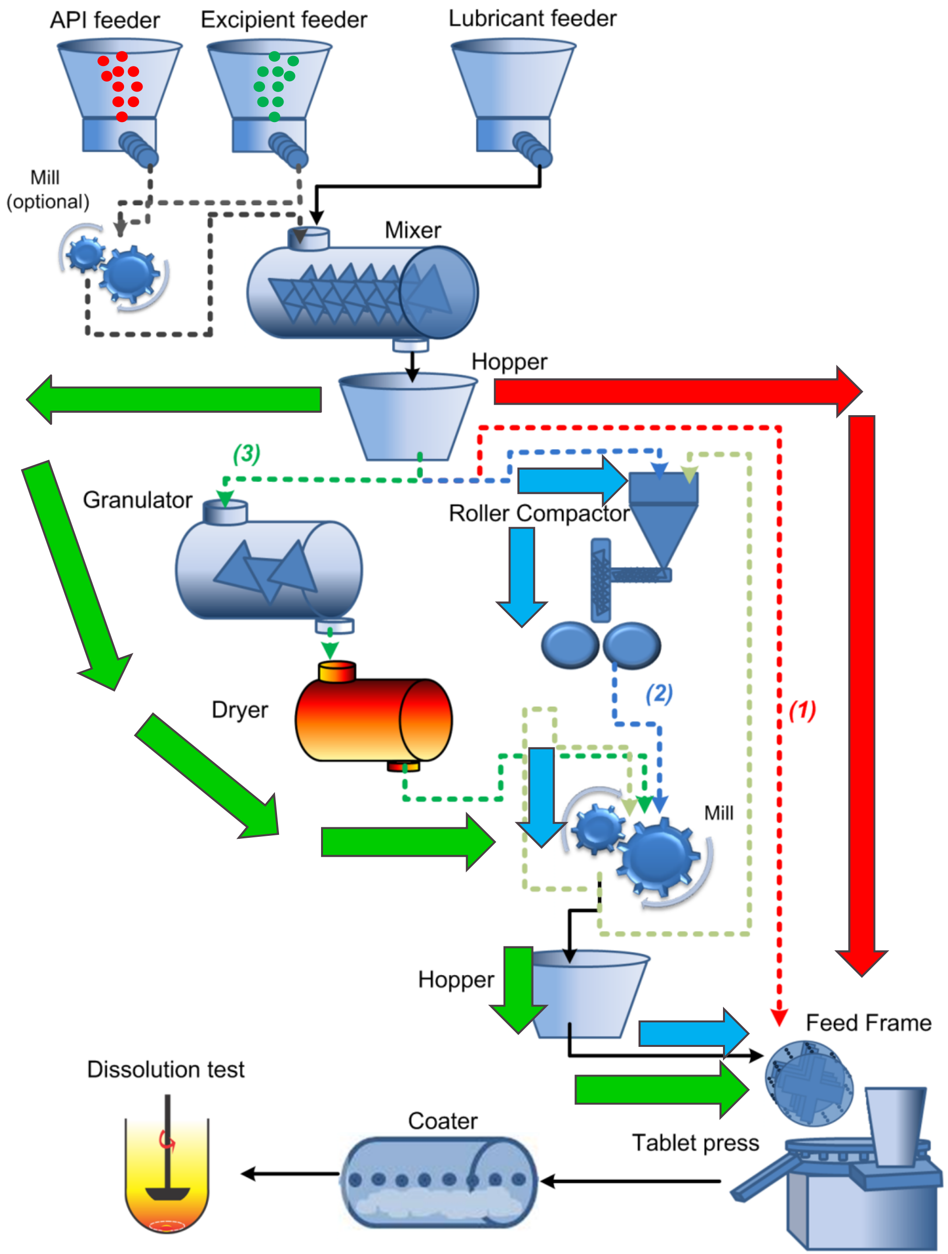
# Advanced Control of a Flexible Multipurpose Continuous Pharmaceutical Tablet Manufacturing Process

R. Ramachandran, R. Singh, A. Sahay

Engineering Research Center for Structured Organic Particulate Systems
Department of Chemical & Biochemical Engineering
Rutgers University, USA

# Flexible multipurpose tablet manufacturing process




Wet
Granulation

Enable:
Continuous
FLEXIBLE
**multipurpose**
platform

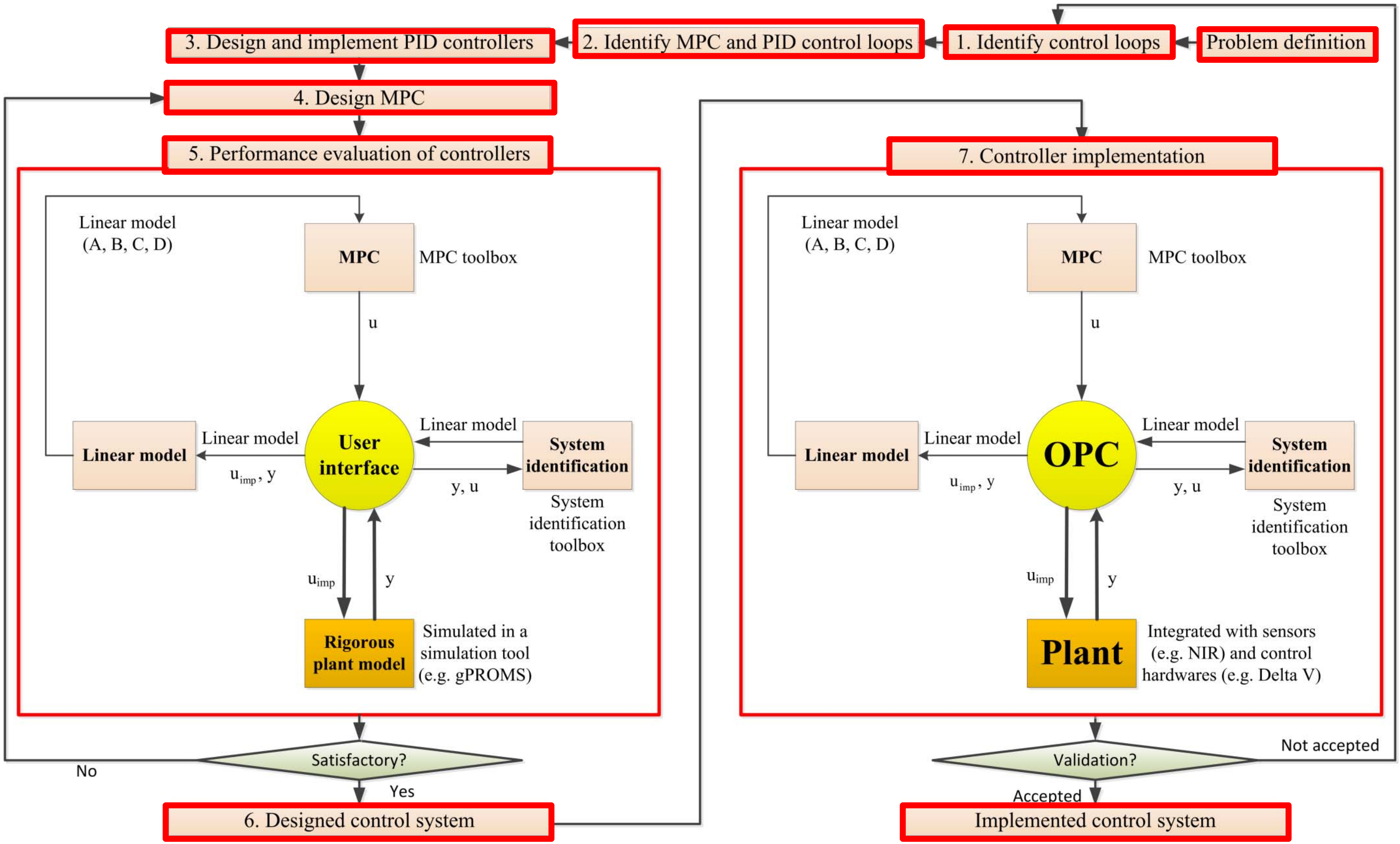
**Ref.: Singh, R.,** Boukouvala, F., Jayjock, E., Ramachandran, R. Ierapetritou, M., Muzzio, F. (2012). PharmPro Magazine, 28 June, 2012, http://www.pharmpro.com/articles/2012/06/business-Flexible-Multipurpose-Continuous-Processing/.

# Continuous direct compaction tablet manufacturing pilot plant



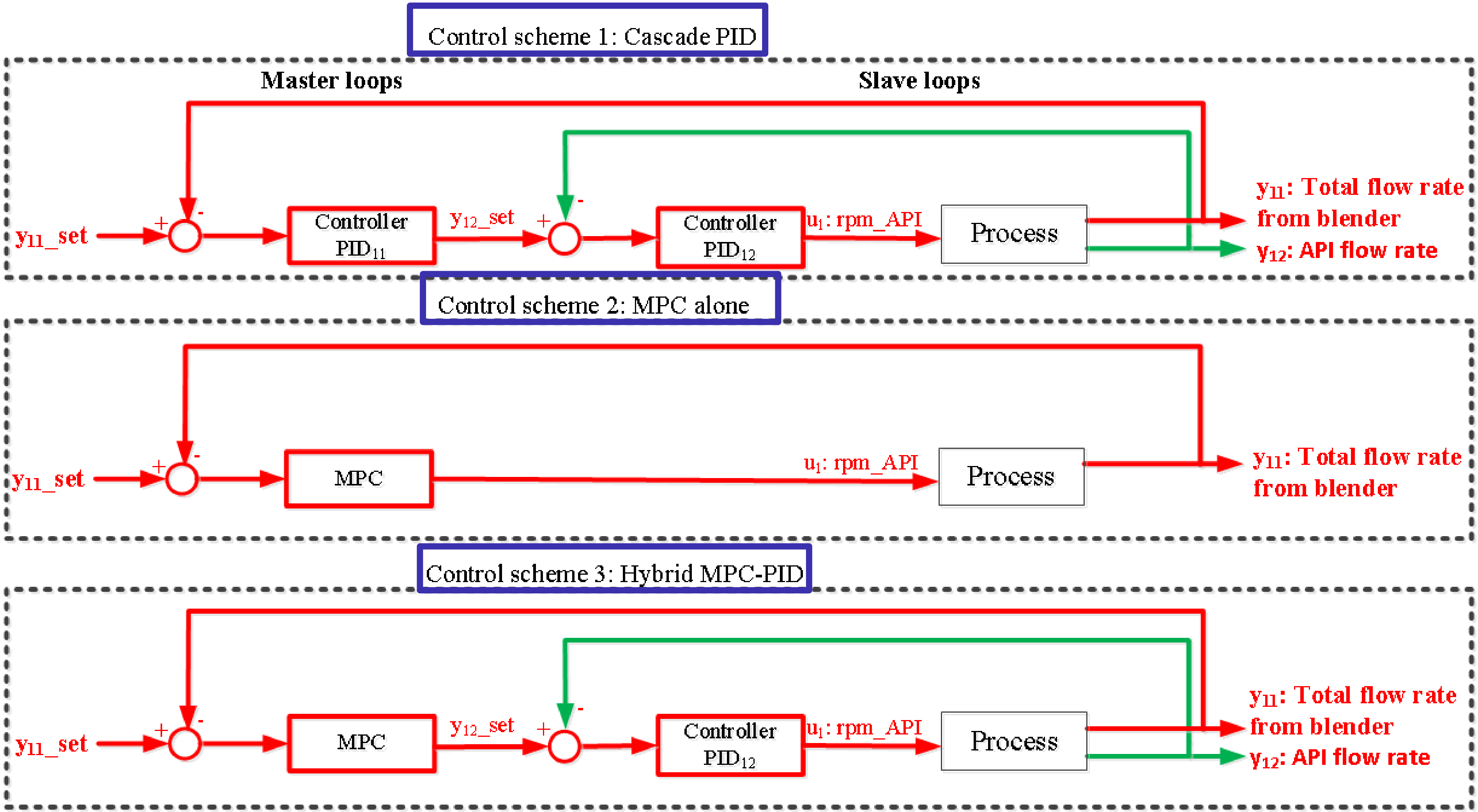
**Ref.: Singh, R.,** Boukouvala, F., Jayjock, E., Ramachandran, R. Ierapetritou, M., Muzzio, F. (2012). GMP news, European Compliance Academic (ECE), August, 2012, http://www.gmp-compliance.org.

# Systematic methodology (Hybrid MPC-PID control scheme)



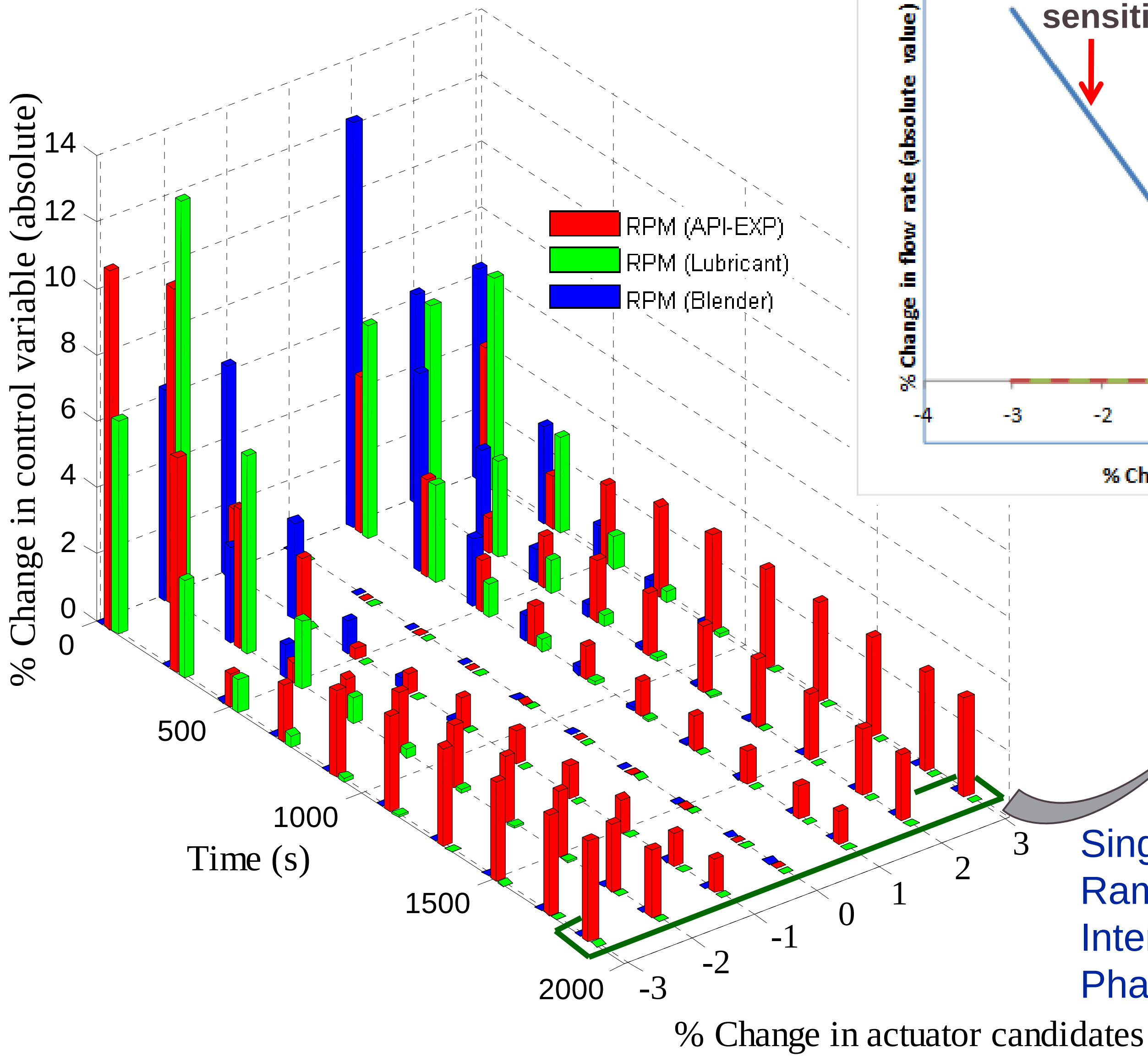

Singh, R., Ierapetritou, M., Ramachandran, R. (2013). European Journal of Pharmaceutics and Biopharmaceutics, http://dx.doi.org/10.1016/j.ejpb.2013.02.019.

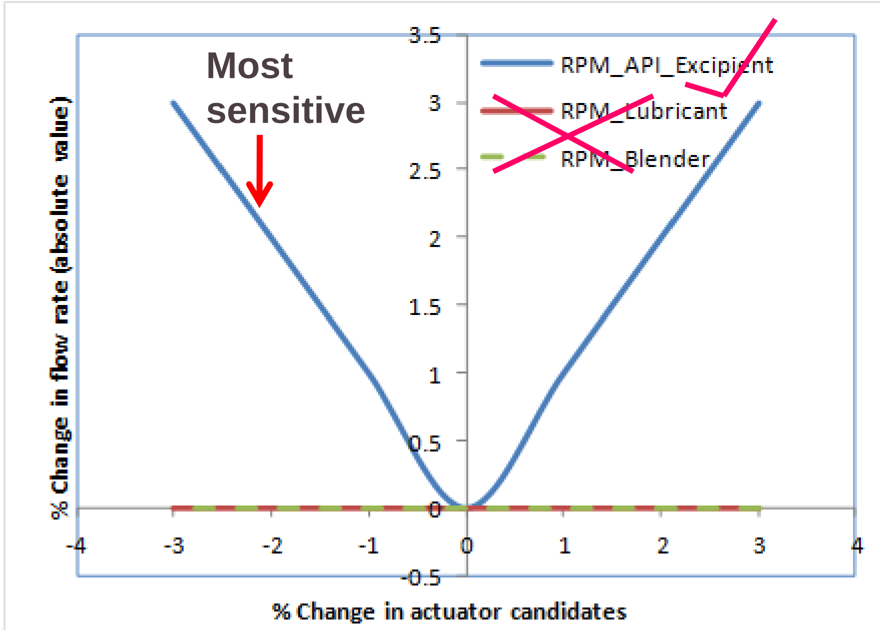
# Steps 1 - 2: Control loops and controller configurations



# Steps 1-2: Control variables and actuators pairing

**Control variable:** Total flow rate



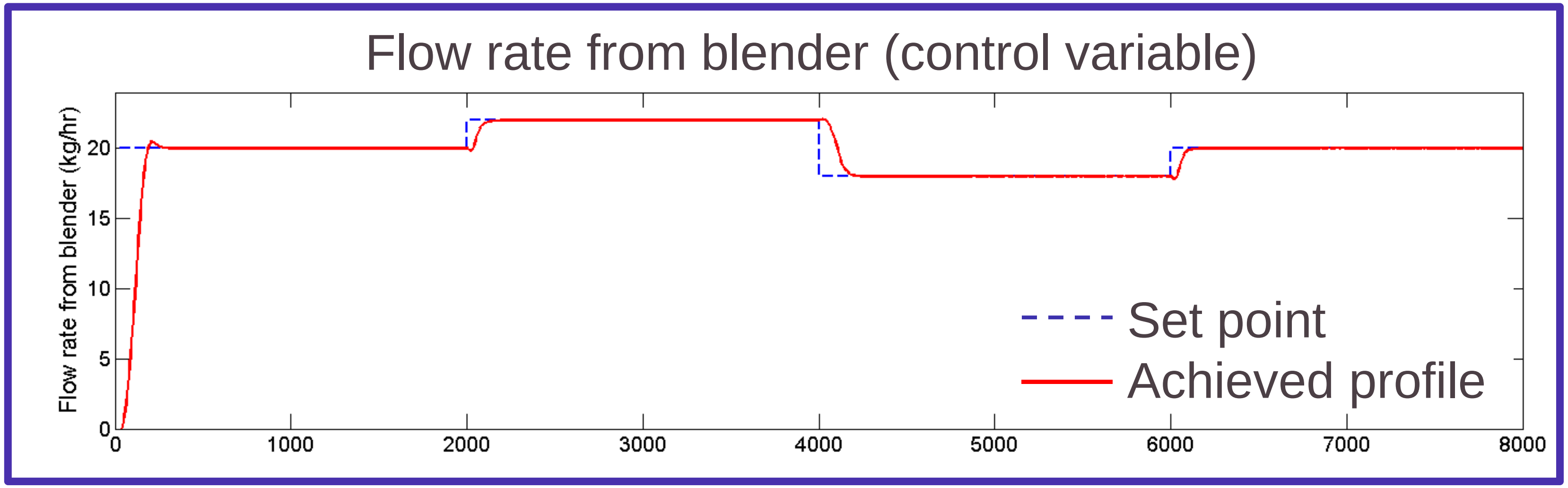

Singh, R., Ierapetritou, M., Ramachandran, R. (2012). International Journal of Pharmaceutics, 438 (1-2), 307-326.

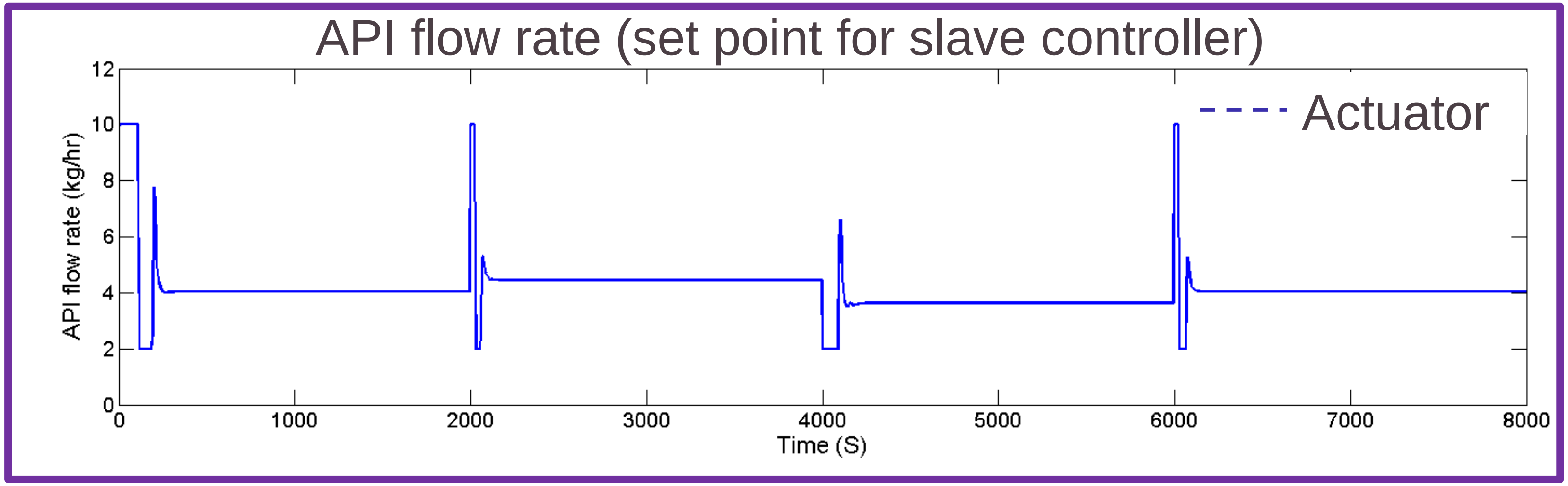
# Steps 1 - 2: Control loops and configurations

| Critical process points | Controlled variables | Intermediate actuator | Final actuator | Control scheme 1 | Control scheme 2 | Control scheme 3 |
|---|---|---|---|---|---|---|
| Blender | Total flow rate ($y_{11}$) | API flow rate ($y_{12}$) | Rotation speed of API feeder ($u_1$) | Cascade PID | MPC | Hybrid MPC-PID |
| | RSD ($y_{21}$) | Lubricant flow rate ($y_{22}$) | Rotation speed of lubricant feeder ($u_2$) | Cascade PID | Cascade PID | Cascade PID |
| | API composition ($y_3$) | - | Rotation speed of blender ($u_3$) | Single loop control PID | Single loop control PID | Single loop control PID |
| | API Excipient ratio ($y_4$) | - | Rotation speed of excipient feeder ($u_4$) | Ratio controller | Ratio controller | Ratio controller |
| Tablet press | Tablet weight ($y_{51}$) | Pre-compression pressure ($y_{52}$) | Feed volume ($u_5$) | Cascade PID | MPC | Hybrid MPC-PID |
| | Tablet dissolution ($y_{61}$) | Hardness ($y_{62}$), Main compression force ($y_{63}$) | Punch displacement ($u_6$) | Cascade PID | MPC | Hybrid MPC-PID/ Cascade PID |


1. Singh, R., Ierapetritou, M., Ramachandran, R. (2012). An engineering study on the enhanced control and operation of continuous manufacturing of pharmaceutical tablets via roller compaction. International Journal of Pharmaceutics, 438 (1-2), 307-326.
2. Ramachandran, R., Arjunan, J., Chaudhury, A, Ierapetritou, M. (2012). Model-Based Control Loop Performance Assessment of a Continuous Direct Compaction Pharmaceutical Processes. *J. Pharm. Innov., 6(3)*, 249-263.
3. Singh, R., Gernaey, K. V., Gani, R., (2010). ICAS-PAT: A Software for Design, Analysis & Validation of PAT Systems. Computers & Chemical Engineering, 34(7), 1108-1136.

# Step 4. Design MPC: Hybrid MPC-PID (set point tracking)

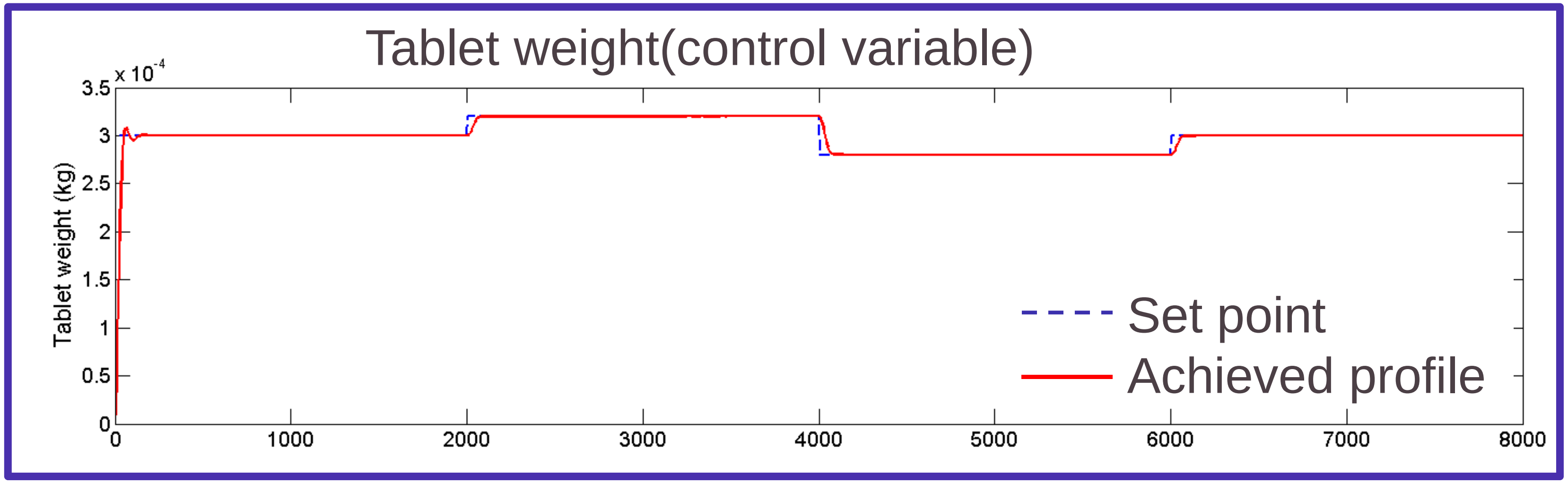


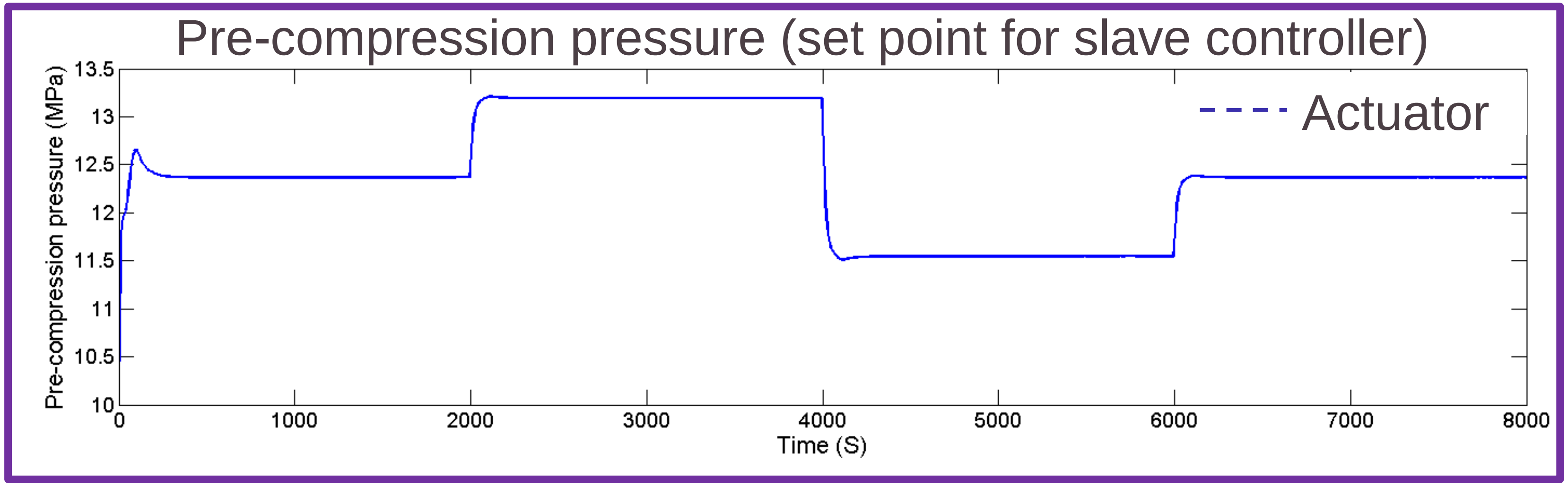




Note:

- Final actuator: Rotational speed of API feeder
- Slave controller: PID

# Step 4. Design MPC: Hybrid MPC-PID (set point tracking)

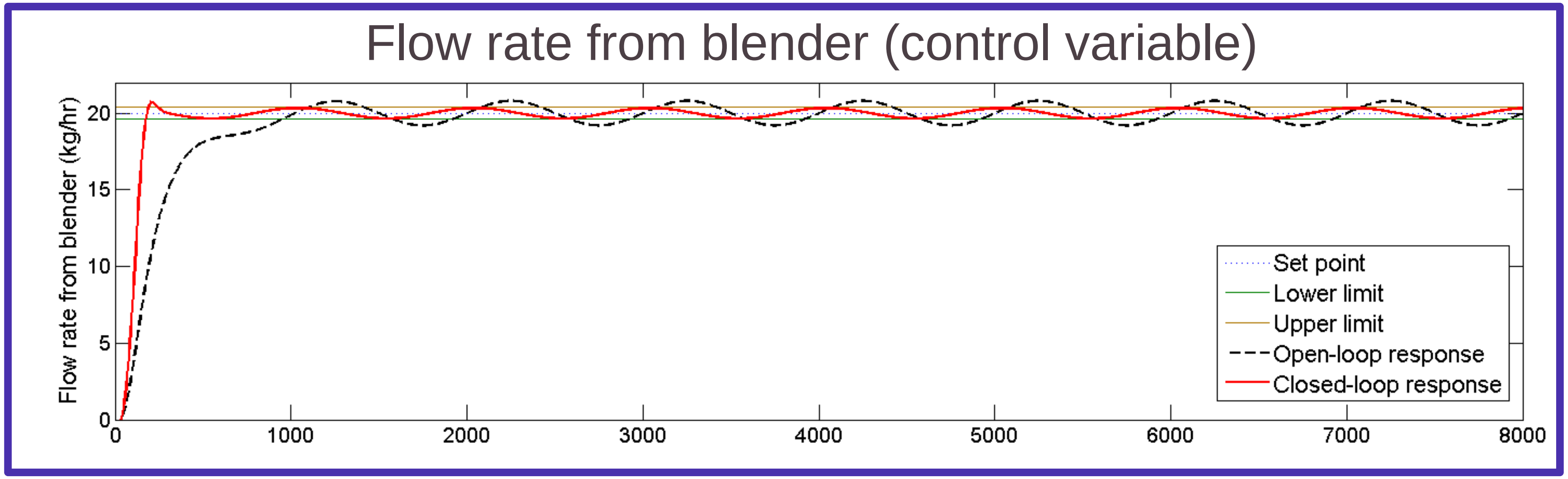


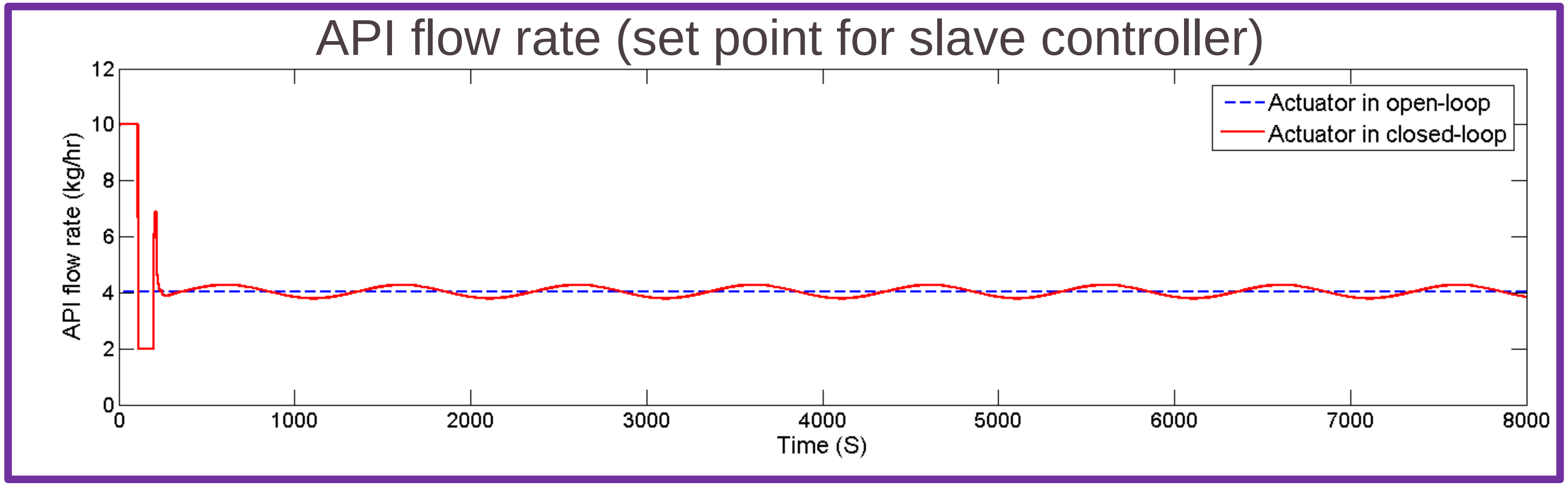




Note:

- Final actuator: Powder feed rate
- Slave controller: PID

# Step 4. Design MPC: Hybrid MPC-PID (disturbances rejection)



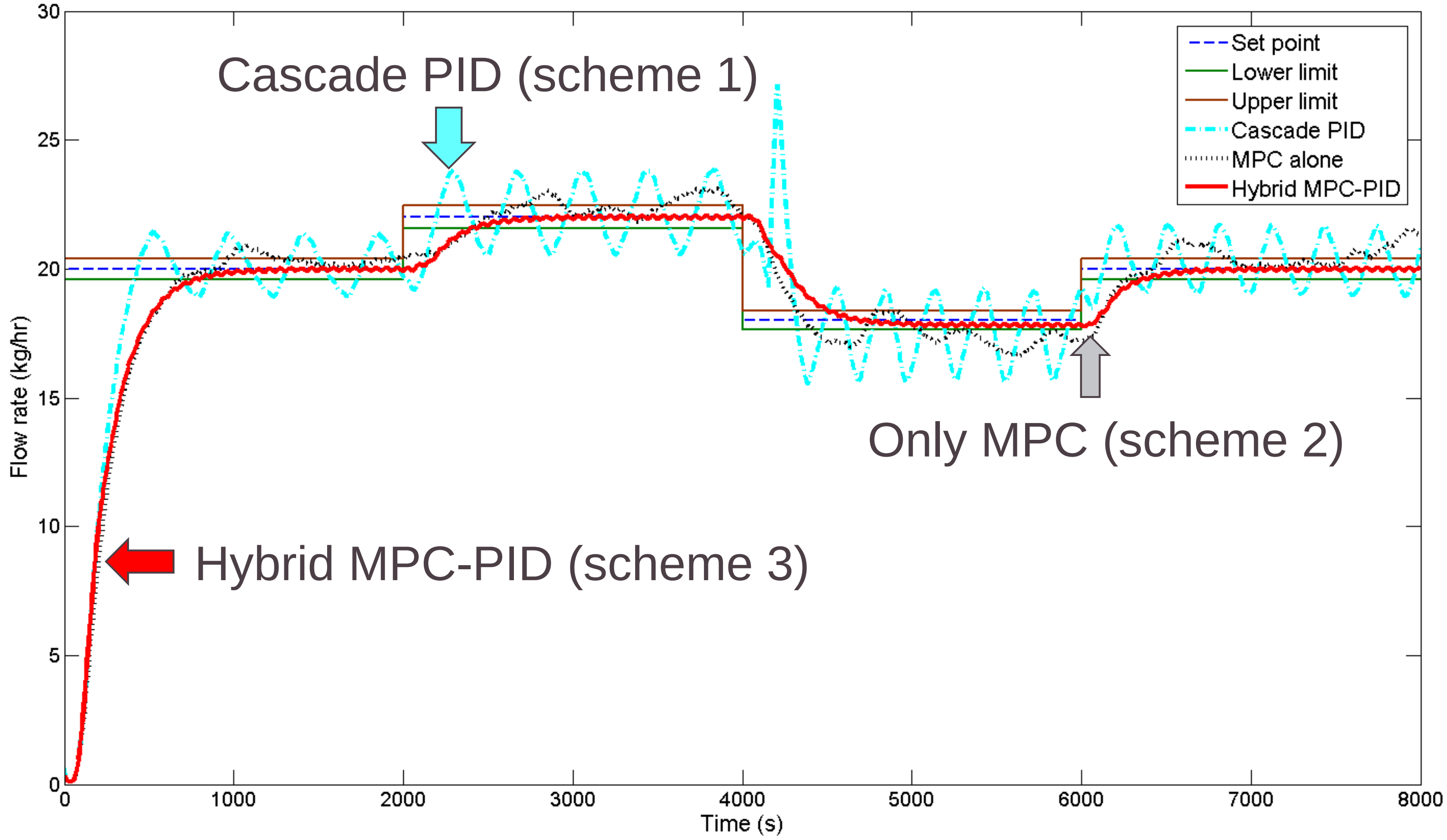




Note:

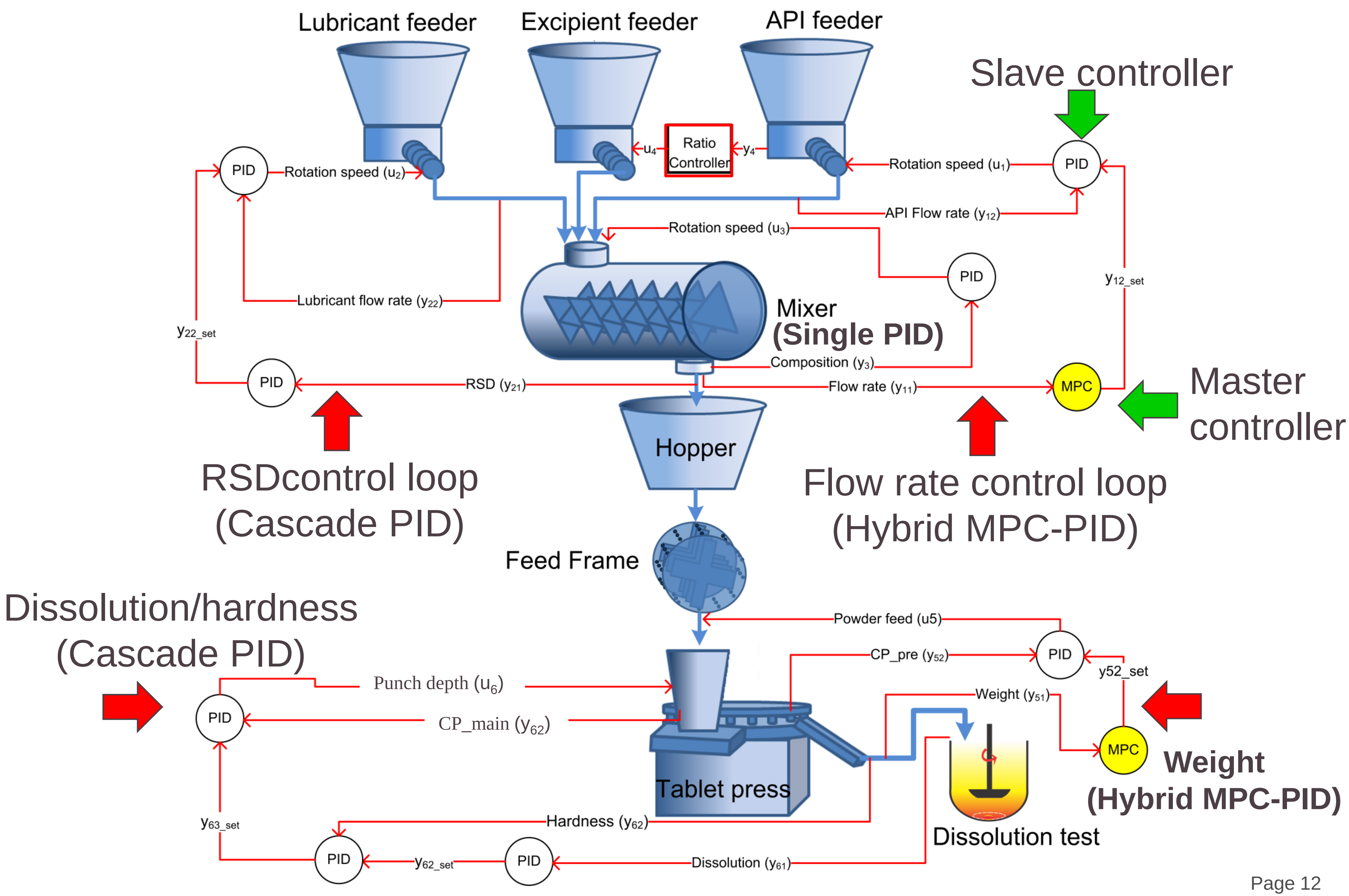
- Final actuator: Rotational speed of API feeder
- Slave controller: PID

# Step 5: Performance evaluation (set point tracking)

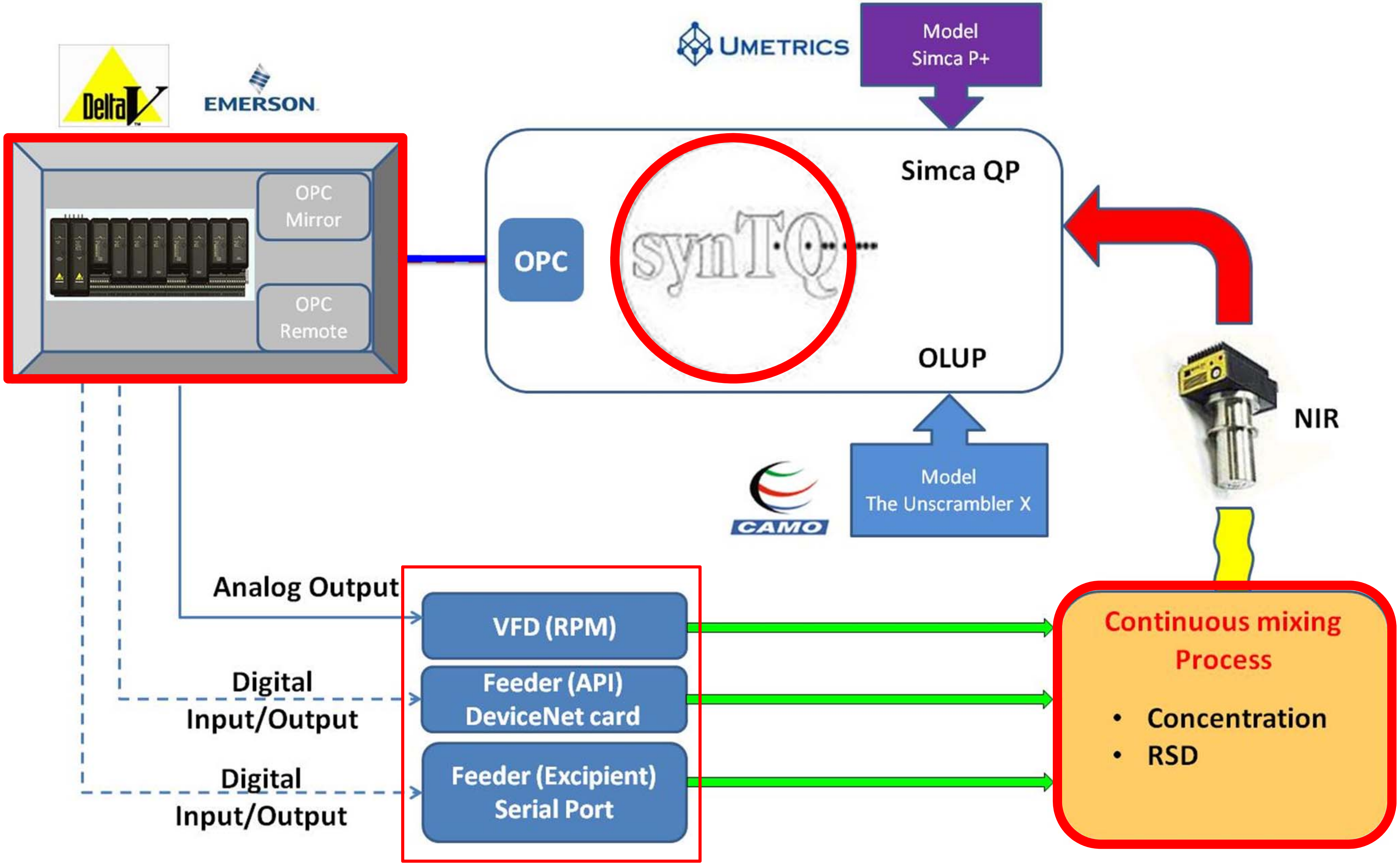
## Control variable: Total flow rate from blender



# Step 6: Designed control system

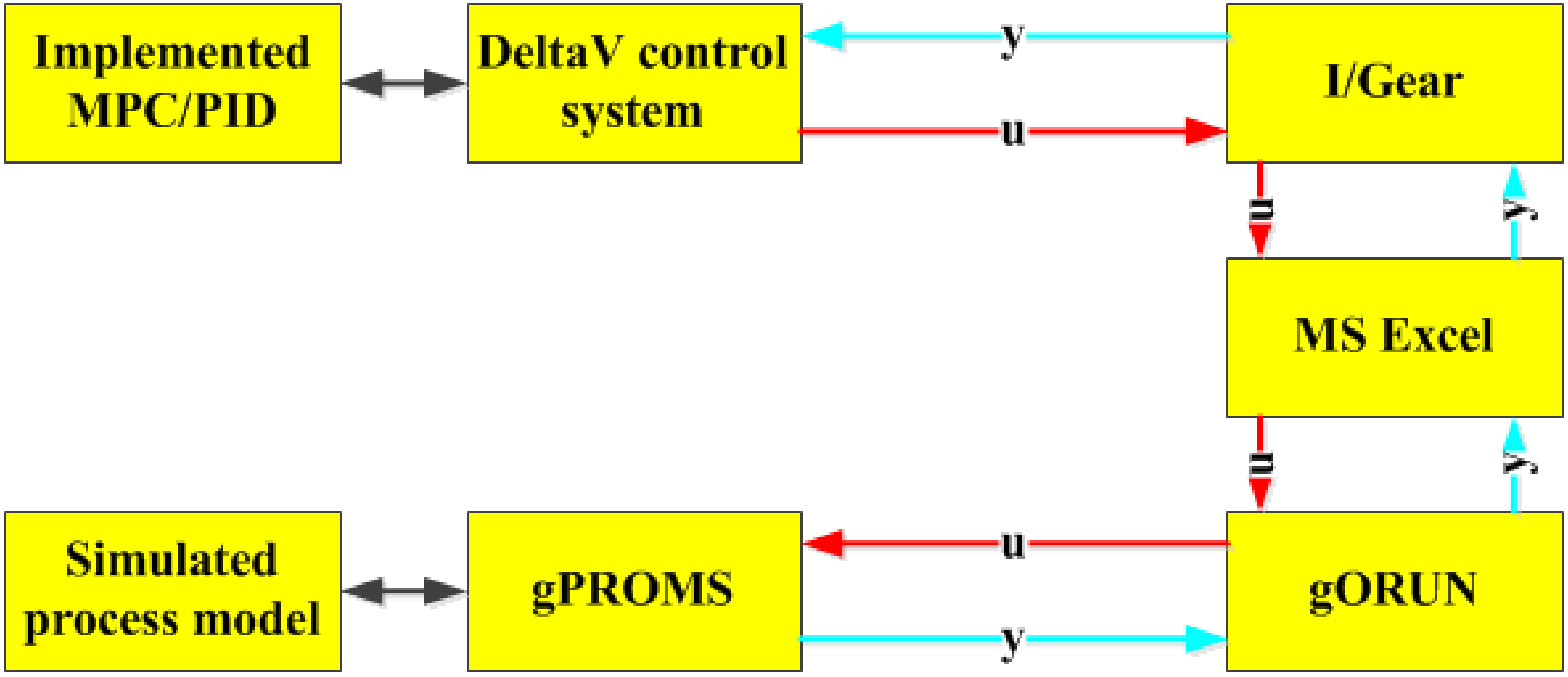


# Step 7: Controller implementation

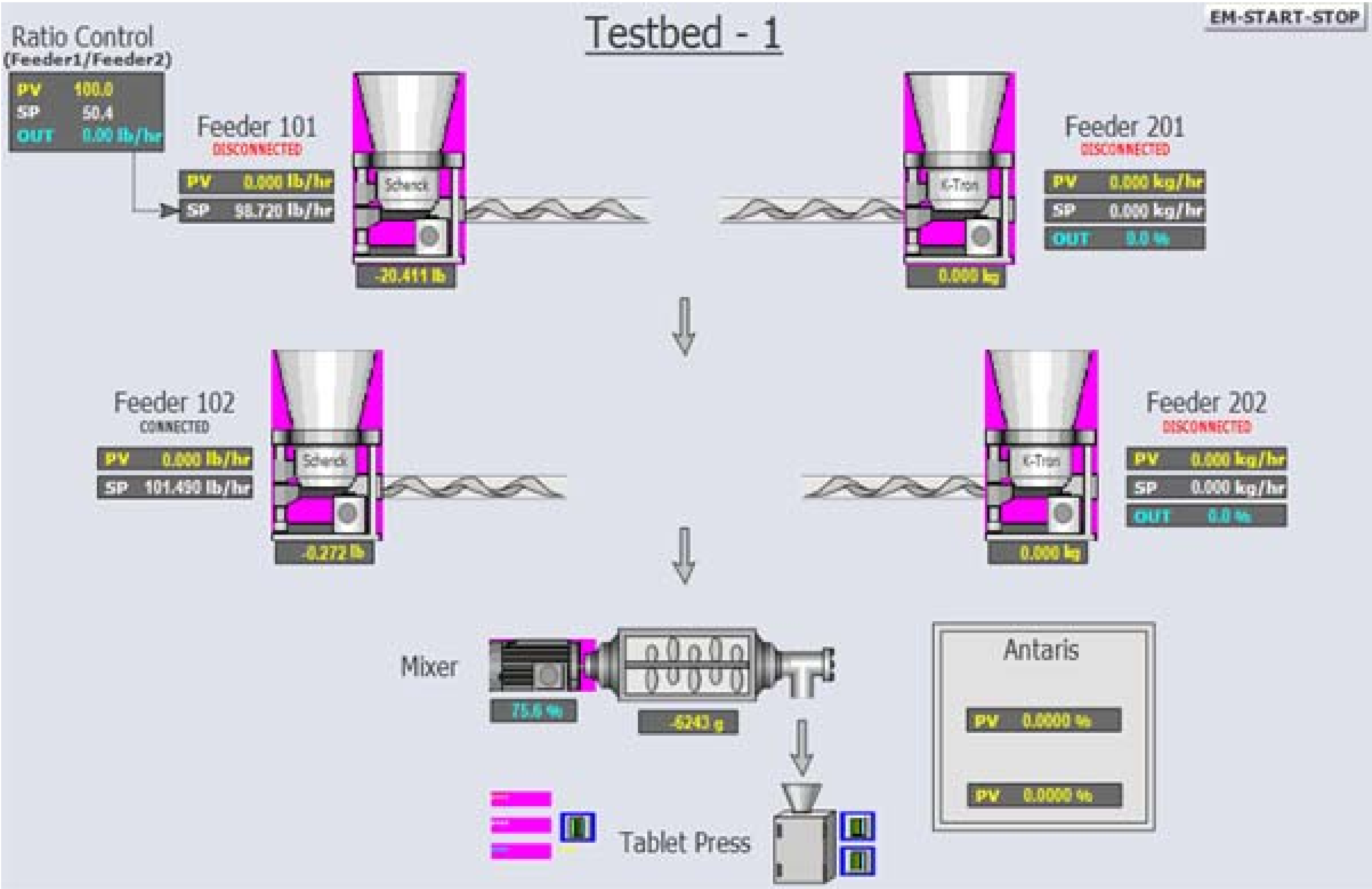



Thanks to Prof. Velazquez Carlos (UPRM) for providing help to prepare this slide

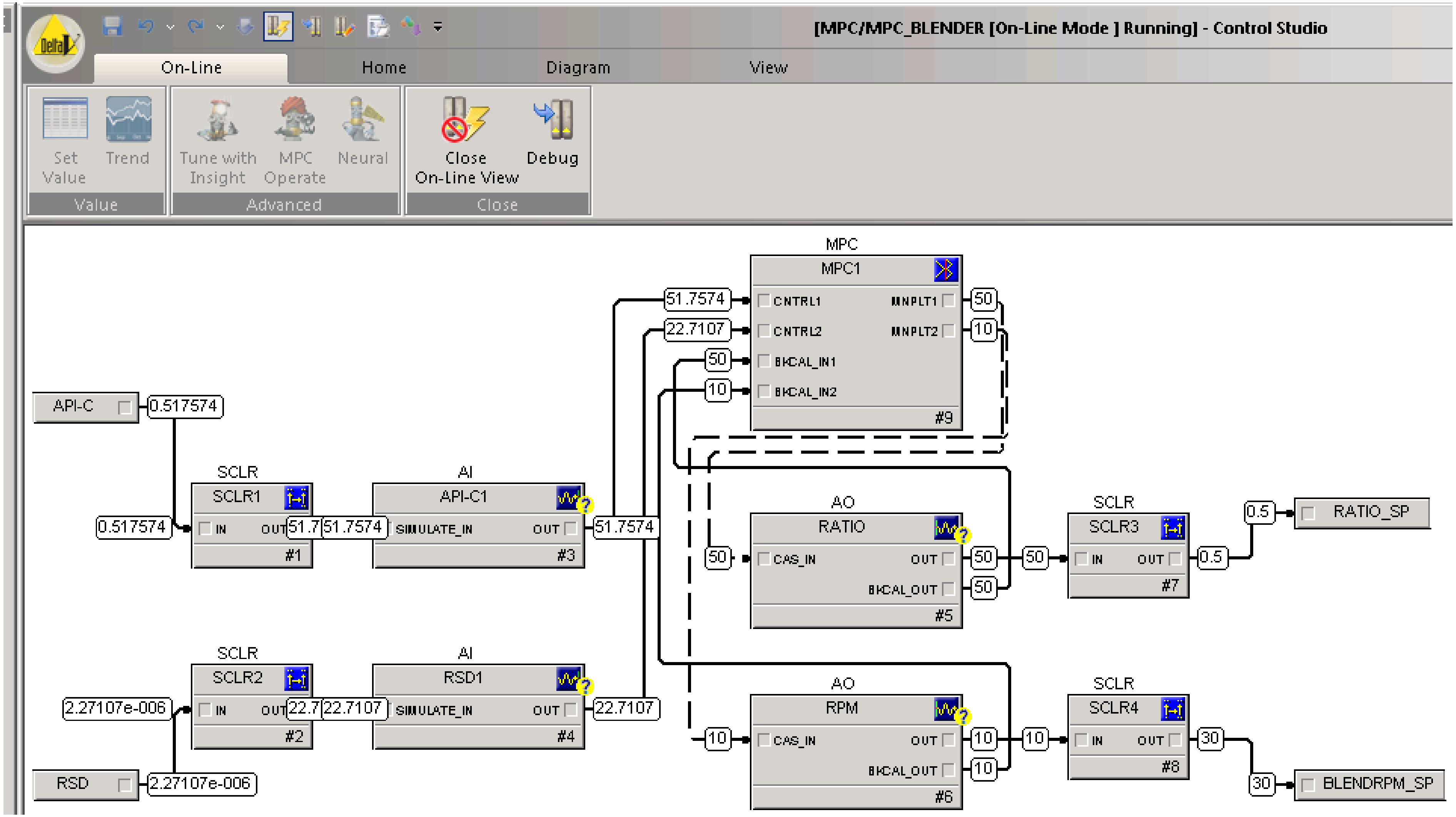
# Integration of gPROMS with DeltaV control system



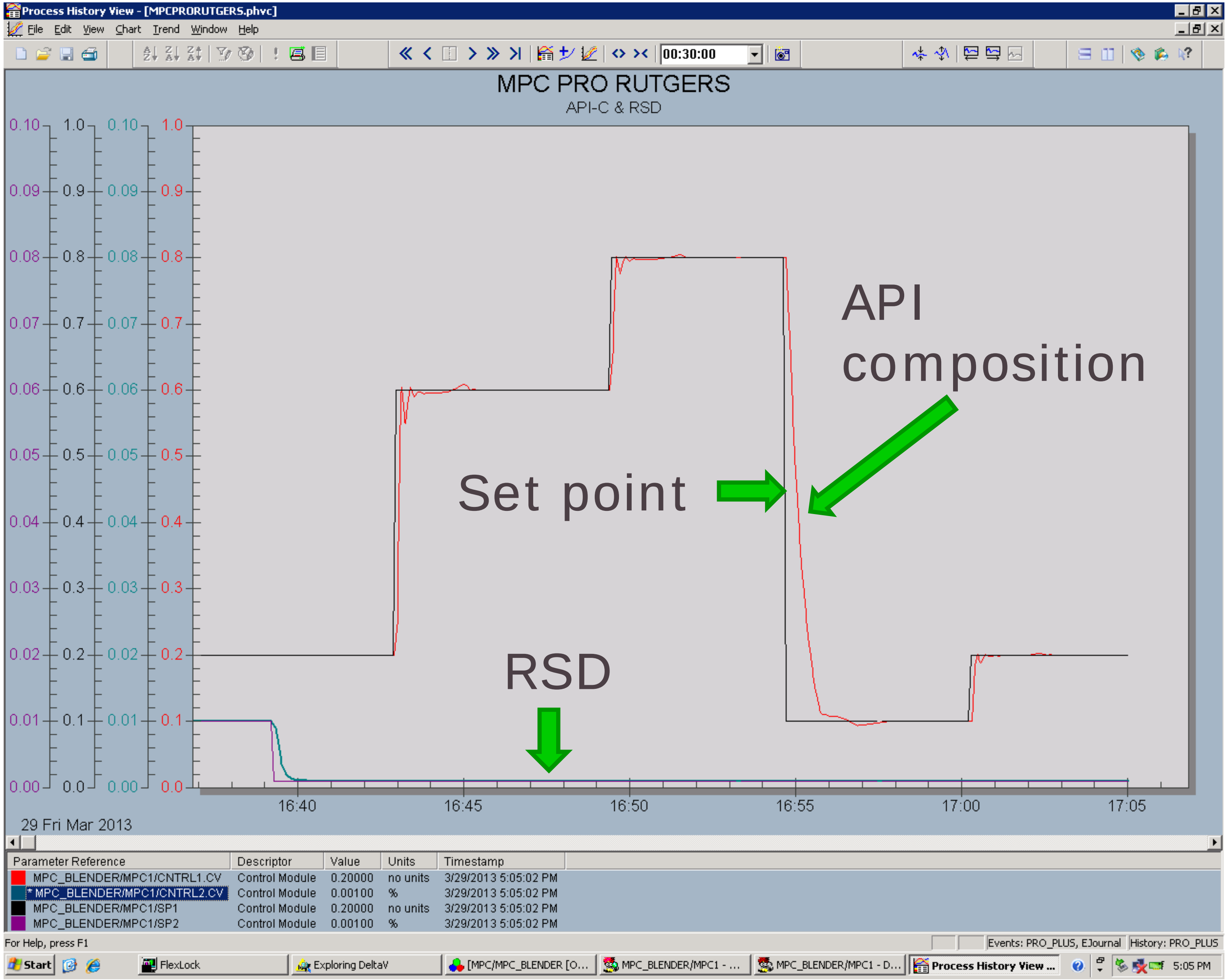
# Step 7: Control interface (DeltaV control system)



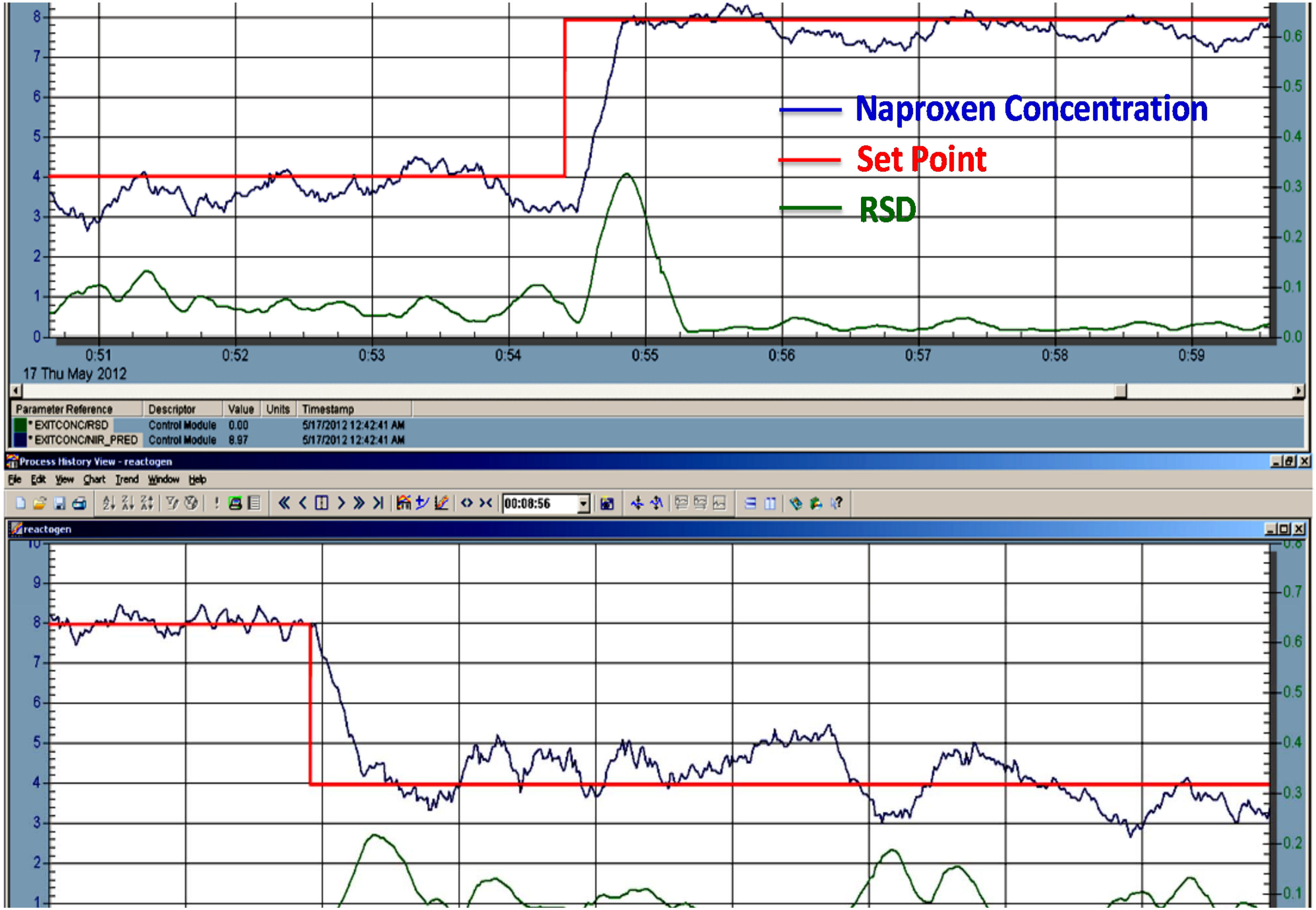
# Implemented MPC in DeltaV control system



# Closed-loop performance (model-based )



# Closed-loop performance (in plant)

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# Conclusions

- **A hybrid MPC-PID controller has been designed for continuous direct compaction tablet manufacturing process**
- **The performance of hybrid control system has been compared with the regulatory control system as well as MPC alone and found to be better**
- **Set-point tracking and disturbances rejection ability of control strategy has been analyzed**
- **The current and future work includes the implementation of hybrid control system in NSF-ERC pilot plant facility**

# References


1. Singh, R., Ierapetritou, M., Ramachandran, R. (2012). An engineering study on the enhanced control and operation of continuous manufacturing of pharmaceutical tablets via roller compaction. International Journal of Pharmaceutics, 438 (1-2), 307-326.
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## Acknowledgements

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# **QUESTIONS?**