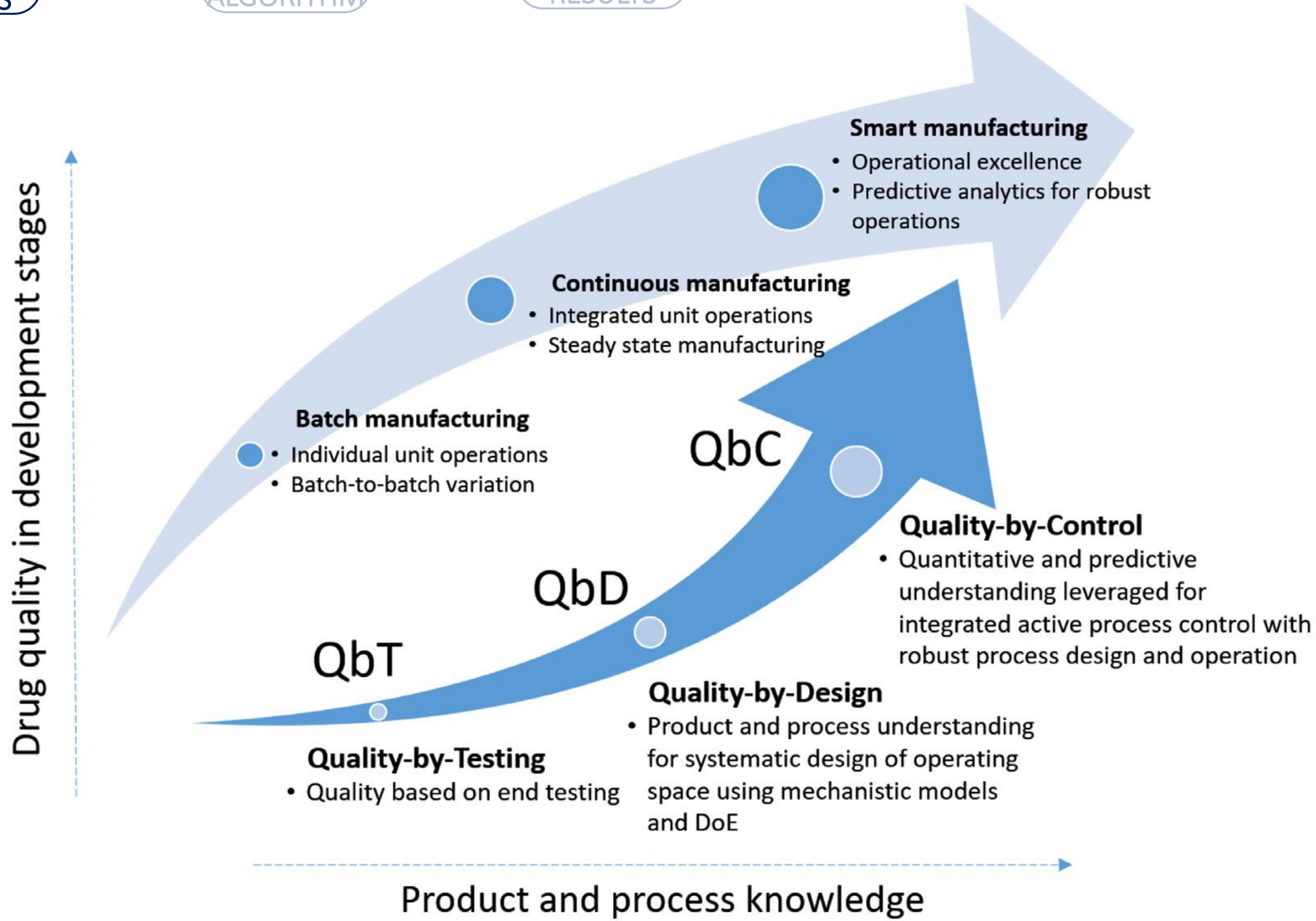
termene scurte pentru dezvoltarea proceselor

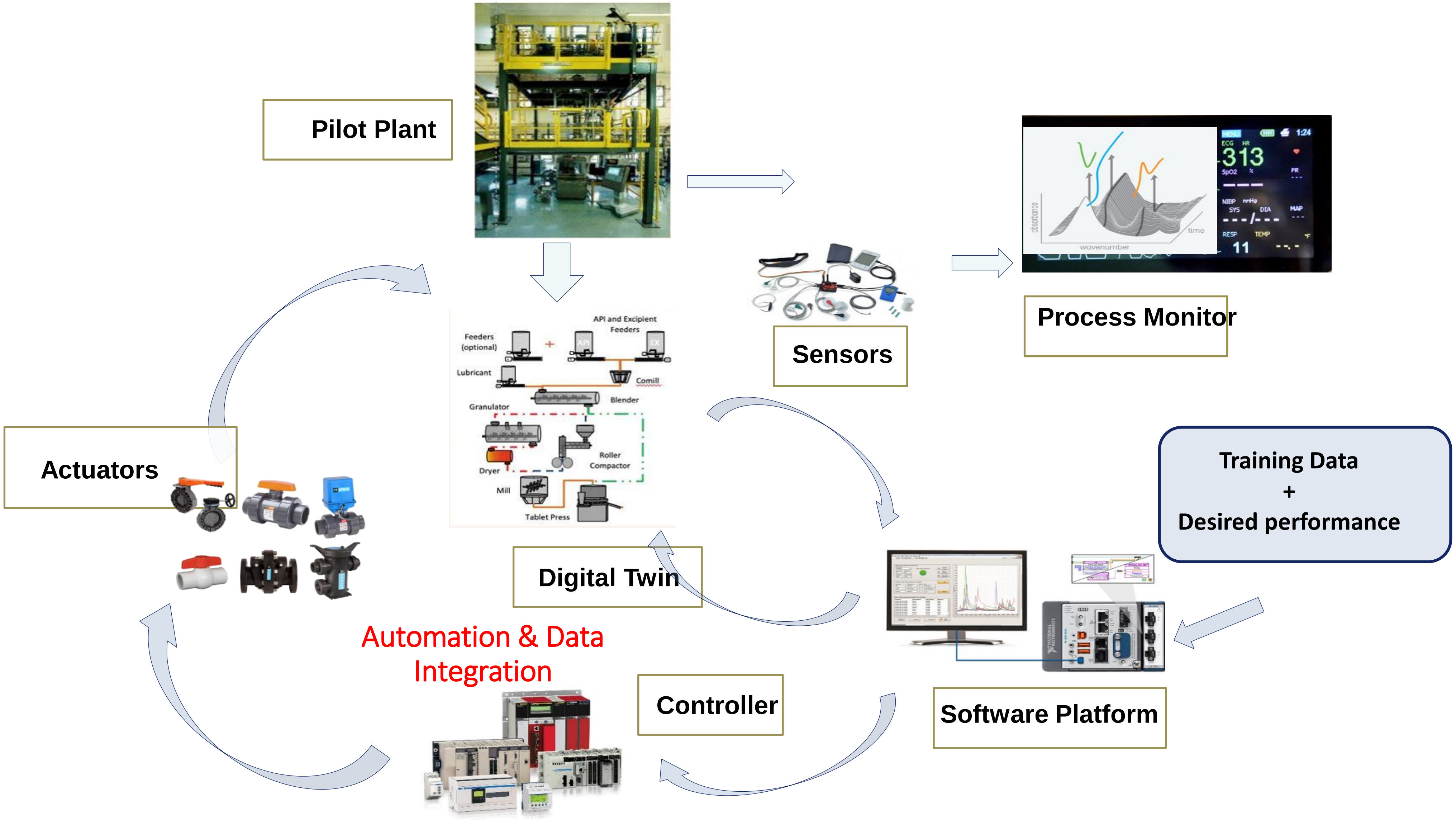
sistem complex de procese, operațiuni și organizații implicate în descoperirea, dezvoltarea și fabricarea de medicamente

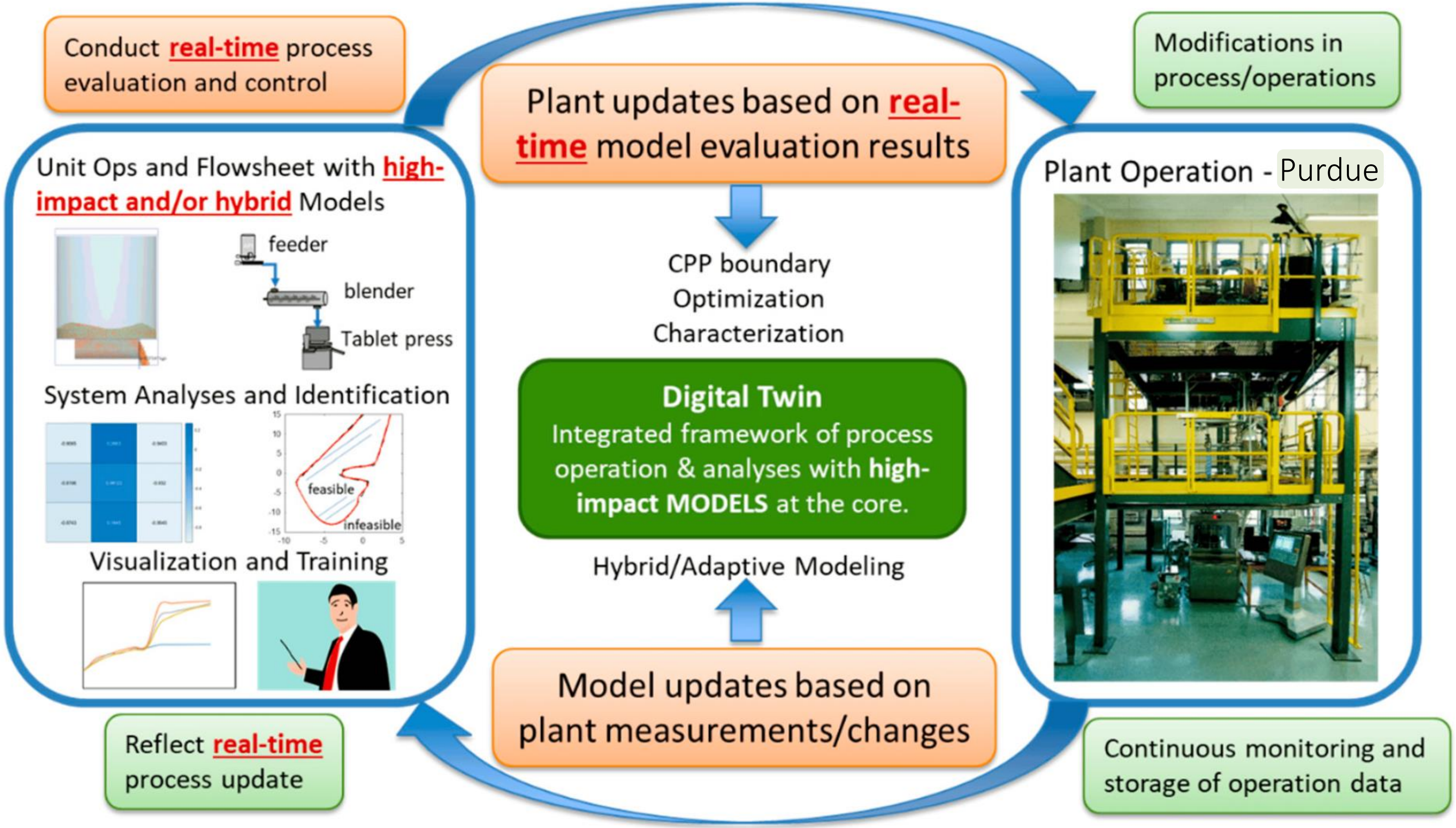
Batch vs Continuous



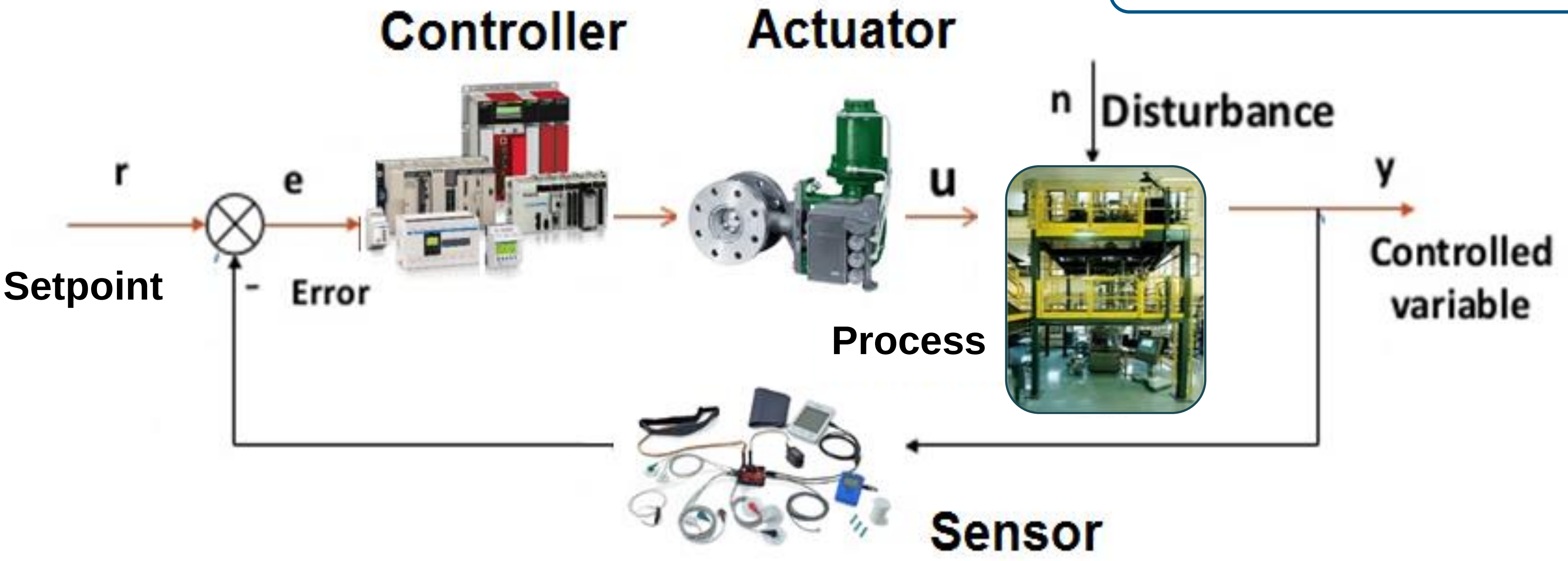
- ↘ variatii in produs
- ↘ timpul necesar pentru control
- ↘ consumul de resurse
- ↘ riscul de epuizare a stocurilor
- ↘ amprenta fizică a echipamentului
- ↗ eficienta operationala
- ↗ productivitatea
- ↗ susteinabilitatea
- medicina personalizată


Drug quality in development stages
Smart manufacturing
• Operational excellence
• Predictive analytics for robust operations
Continuous manufacturing
• Integrated unit operations
• Steady state manufacturing
Batch manufacturing
• Individual unit operations
• Batch-to-batch variation
QbC
QbD
QbT
Quality-by-Control
• Quantitative and predictive understanding leveraged for integrated active process control with robust process design and operation
Quality-by-Design
• Product and process understanding for systematic design of operating space using mechanistic models and DoE
Quality-by-Testing
• Quality based on end testing
Product and process knowledge

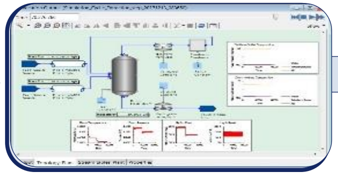

Pilot Plant
Process Monitor
Sensors
Feeders (optional)
API and Excipient Feeders
Lubricant
Comill
Blender
Granulator
Roller Compactor
Dryer
Mill
Tablet Press
Digital Twin
Actuators
Training Data
+
Desired performance
Automation & Data Integration
Controller
Software Platform

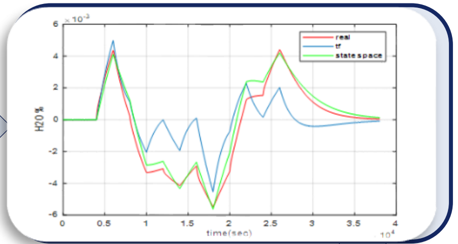

Conduct real-time process evaluation and control
Plant updates based on real-time model evaluation results
Modifications in process/operations
Unit Ops and Flowsheet with high-impact and/or hybrid Models
feeder
blender
Tablet press
System Analyses and Identification
feasible
infeasible
Visualization and Training
CPP boundary
Optimization
Characterization
Digital Twin
Integrated framework of process operation & analyses with high-impact MODELS at the core.
Hybrid/Adaptive Modeling
Plant Operation - Purdue
Model updates based on plant measurements/changes
Reflect real-time process update
Continuous monitoring and storage of operation data

Abordarea controlului bazat pe model în vederea dezvoltării și optimizării



- **Reduce considerabil procesul de dezvoltare** (Problema de design a controlerului→ Problema de control a procesului)
- Urmărire extinsa a punctului de referință [cu un model de proces adecvat]
- Adaugare de constrangeri [siguranta si/sau business]
- Robust la incertitudinea în parametrii modelului de proces și la nepotrivirea modelelor





$$x_{k+1} = Ax_k + Bu_k$$
$$y_k = Cx_k + Du_k$$

Parametrii de proiectare a controlerului

Referinta
- Valoarea dorită a ieșirii procesului

Constrangeri
- Limite pe intrari/iesiri
- saturatia elementului de executie

Measurement device/ State Estimation

Date masurabile

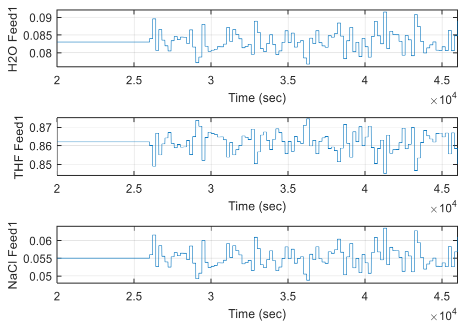
Date nemasurabile estimate

Controller

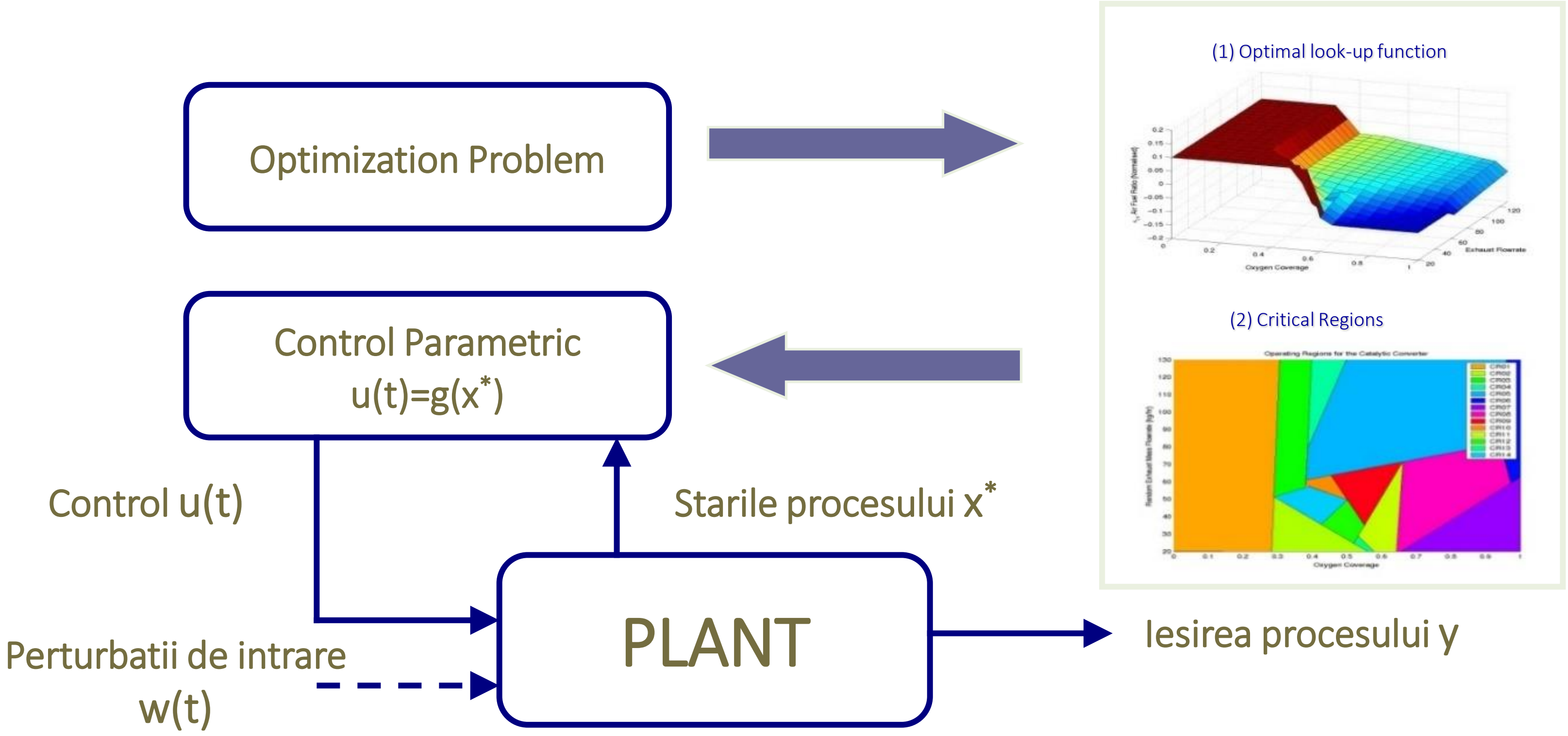
PID
MPC
mpMPC

Testate pentru:
- **Schimbari de referinta**
- **perturbatii**

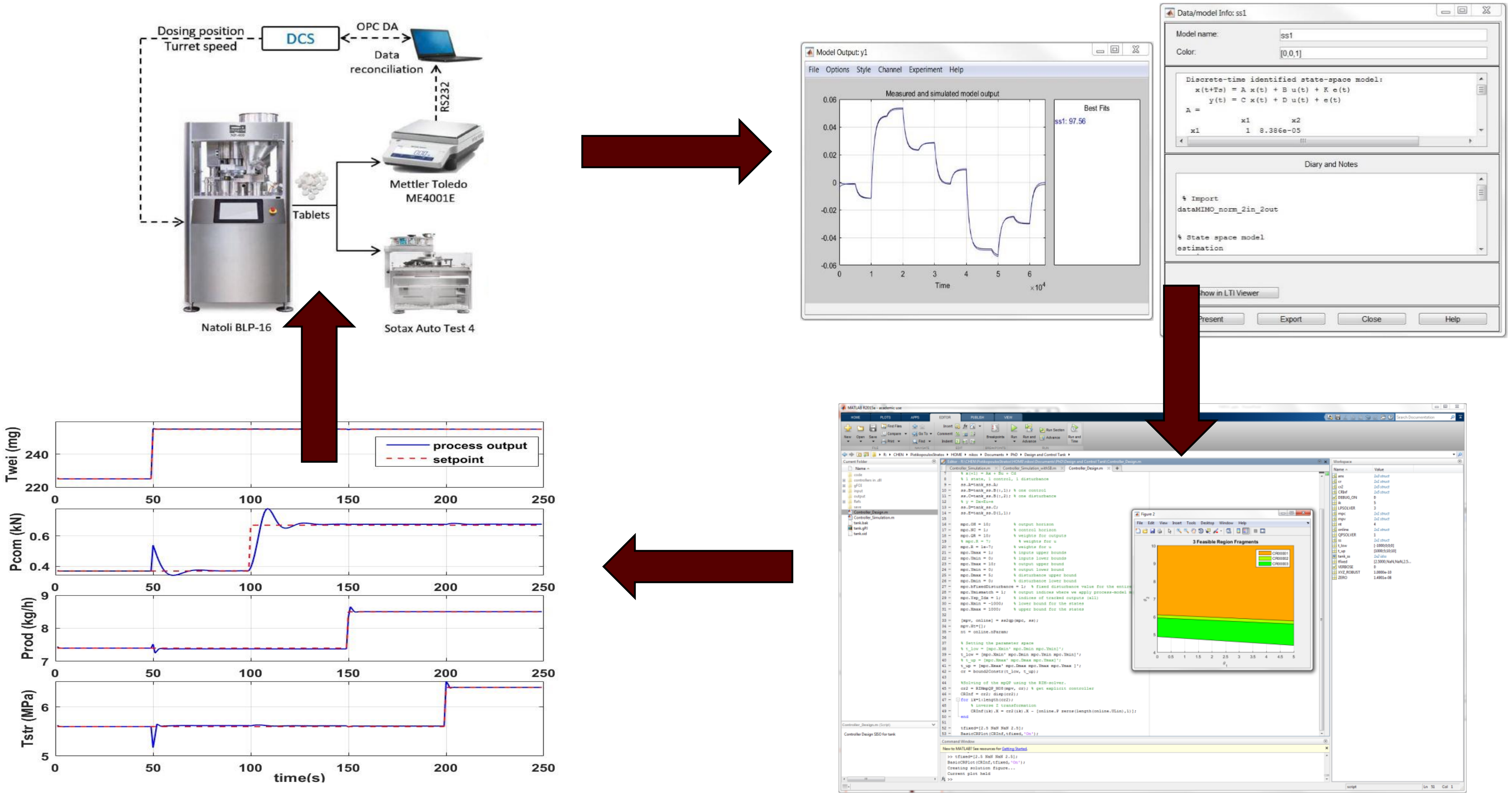
Variabile manipulate/ comanda



Perturbatii



- Optimizarea online este inlocuita de o harta look-up
- In loc de optimizare online, controlul este obtinut prin evaluari de functii
- Optimizare online via optimizare offline


Dosing position
Turret speed
DCS
OPC DA
Data reconciliation
RS232
Tablets
Mettler Toledo ME4001E
Natoli BLP-16
Sotax Auto Test 4
Model Output: y1
File Options Style Channel Experiment Help
Measured and simulated model output
Best Fits
ss1: 97.56
Time
Data/model Info: ss1
Model name: ss1
Color: [0,0,1]
Discrete-time identified state-space model:
x(t+Ts) = A x(t) + B u(t) + K e(t)
y(t) = C x(t) + D u(t) + e(t)
Diary and Notes
% Import
dataMIMO_norm_2in_2out
% State space model
estimation
Show in LTI Viewer
Present
Export
Close
Help
3 Feasible Region Fragments
Twei (mg)
Pcom (kN)
Prod (kg/h)
Tstr (MPa)
process output
setpoint
time(s)

[1] Nascu, I., Diangelakis, N. A., Huang, Y.-S., Nagy, Z. K., Birs, I. and Nascu, I. (2023) 'Multi-parametric Model Predictive Control Strategies for a Rotary Tablet Press in Pharmaceutical Industry', IEEE INTERNATIONAL CONFERENCE ON SYSTEMS, MAN, AND CYBERNETICS

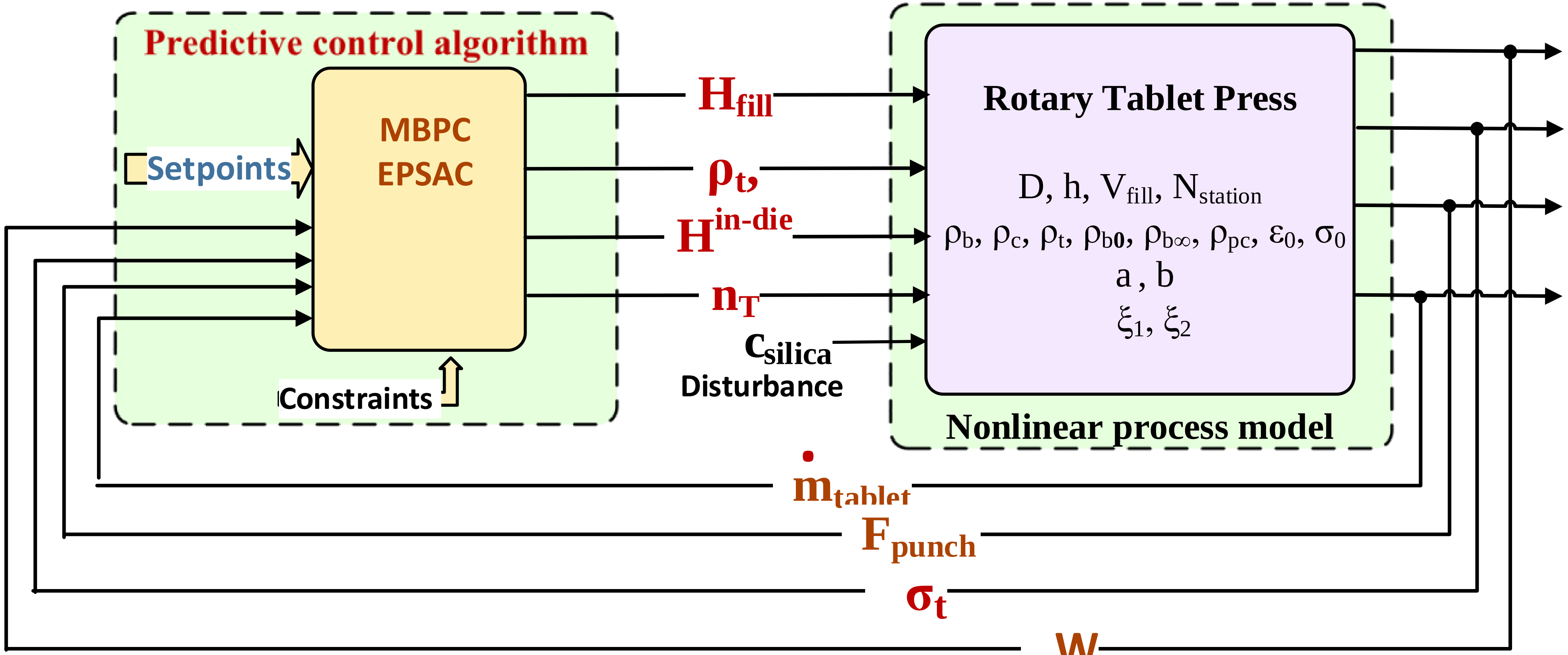
[2] Nascu, I., Diangelakis, N. A., Susca, M., Mihaly, V., Nagy, Z. K.,(2024) ‘Model Predictive Control Strategies for Continuous Manufacturing Processes ', Proceedings of the 34th European Symposium on Computer Aided Process Engineering / 15th International Symposium on Process Systems Engineering (ESCAPE34/PSE24), June 2-6, 2024, Florence, Italy

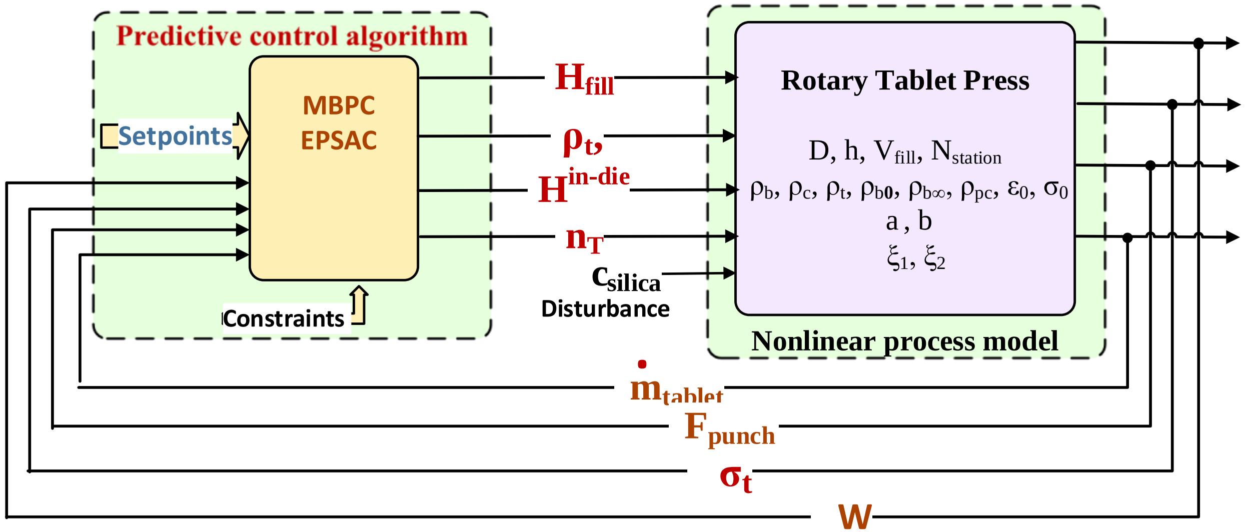
[3] Nascu, I., Nascu, I., Nagy, Z. K.,(2024) ‘Model Predictive Control Strategies for a Rotary Tablet Press in Continous Pharmaceutical Industry', Proc. of the International Conference on Electrical, Computer, Communications and Mechatronics Engineering (ICECCME 2024)

Dezvoltarea de strategii de control avansat și optimizare pentru procese din industria farmaceutica prin integrarea conceptelor de digital twin și machine learning

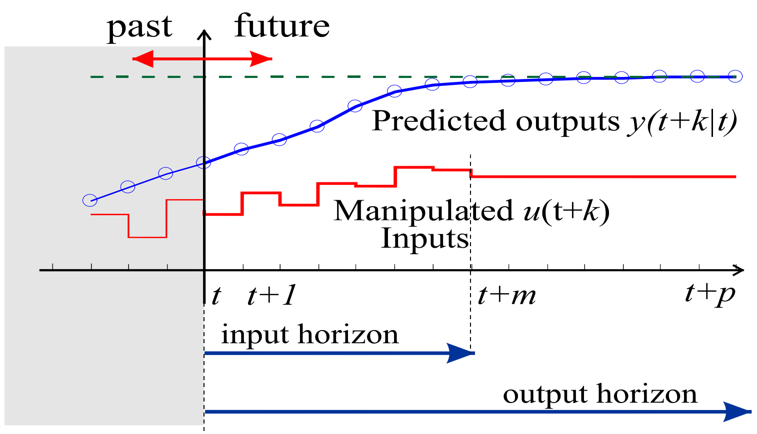
Ioana Nascu

Departamentul de Automatica, Universitatea Tehnica din Cluj Napoca, Romania

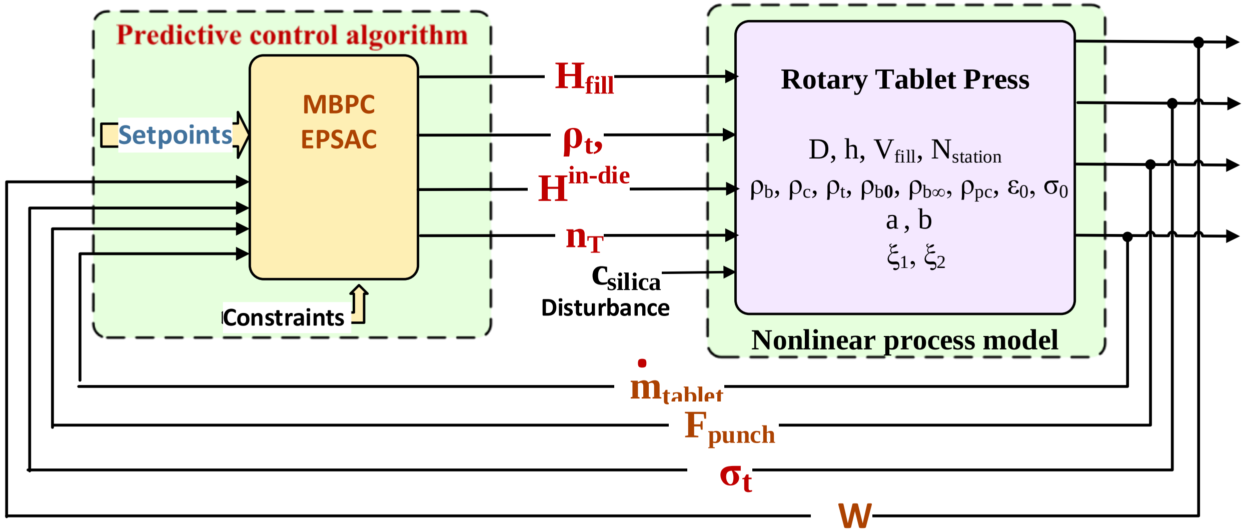

Predictive control algorithm
MBPC
EPSAC
Setpoints
Constraints
H_{fill}
ρ_t,
$H^{in\text{-}die}$
n_T
c_{silica}
Disturbance
Rotary Tablet Press
D, h, V_{fill}, $N_{station}$
ρ_b, ρ_c, ρ_t, ρ_{b0}, $\rho_{b\infty}$, ρ_{pc}, ε_0, σ_0
a , b
ξ_1, ξ_2
Nonlinear process model
$\dot{m}_{tablet}$
F_{punch}
σ_t
W



$$J(N_1,N_2,N_u)=E\left\{\sum_{j=N_1}^{N_2}[y(t+j)-y_r(t+j)]^2+\right.$$
$$\left.+\sum_{j=1}^{N_u}[\rho(j)[\Delta u(t+j-1)]^2\right\}$$

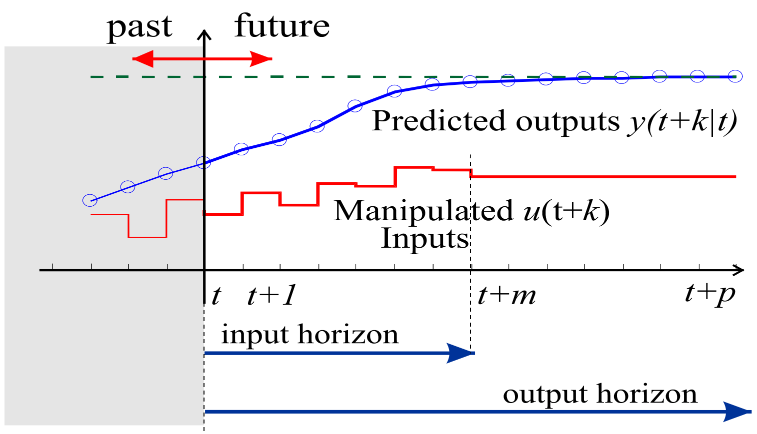


- q^{-1} - the backward *shift operator* ($q^{-1}y(k) = y(k - 1)$);
- Δ - the differencing operator ($1-q^{-1}$);
- $N = N_2 - N_1$ - the prediction horizon
- Nu - the control horizon.
- ρ(j) - a control-weighting sequence.
- y_r - the future reference sequence.



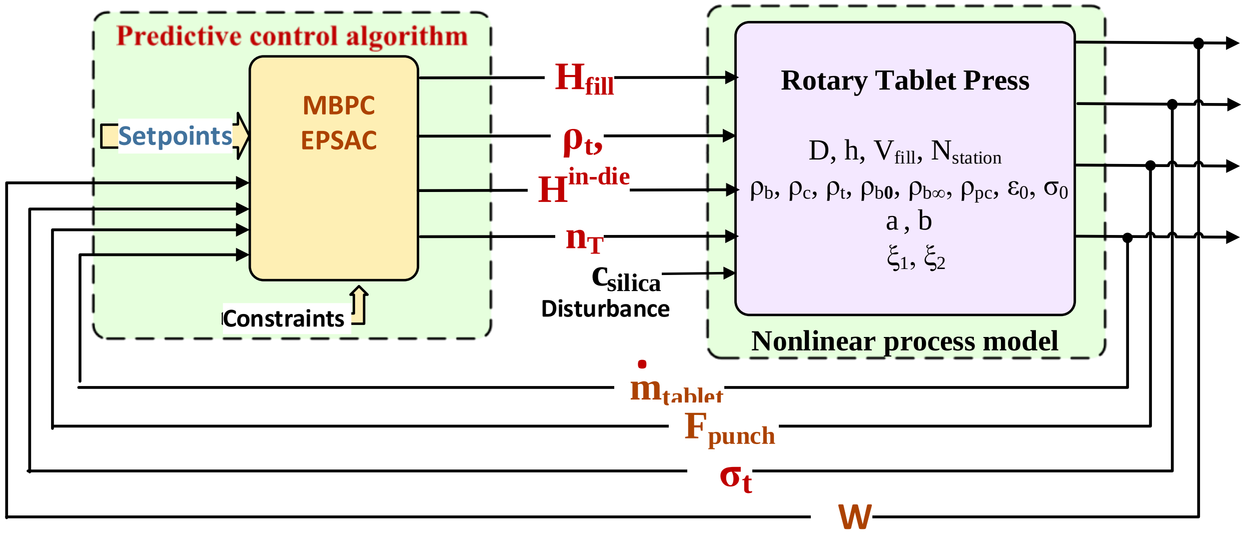
$$J(N_1, N_2, N_u) = E\left\{ \sum_{j=N_1}^{N_2} [y(t+j) - y_r(t+j)]^2 + \right.$$

$$\left. + \sum_{j=1}^{N_u} [\rho(j)[\Delta u(t+j-1)]^2 \right.$$



Inputs:
- H_{fill} **- Dose position**
- ρ_t **- pre-compression thickness**
- H^{in-die} **- Tablet density**
- n_T **- Turret speed**

Outputs:
- m_{tablet} **– Tablet weight**
- σ_t **- pre-compression force**
- F_{pc} **– Production rate**
- W **– Tensile strength**



Model parameters (experimental data):

$\xi_1 = 0.036$, $\xi_2 = 0.03$, ρ_b=0.365 g/cm^3, ρ_c=0.265, a = 0.8, $1/b$= 10.26 MPa, ρ_t = 1.53 g/cm^3, , ε_0=0.08, $\rho_{c,\varepsilon,}$ = 0.57, σ_0 = 11.67 MPa, ρ_0=0.57, ρ_∞=0.61, b_1 = 0.31, b_1 = 0.38, b_1 = 8.4, $\rho_{b,\infty}$ = 0.45 g/cm^3, $\rho_{b,0}$ = 0.33 g/cm^3, r_1 = 0.361, r_2= 1.394, r_3 =23.326.

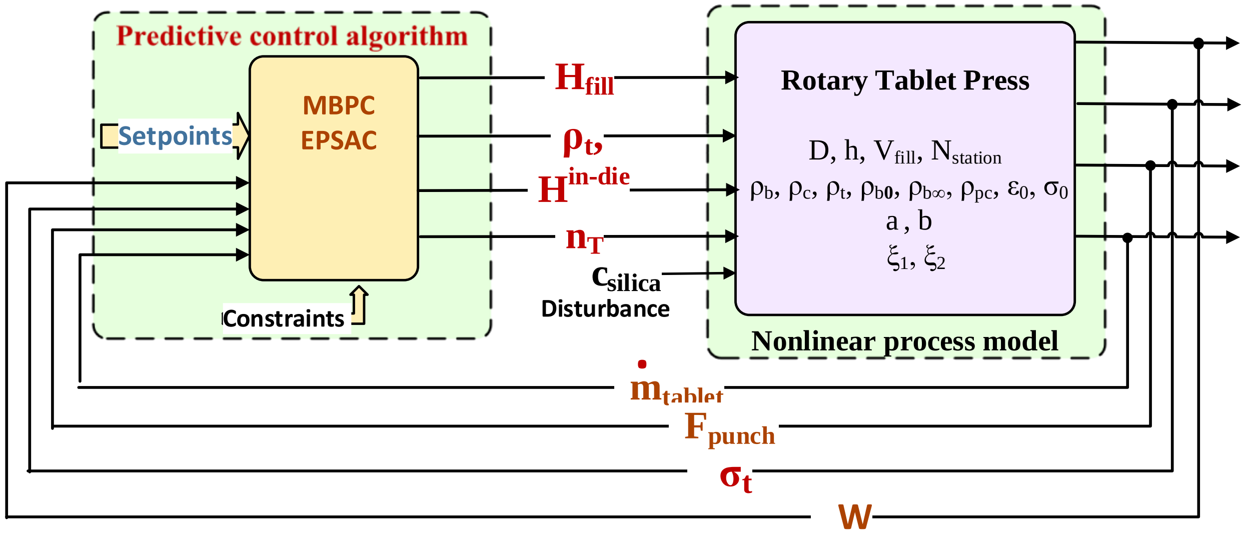
Inputs:

- H_{fill} **- Dose position**
- ρ_t **- pre-compression thickness**
- H^{in-die} **- Tablet density**
- n_T **- Turret speed**

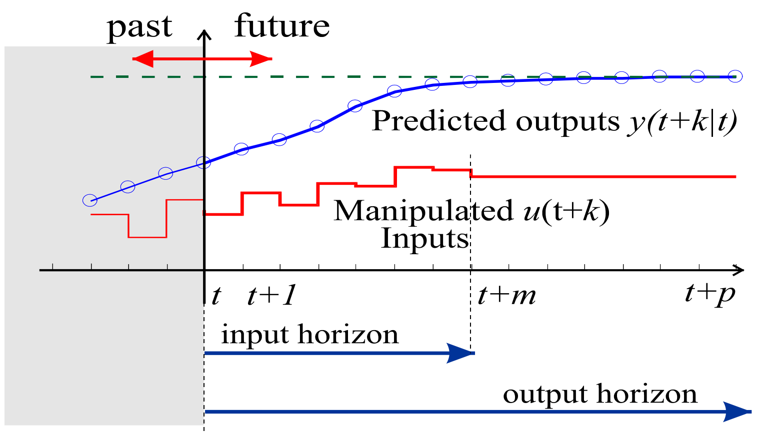
Outputs:

- m_{tablet} **– Tablet weight**
- σ_t **- pre-compression force**
- F_{pc} **– Production rate**
- W **– Tensile strength**

Control Design



$$J(N_1,N_2,N_u) = E\left\{\sum_{j=N_1}^{N_2}[y(t+j)-y_r(t+j)]^2 + \right.$$
$$\left. + \sum_{j=1}^{N_u}[\rho(j)[\Delta u(t+j-1)]^2 \right.$$



Tunning parameters:

- Control horizon N_{ui}=1
- N_1=5, N_2= N_3= N_4=10
- Ts=1 s

Constraints :

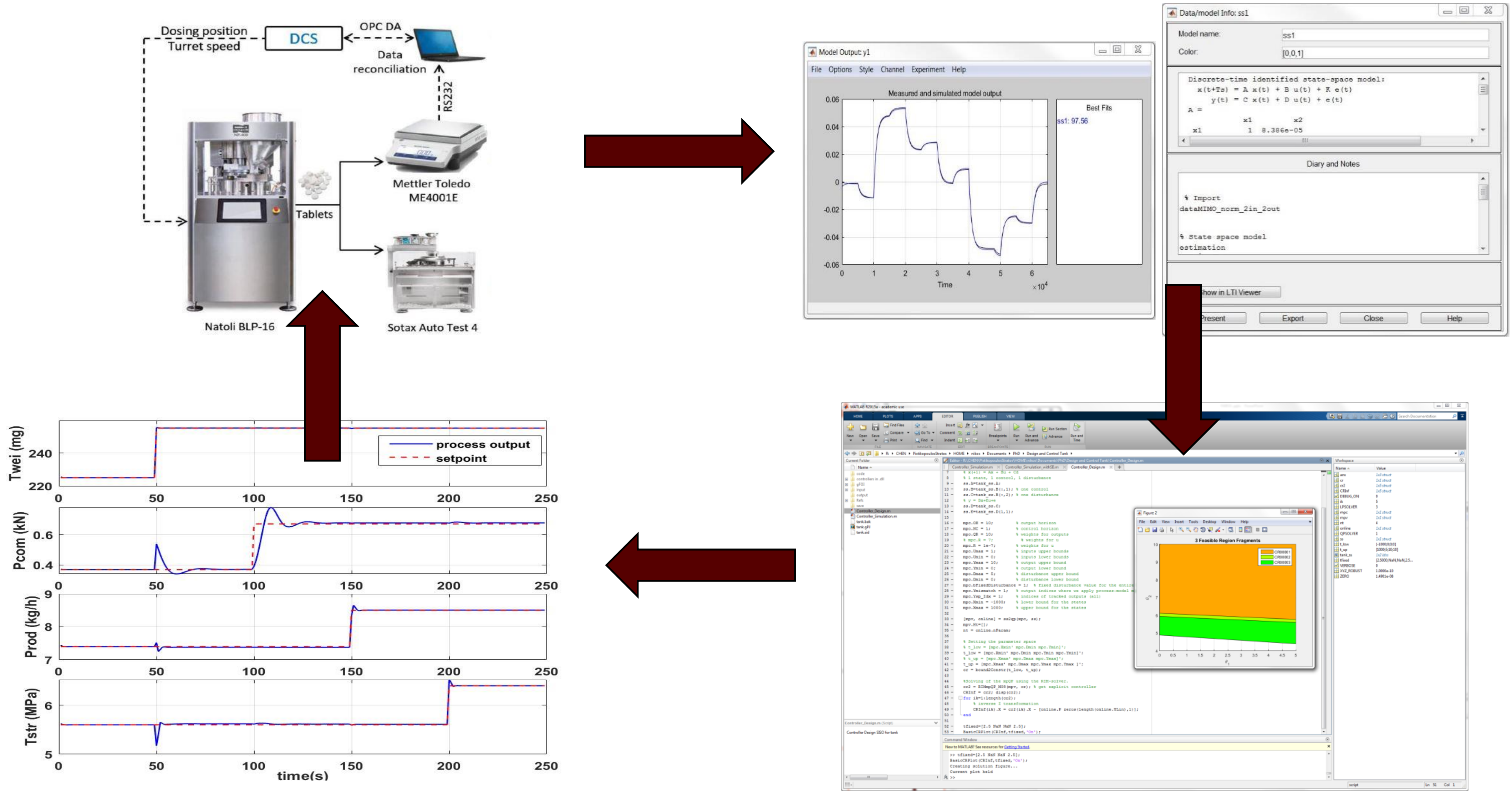
- **dosing position [6 20]mm**
- **pre-compression thickness [0.5 14] mm**
- **main compression thickness [0.5 6] mm**
- **turret speed between [0 60] rpm**

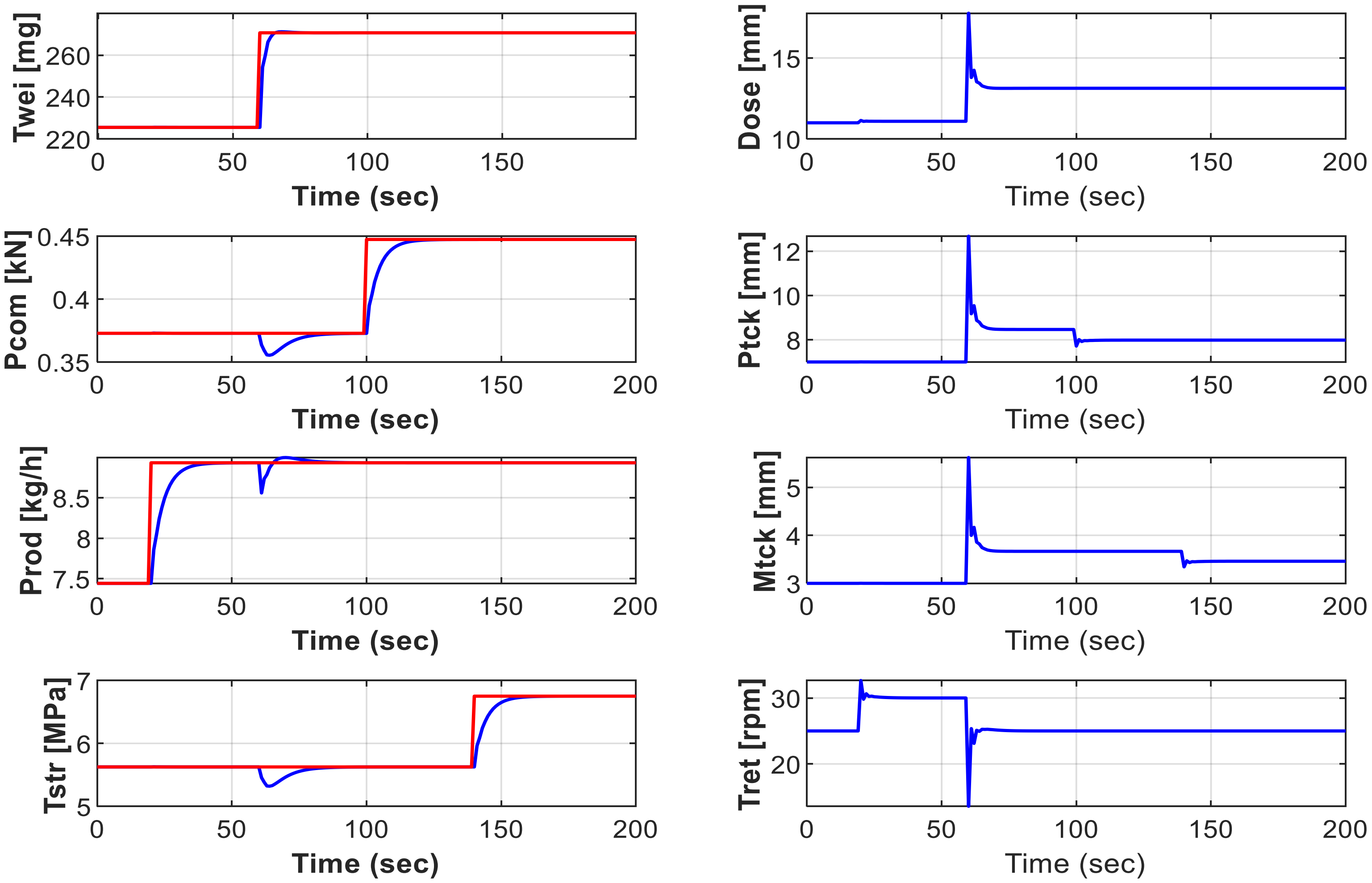
1 PROCESS

2 ALGORITHM

3 RESULTS

REPORT





Setpoint Changes Tracking

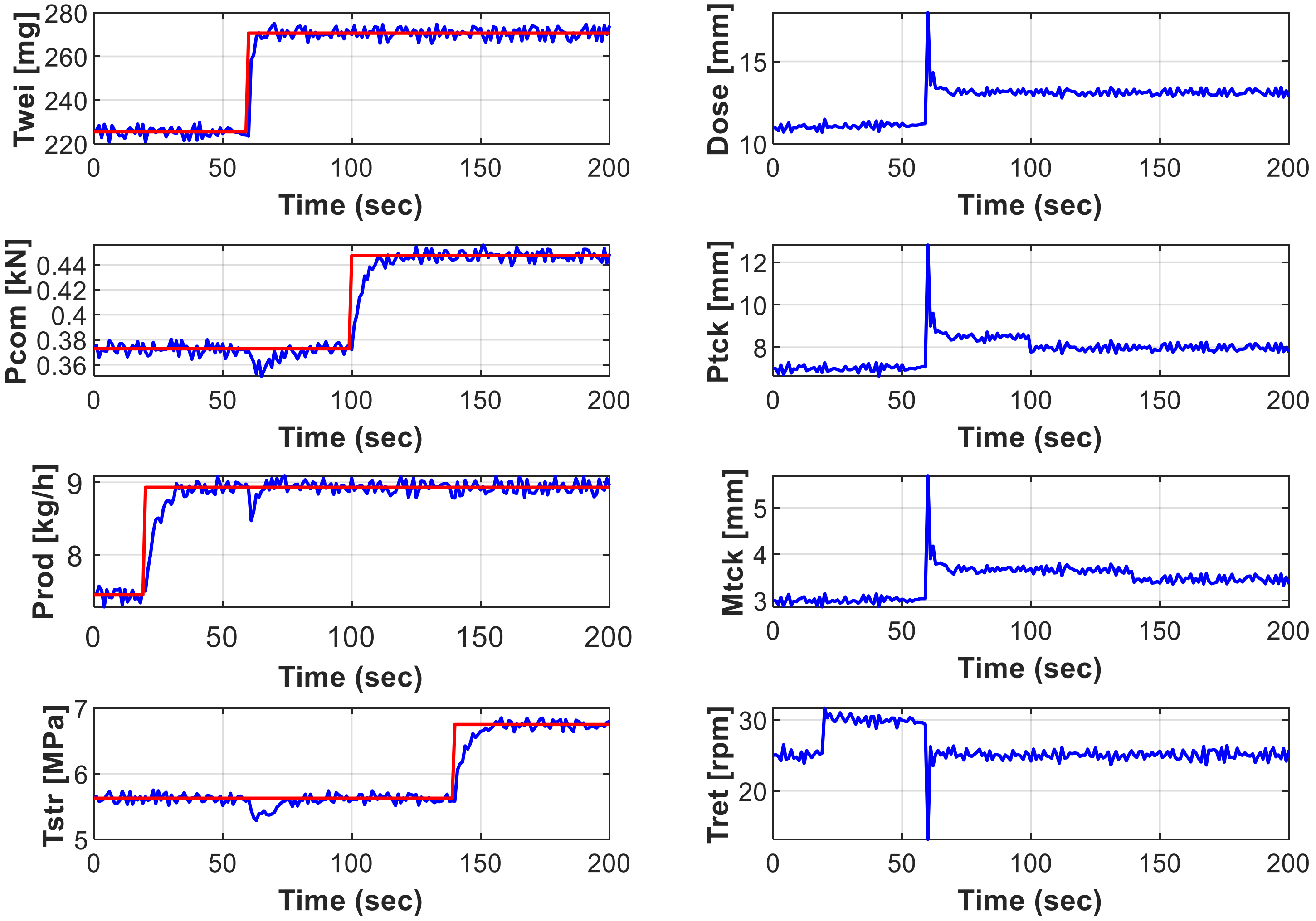
Simulation results for closed loop setpoint changes tracking

setpoint change in tablet weight (t=60 s) has the most significant impact on all outputs

good performance characteristics: (i) fast settling time, (ii) small overshoot and undershoot, and (iii) no setpoint offset for consecutive changes in all references

Efficiently manages the interdependencies between inputs and outputs

Setpoint Changes Tracking - noise



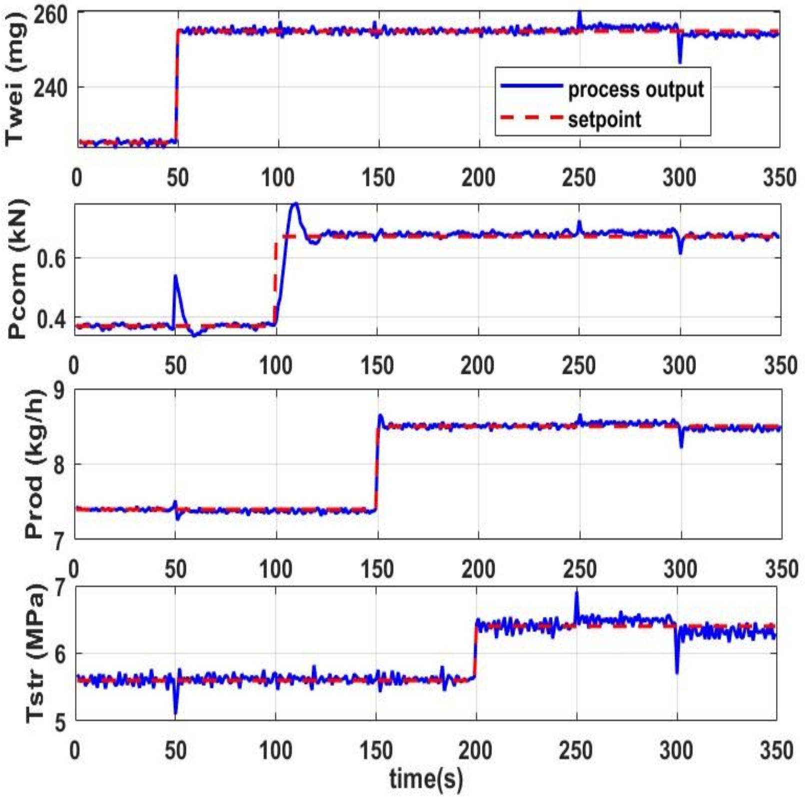
Simulation results for closed loop setpoint changes tracking with noise

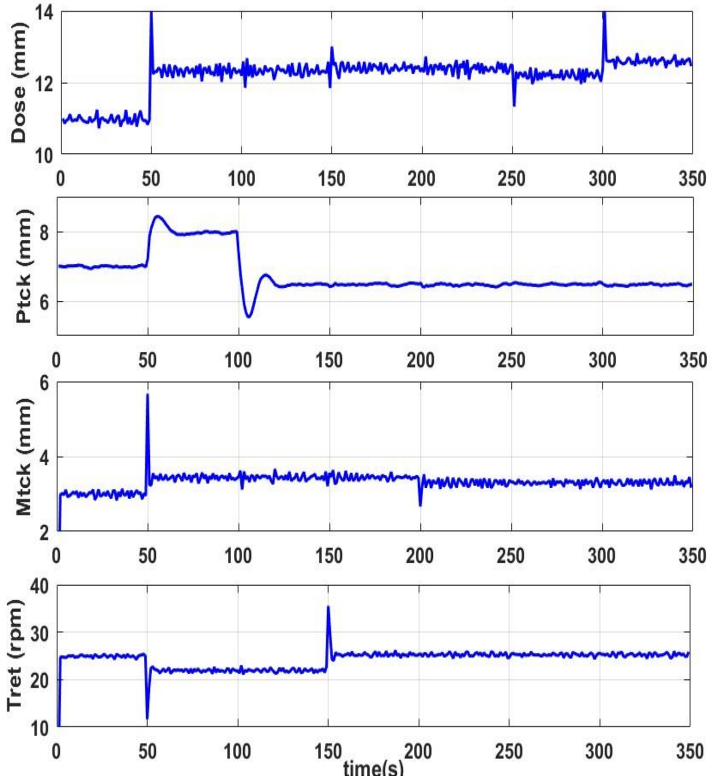
Noise is introduced to the real sensor variability, sourced from historical plant data

Design parameters selection - attenuates oscillations arising from measurement noise while maintaining a balance between response time and the propagation of the oscillations in the control loop.

One can achieve damping of the oscillations by reducing the controller's aggressiveness

Disturbance rejection - noise





Simulation results for closed loop disturbance rejection with noise

Disturbances can occur throughout any of the upstream unit operations , e.g., during refill, within the feeder unit operations, when the feeder changes from gravimetric mode to volumetric mode, leading to an increase in the bulk density because of compression or a decrease in bulk density given by aeration

Disturbance on the bulk density is given by changes in step on the silica concentration from the nominal value of 0.2% to 0.35% at t=250 s and from 0.2% to 0.05% at t=300 s

Model Predictive Control Strategies for Continuous Manufacturing Processes

Ioana Nascu[a], Nikolaos A. Diangelakis[b], Mircea Șușcă[a], Vlad Mihaly[a] and Zoltan K. Nagy[c]

a Department of Automation Technical University of Cluj Napoca, Romania

b School of Chemical and Environmental Engineering Technical University of Crete

c Davidson School of Chemical Engineering, Purdue University, West Lafayette, USA