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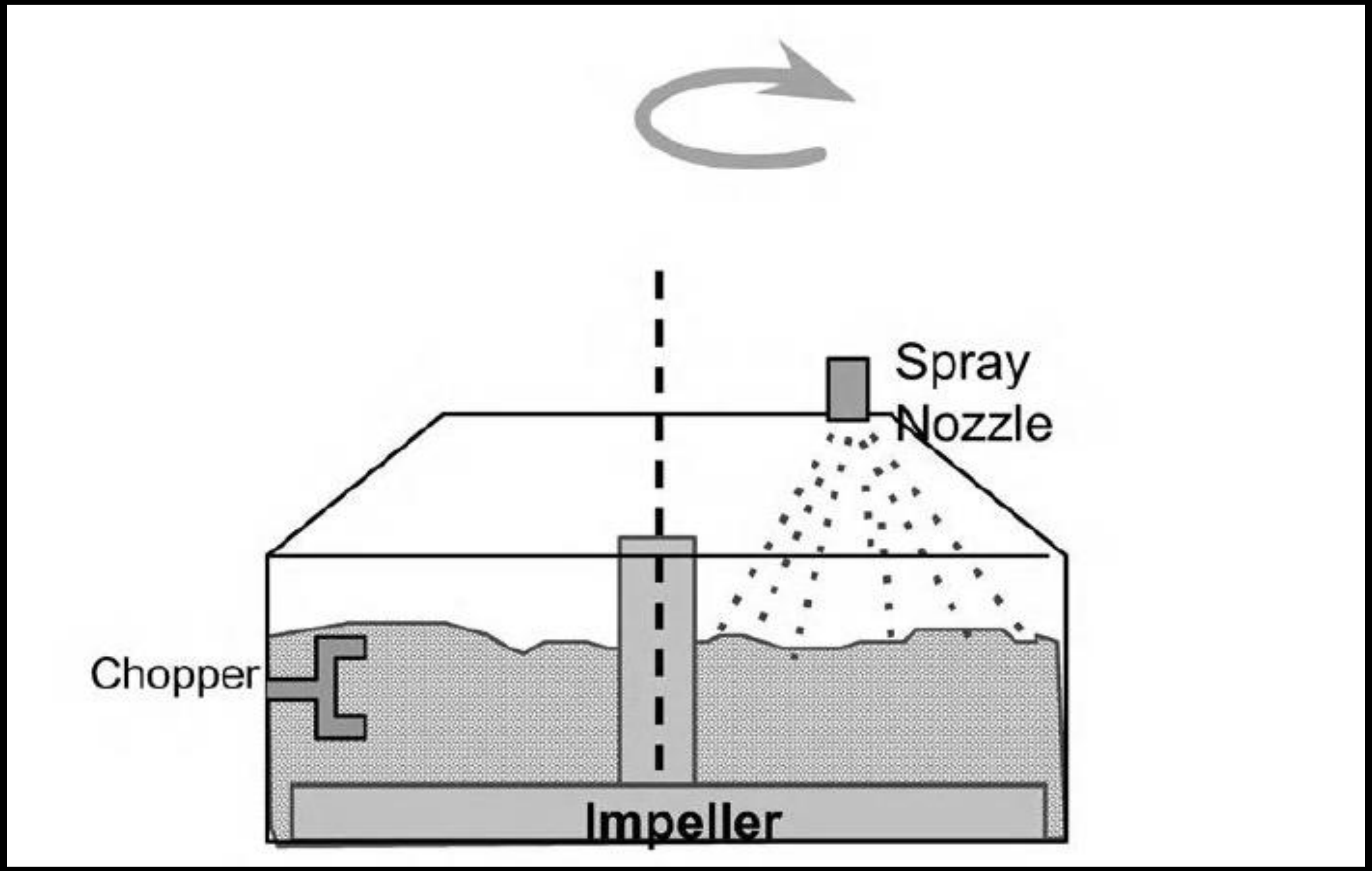
# Self-Optimizing High Shear Wet Granulation with DeepMPC

# HSWG (High Shear Wet Granulation)

**Old technology, but very common in pharmaceutical industry!**

**The principle is agglomeration that is the formation of agglomerates or aggregates by sticking together of smaller particles.**




**It consists of agglomerating one or different powders by spraying a liquid binder over the bed of powders under a vigorous mixing.**

From: **The science and engineering of granulation processes**, *Jim Litster and Bryan Ennis*

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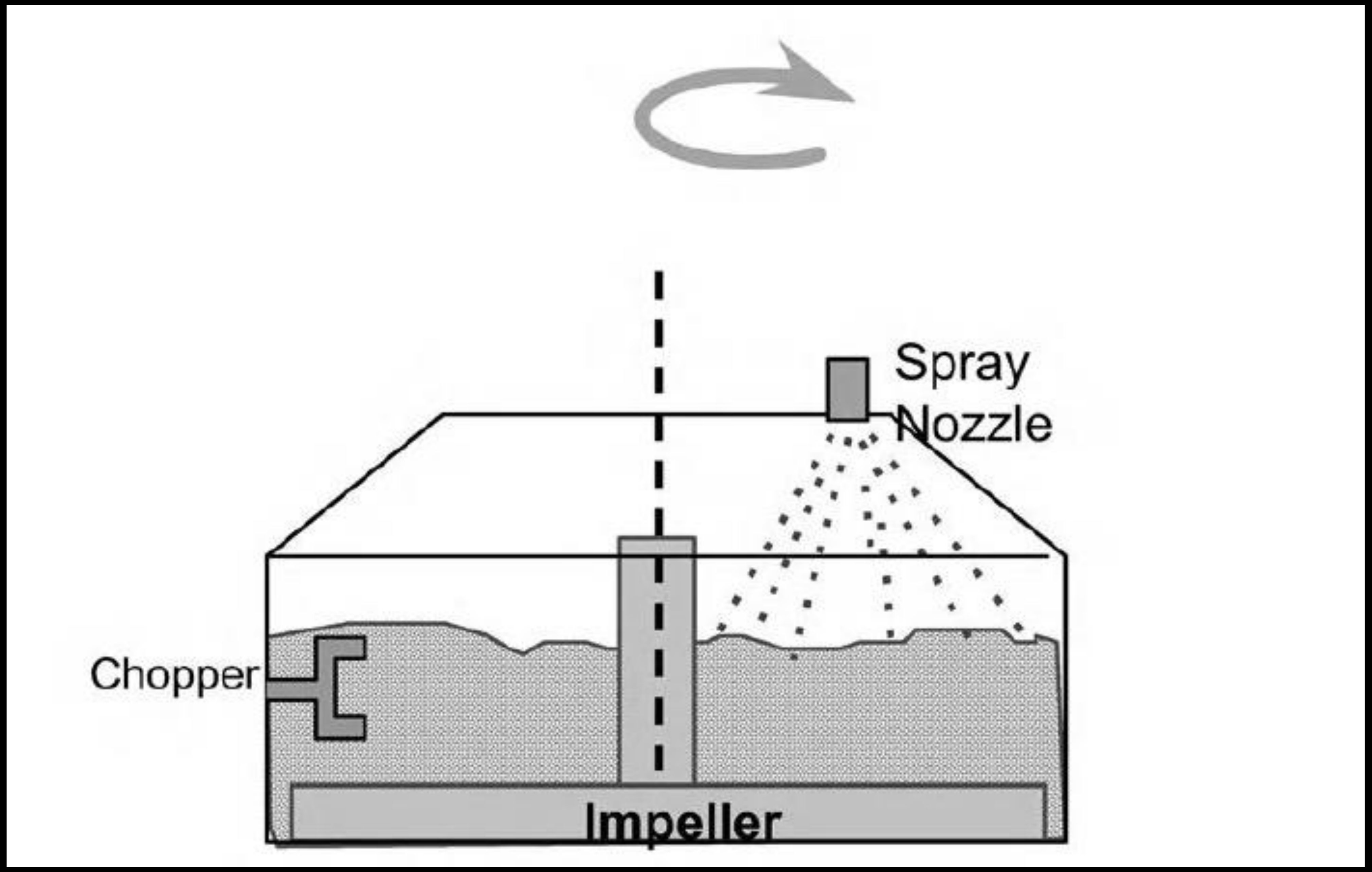
# GRANULATION PHASES




The process consists of 3 phases:

1. Mixing
2. Wetting
3. Massing

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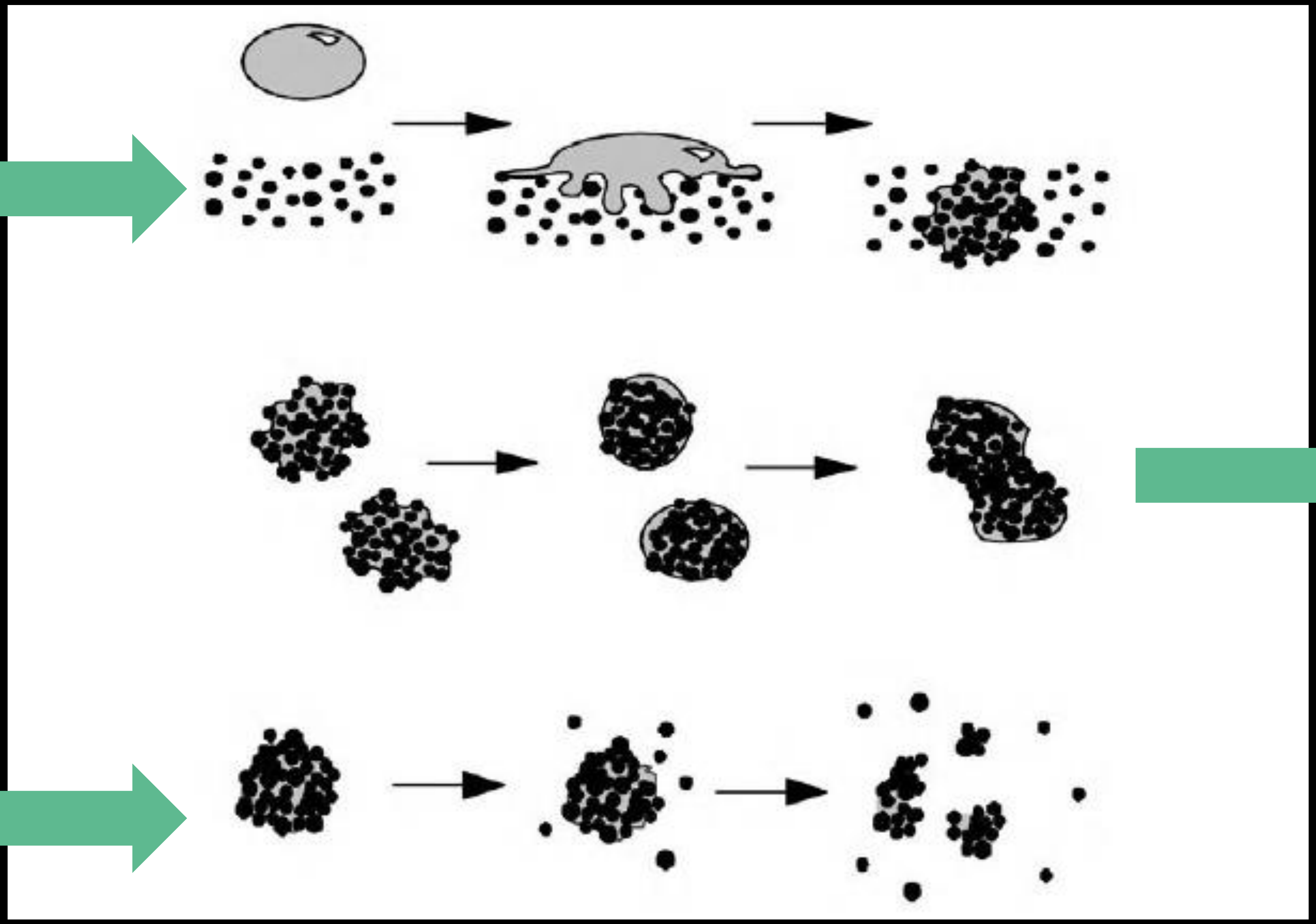
Influenced by:
1. RM properties
2. Agitation
3. Degree of filling
4. Liquid flowrate
5. Nozzle characteristics
6. Etc.

## *Nucleation and wetting*

- *Drop controlled*
- *Mechanical dispersion controlled*
- *Intermediate*



- **Steady growth regime**
- **Induction growth regime**

## *Consolidation and growth*

- *Coalescence*
- *Layering*

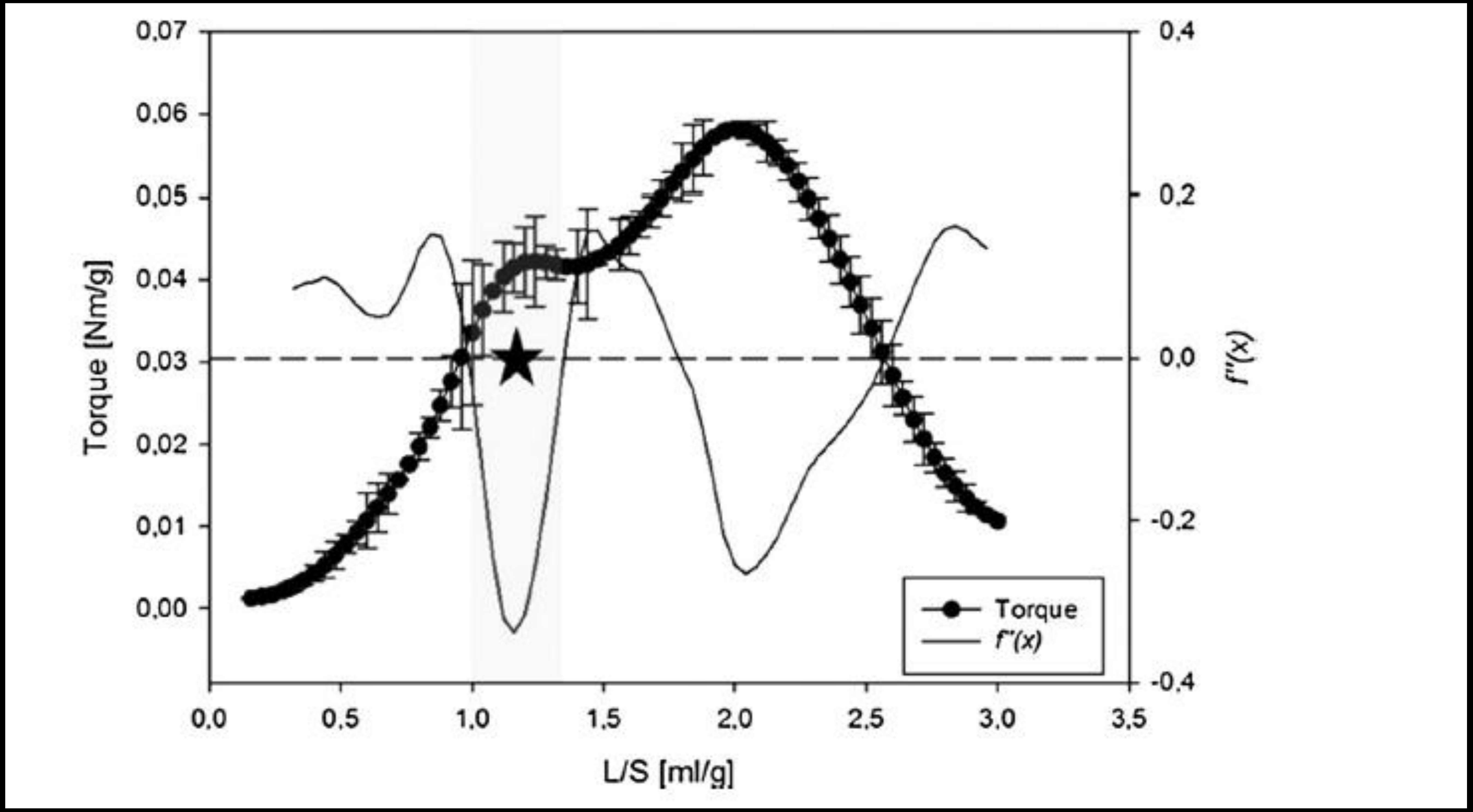
## *Breakage and attrition*

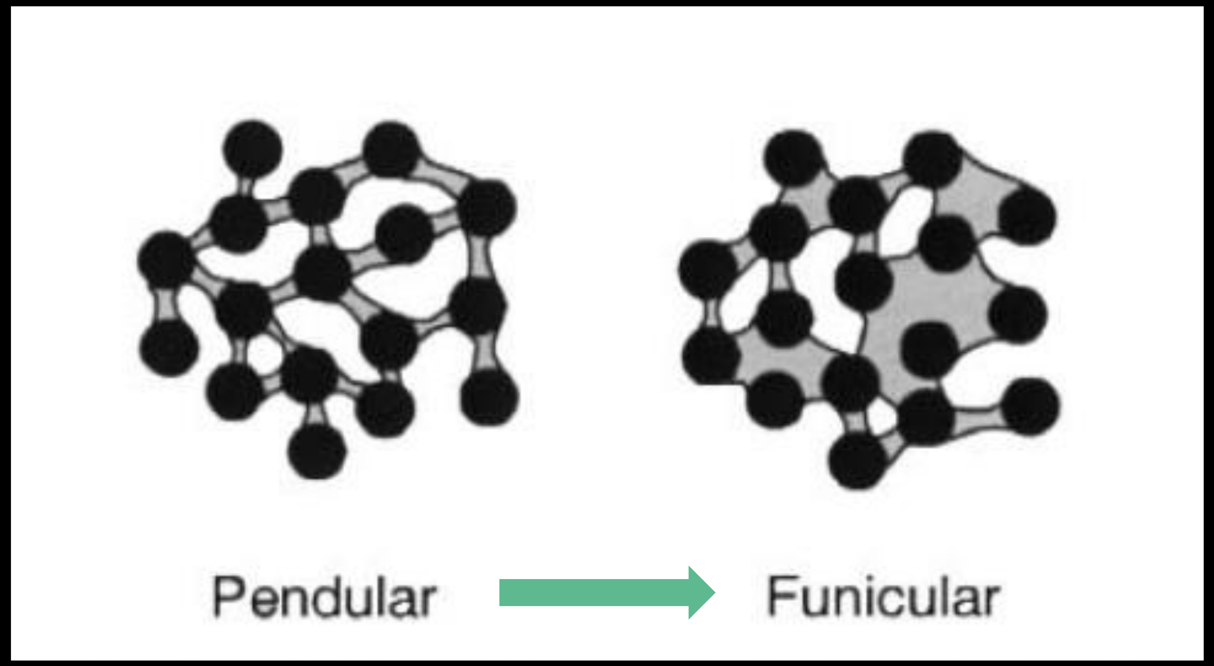
From: <u>**The science and engineering of granulation processes**</u>, *Jim Litster and Bryan Ennis*

# L/S ratio

***Heuristic and empirical approach***

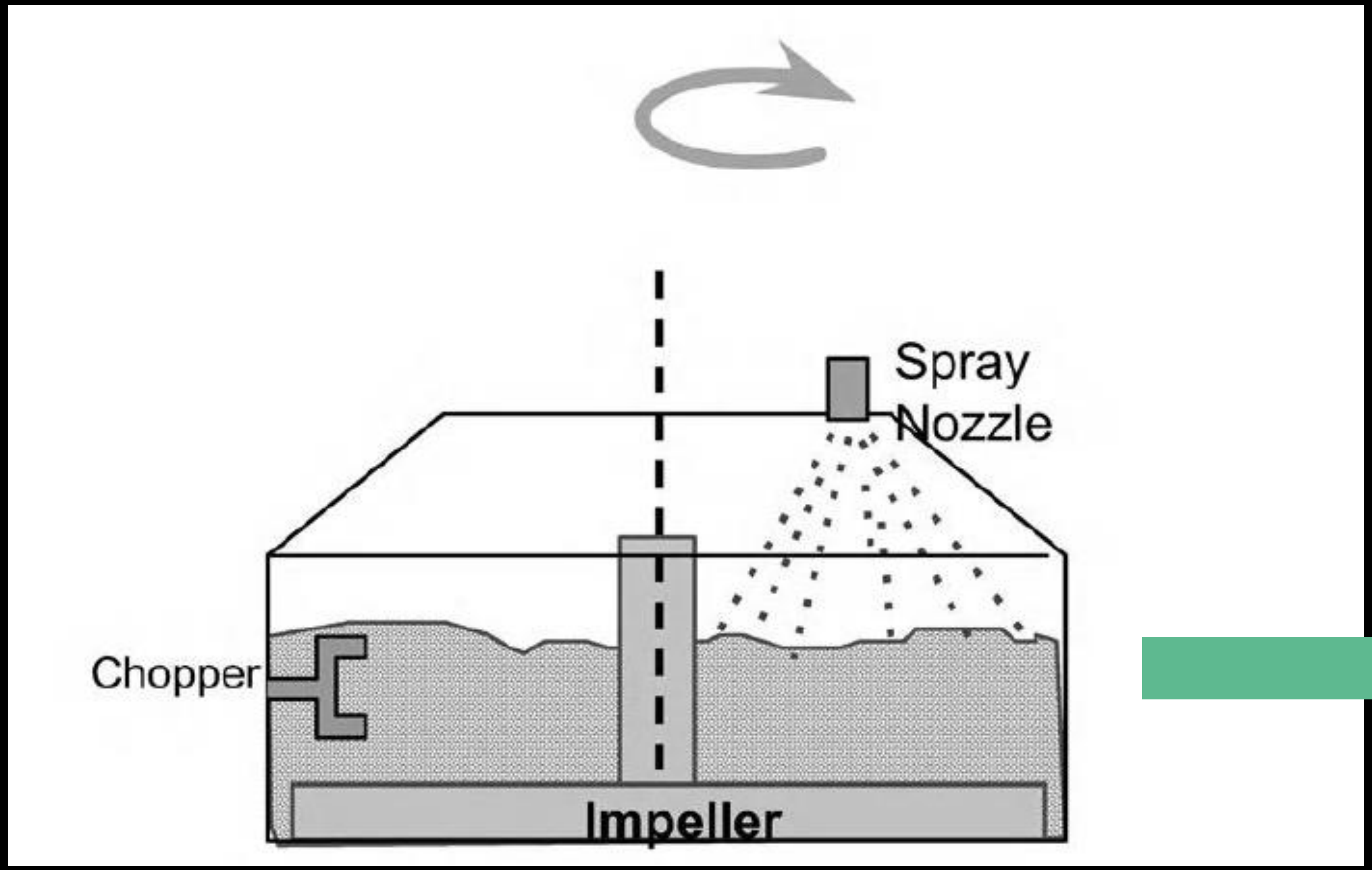
# *More scientific approach: torque rheometer*




***Optimal amount of liquid!***

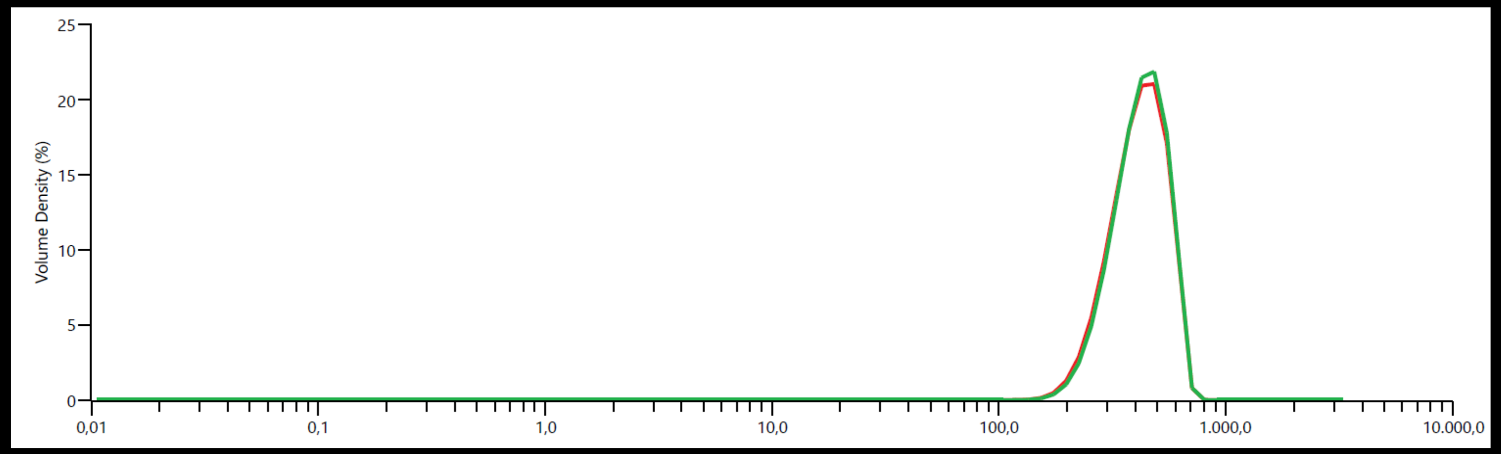
From: **[Prediction of the growth kinetics andagglomeration mechanisms using a mixer torquerheometer]**
*E. Franceschinis, F. Schmid, R. Baggio, M. Dal Zotto, N. Realdon, A.C. Santomaso*




**HOW?**

**Target:**

1. *Particle size distribution*




2. *Composition*
3. *Granule porosity*

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# VARIABLES AFFECTING HSWG

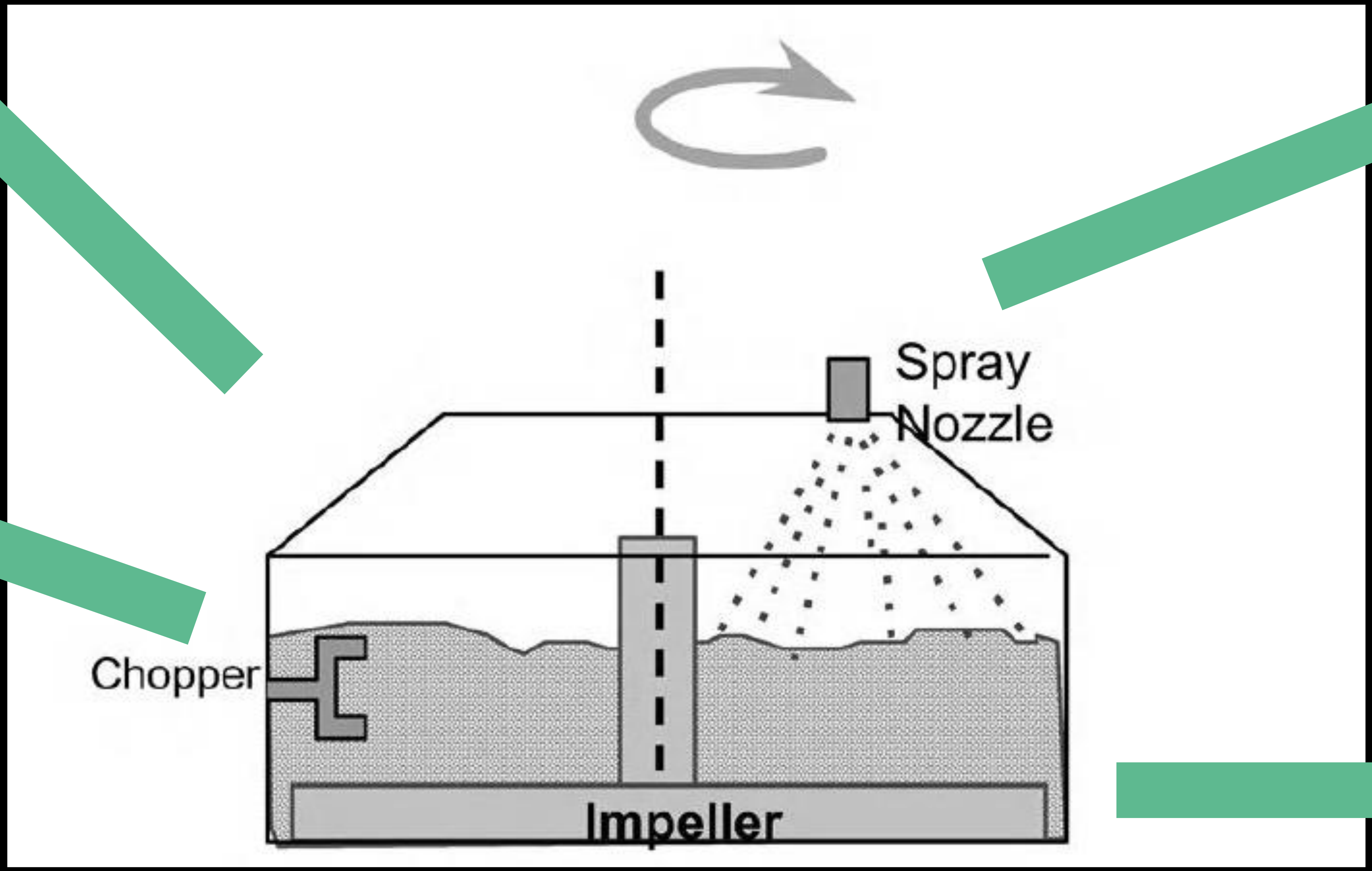
***Fixed recipe***

Massing time

Amount of granulating liquid

Liquid addition rate

Chopper speed




Impeller speed

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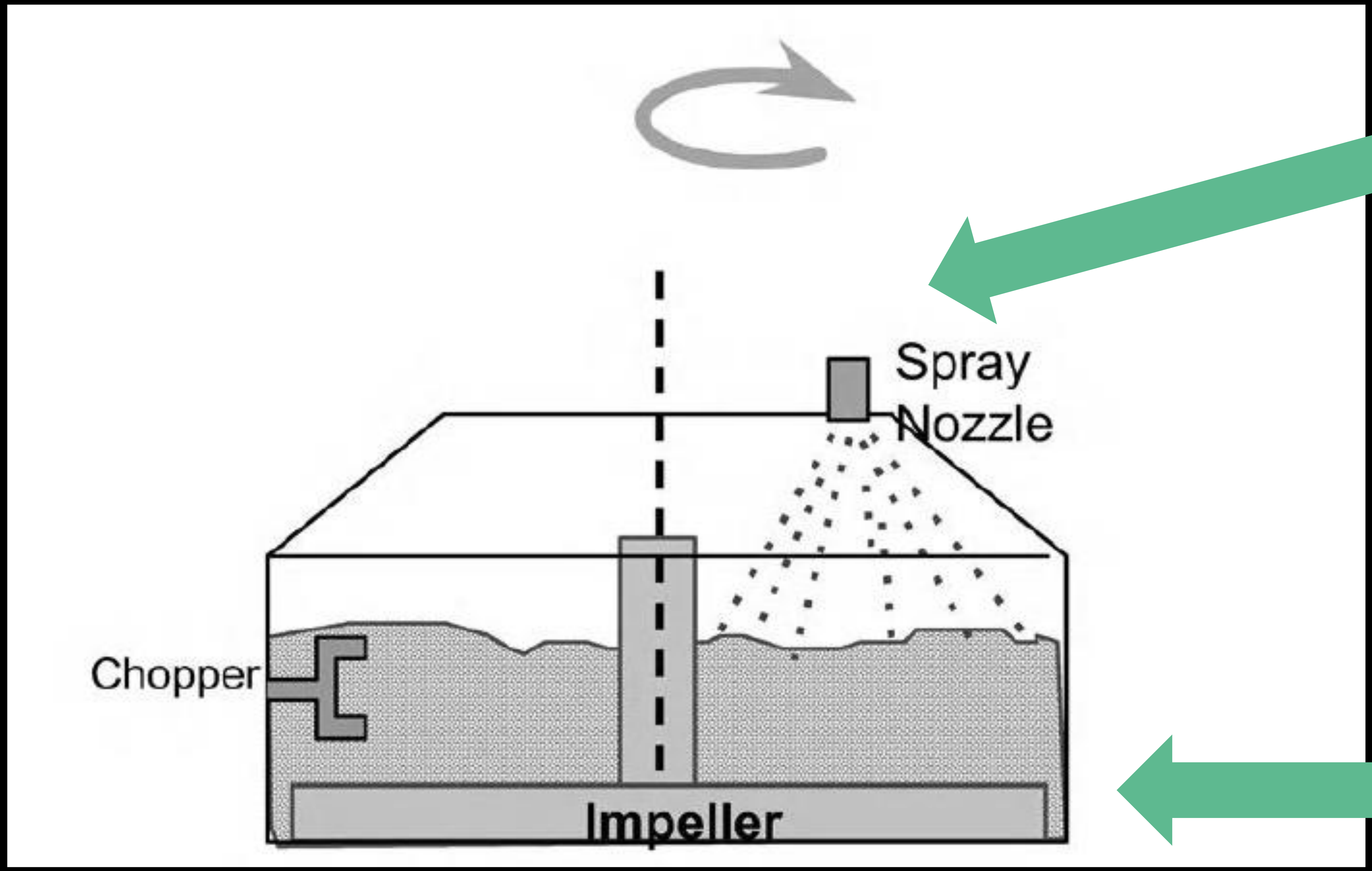
**DISTURBS**

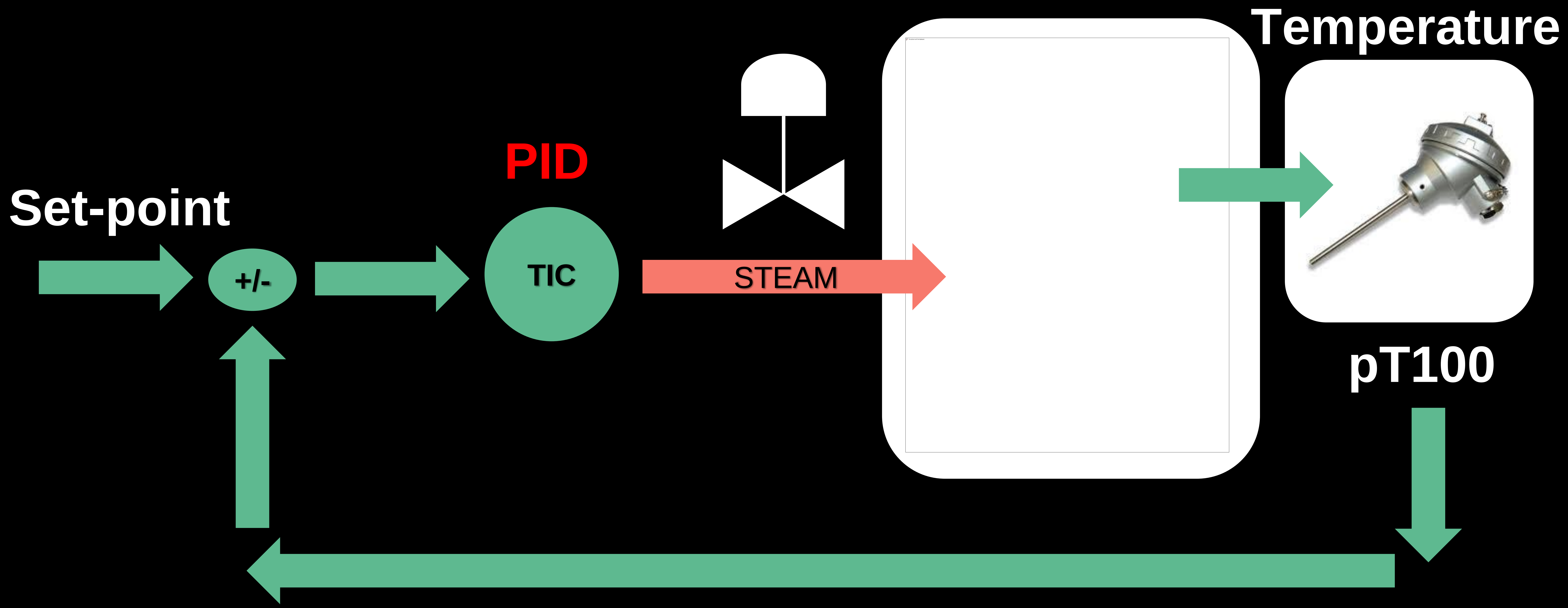



Binder or liquid characteristics

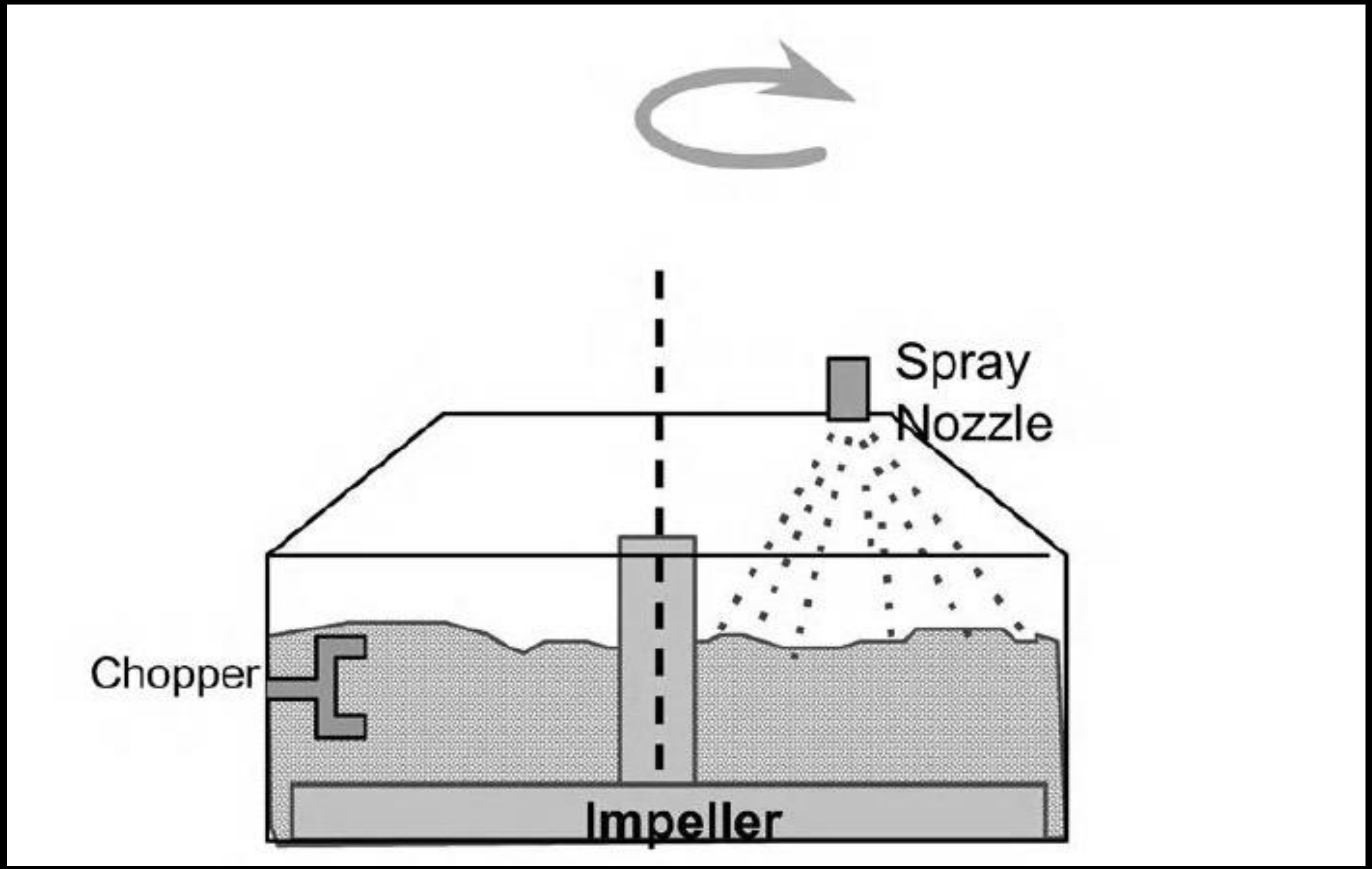
Rheology of the mass

Humidity of raw material
PSD of raw material
Impurities

# FEEDBACK CONTROL



# HOW TO IMPLEMENT CONTROL?




**We need to know:**

1. **The variables that describe the state of the system, to be measured.**

2. **The model of the dynamics.**

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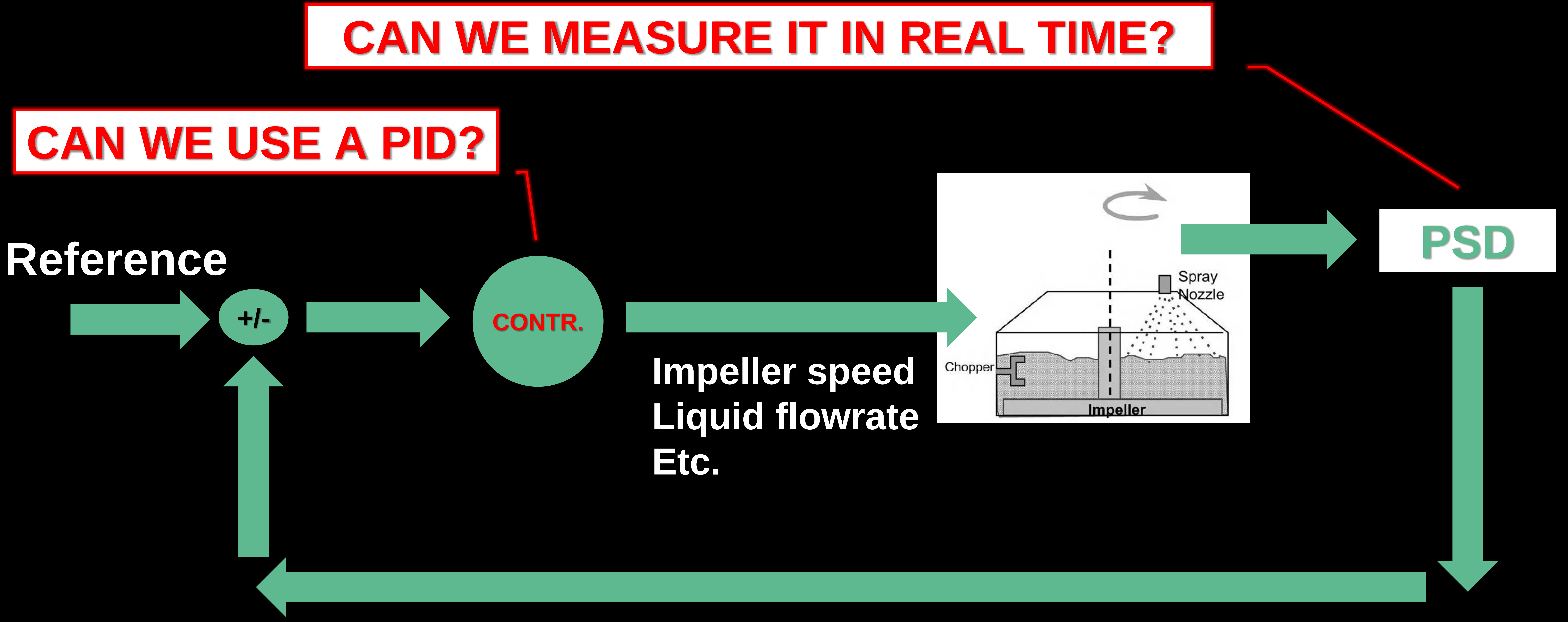
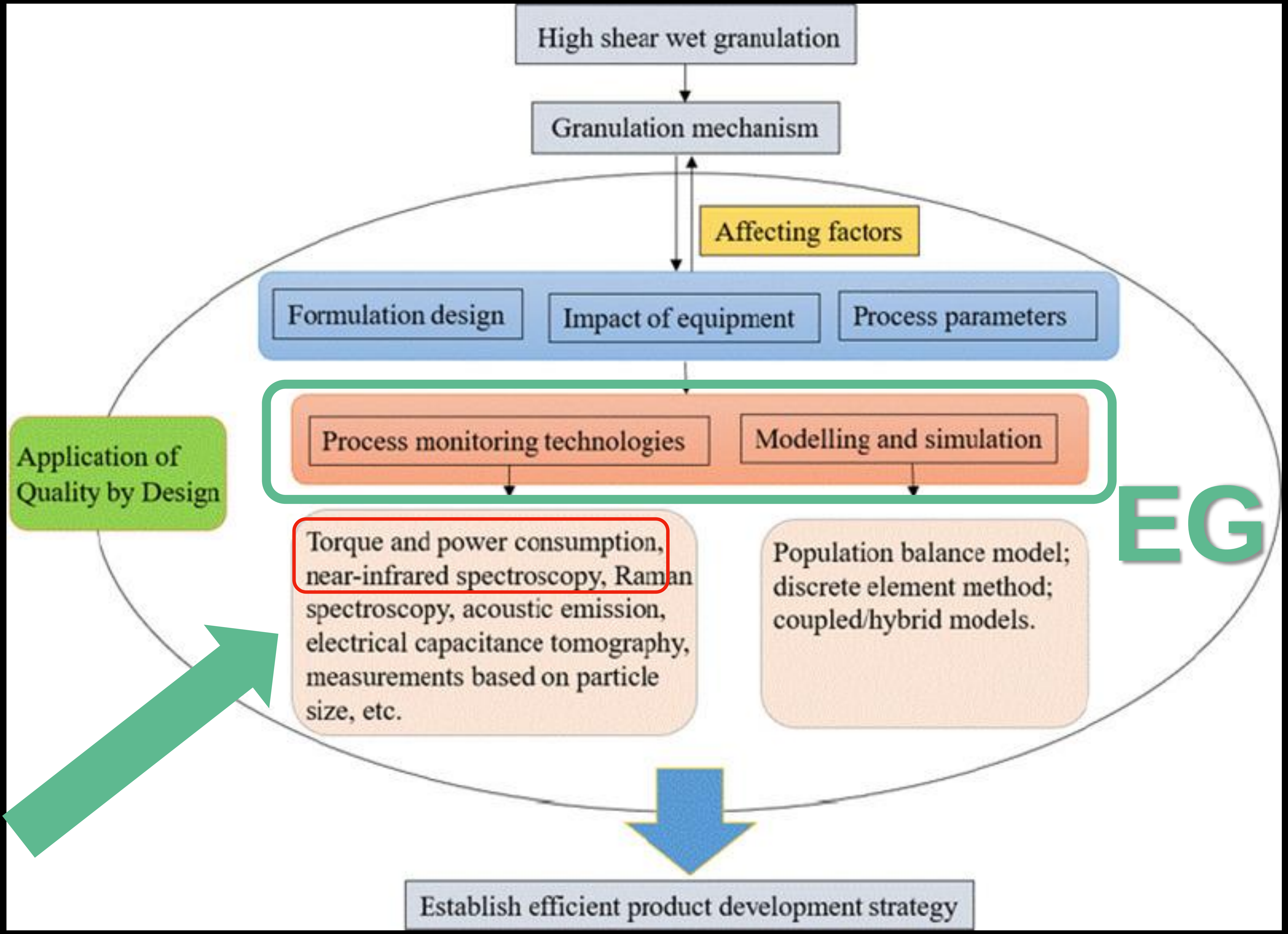

CAN WE MEASURE IT IN REAL TIME?
CAN WE USE A PID?
Reference
+/-
CONTR.
Impeller speed
Liquid flowrate
Etc.
Spray Nozzle
Chopper
Impeller
PSD

# PAT

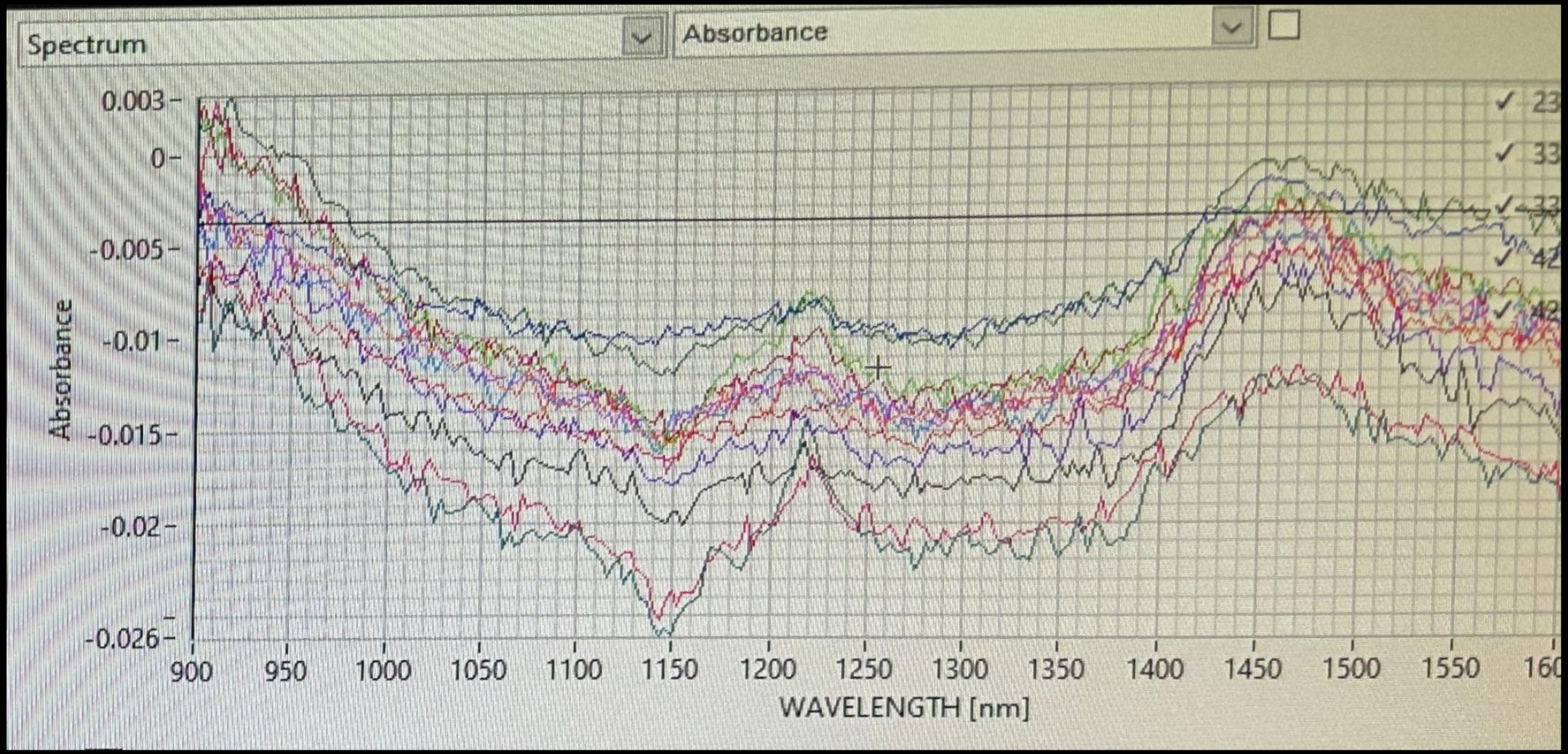



PAT is defined as "*a system for designing, analyzing and* ***controlling*** *manufacturing by* ***measuring*** *the critical quality and performance attributes of raw materials and processes*"

From: **A review of high shear granulation for better process understanding, control and product development,**
*Binbin Liu, Jiamiao Wang, Jia Zeng, Lijie Zhao, Youjie Wang, Yi Feng, Ruofei Du.*

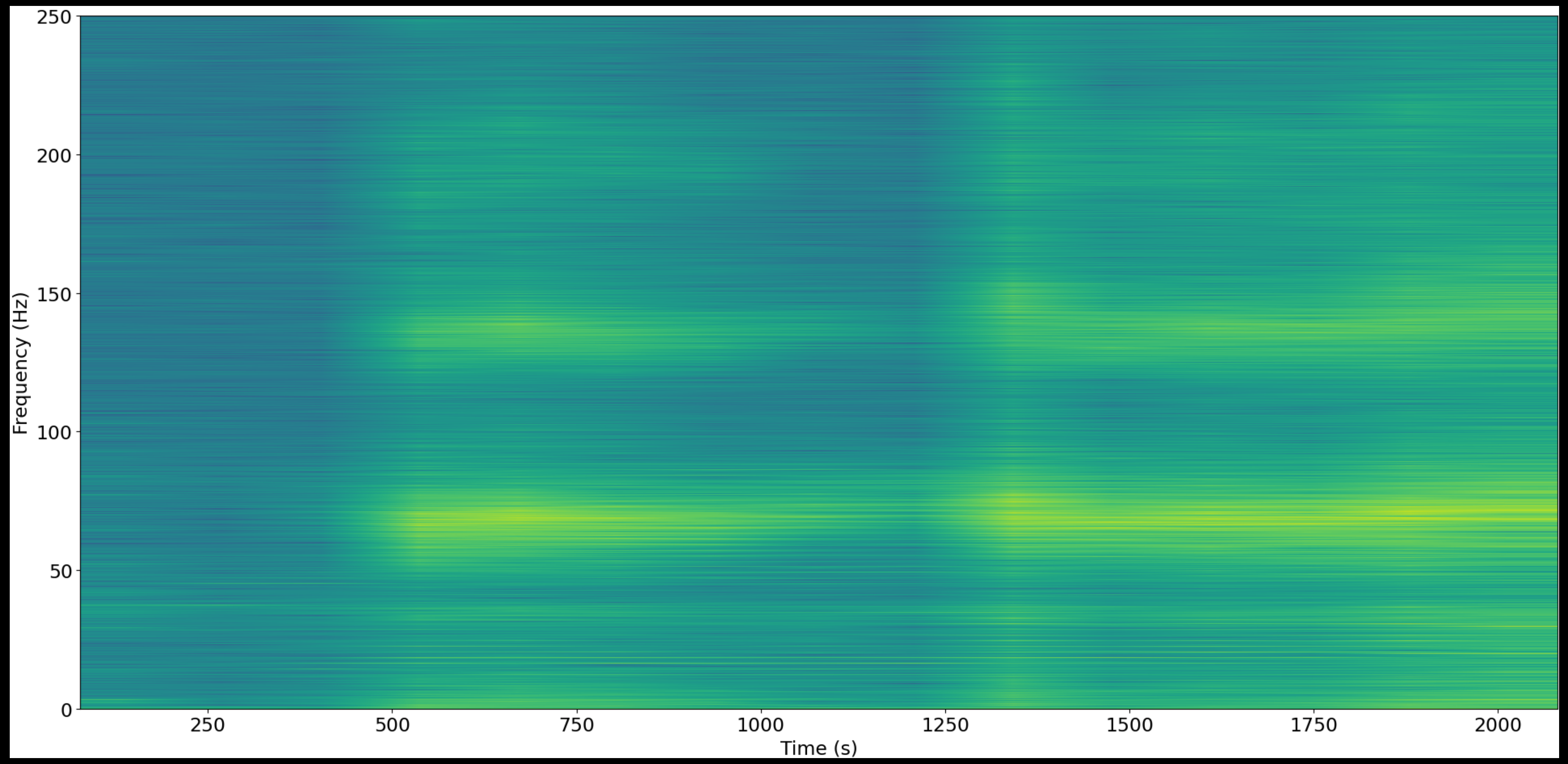
# MEASURING

## NIR Spectroscopy




## PAT!!

## Kinestetic Tactile (Torque and Power)

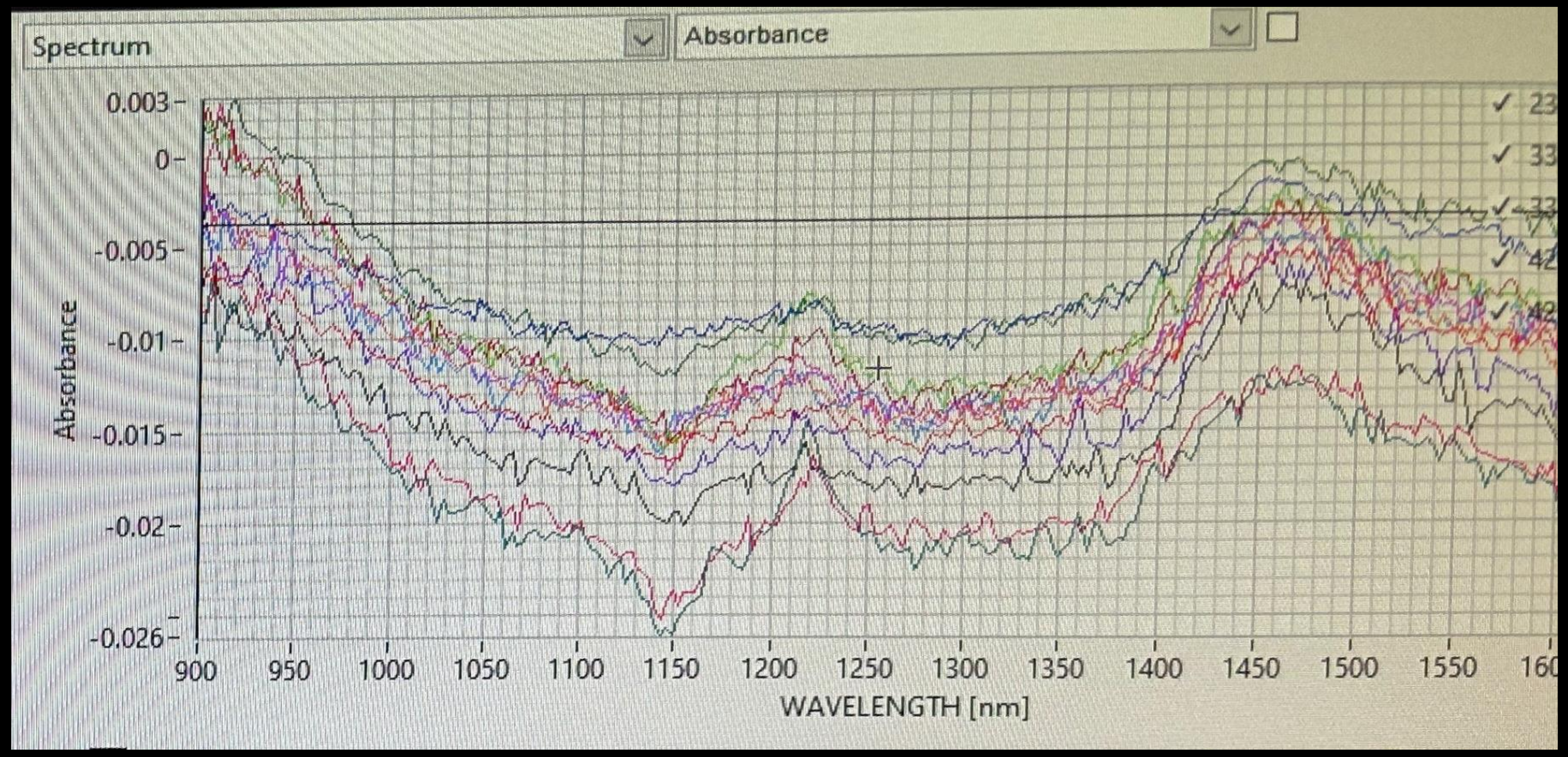



Power consumption and torque measurements are some of the earliest process analytical technology (PAT) tools developed to monitor high shear wet granulation (HSWG) and have been widely used to monitor granular growth and determine the optimal operational process end point.

*(Liu et al., 2020; Hansuld and Briens, 2014; Campbell et al., 2011)*

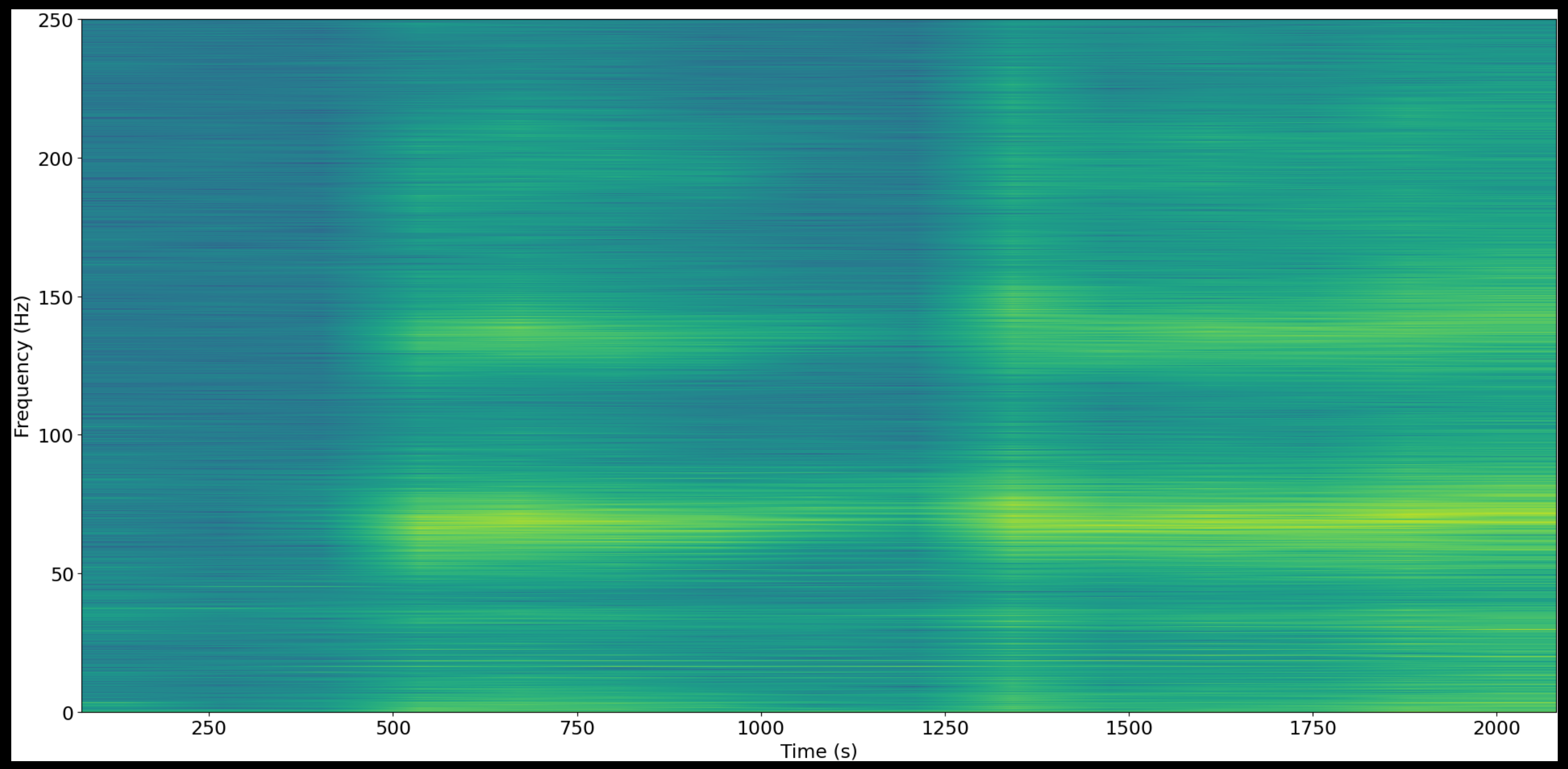
# PROBLEM!

## NIR Spectroscopy




How can we use it them to control the process?

## Haptic sensor




Discrete signals → **Streaming!** ↓ **As pseudo continuous signal**

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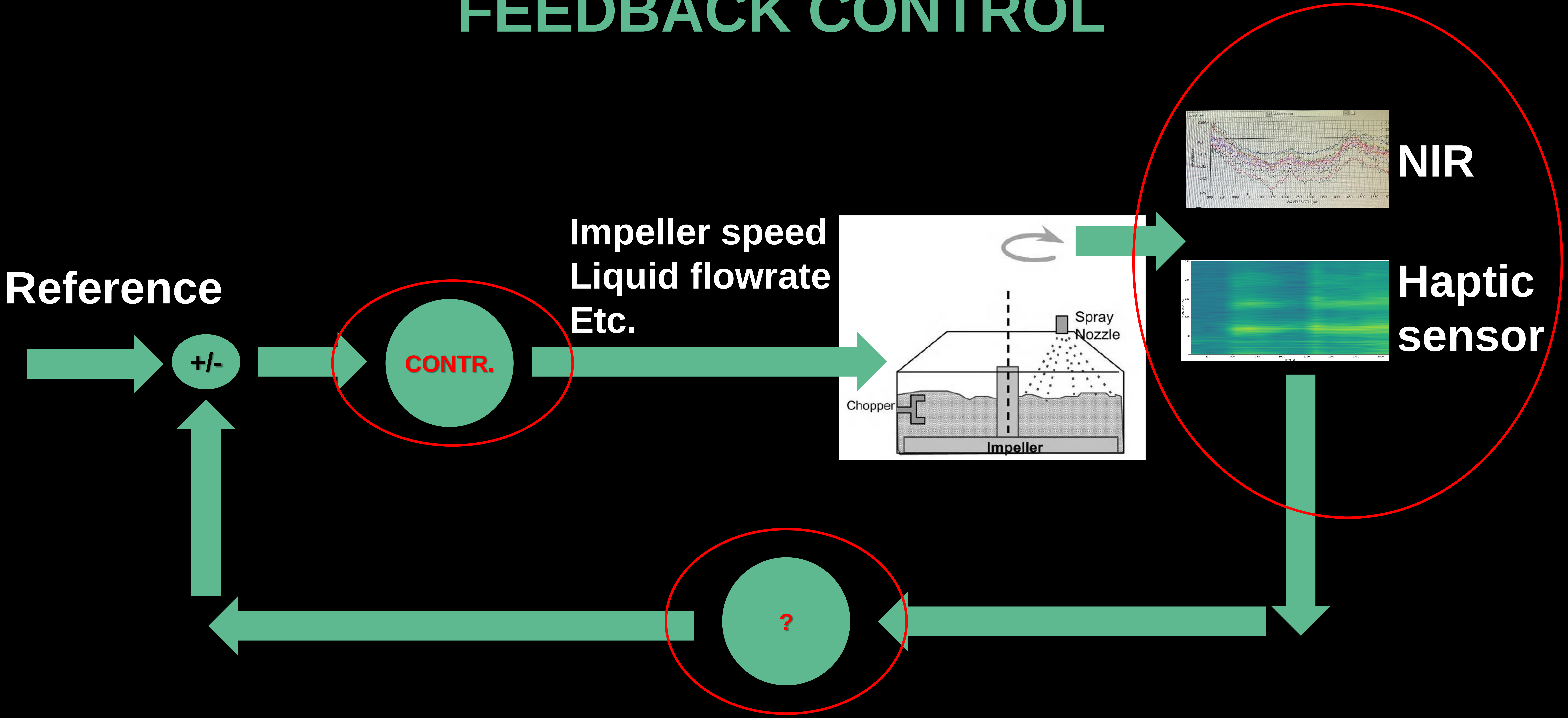
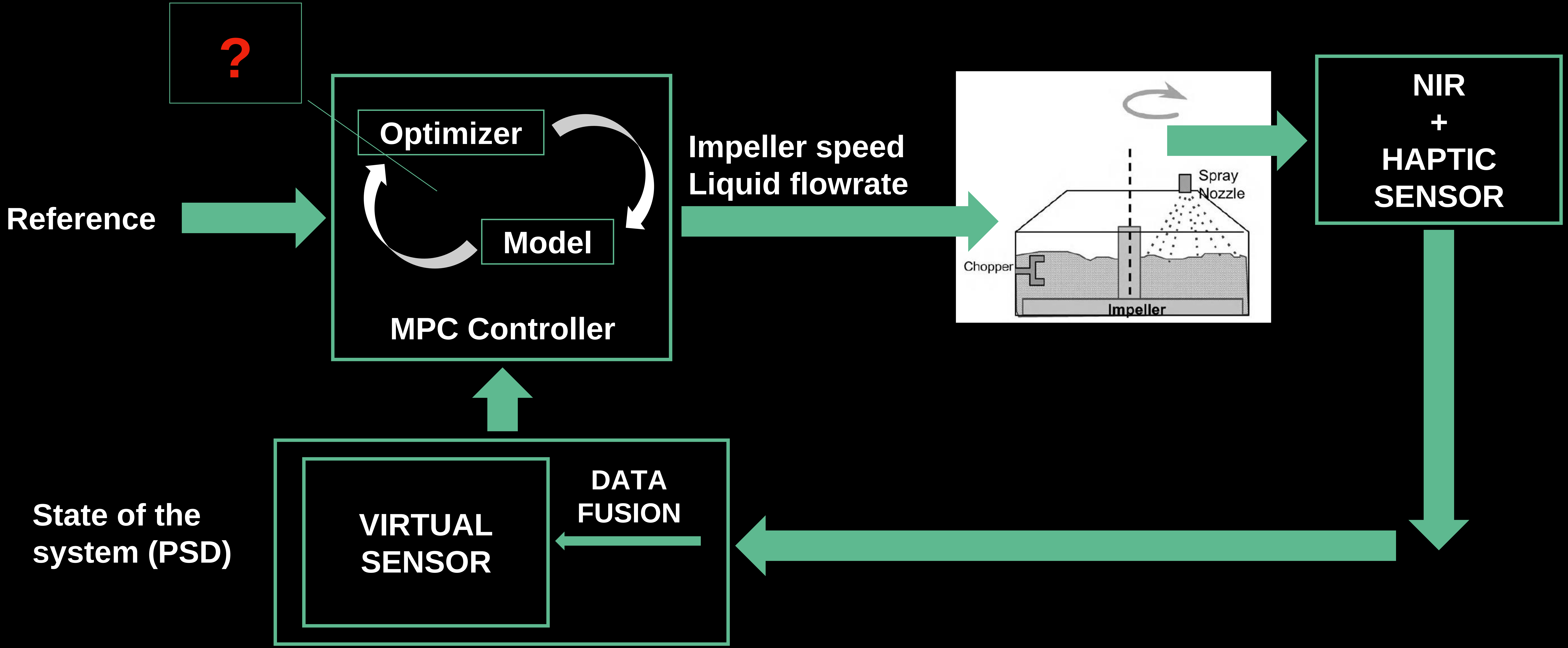
# FEEDBACK CONTROL



# OUR APPROACH



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# DYNAMIC SYSTEM

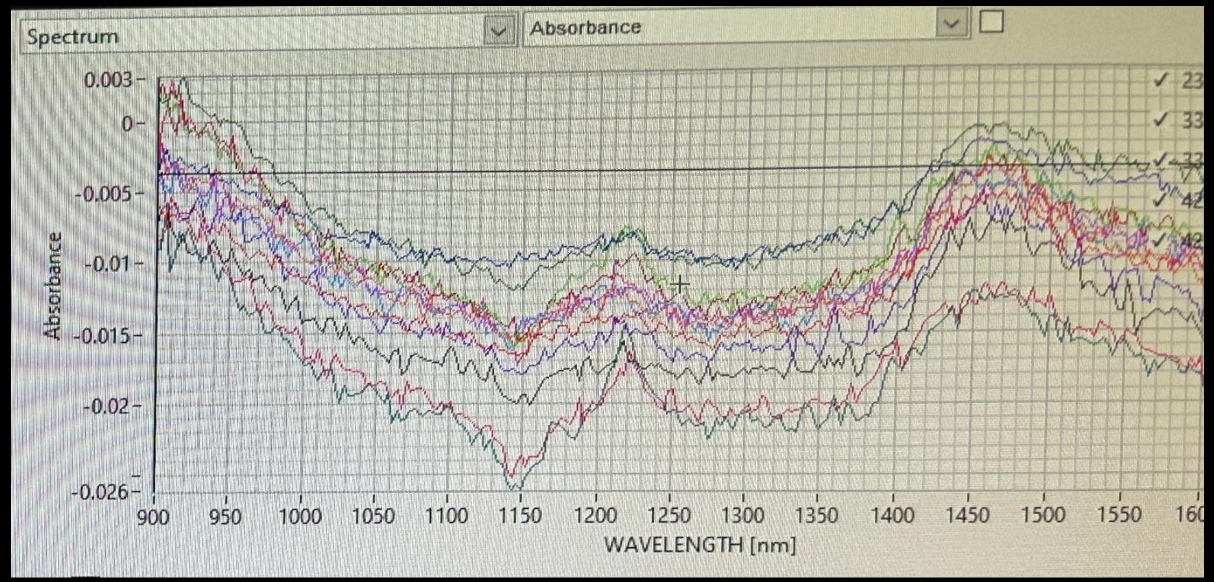
$$\frac{d}{dt}\mathbf{x}(t) = \mathbf{f}(\mathbf{x}(t)).$$

$$\mathbf{X} = \begin{bmatrix} \mathbf{x}^T(t_1) \\ \mathbf{x}^T(t_2) \\ \vdots \\ \mathbf{x}^T(t_m) \end{bmatrix} = \overbrace{\begin{bmatrix} x_1(t_1) & x_2(t_1) & \cdots & x_n(t_1) \\ x_1(t_2) & x_2(t_2) & \cdots & x_n(t_2) \\ \vdots & \vdots & \ddots & \vdots \\ x_1(t_m) & x_2(t_m) & \cdots & x_n(t_m) \end{bmatrix}}^{\text{state}} \Big\downarrow \text{time}$$

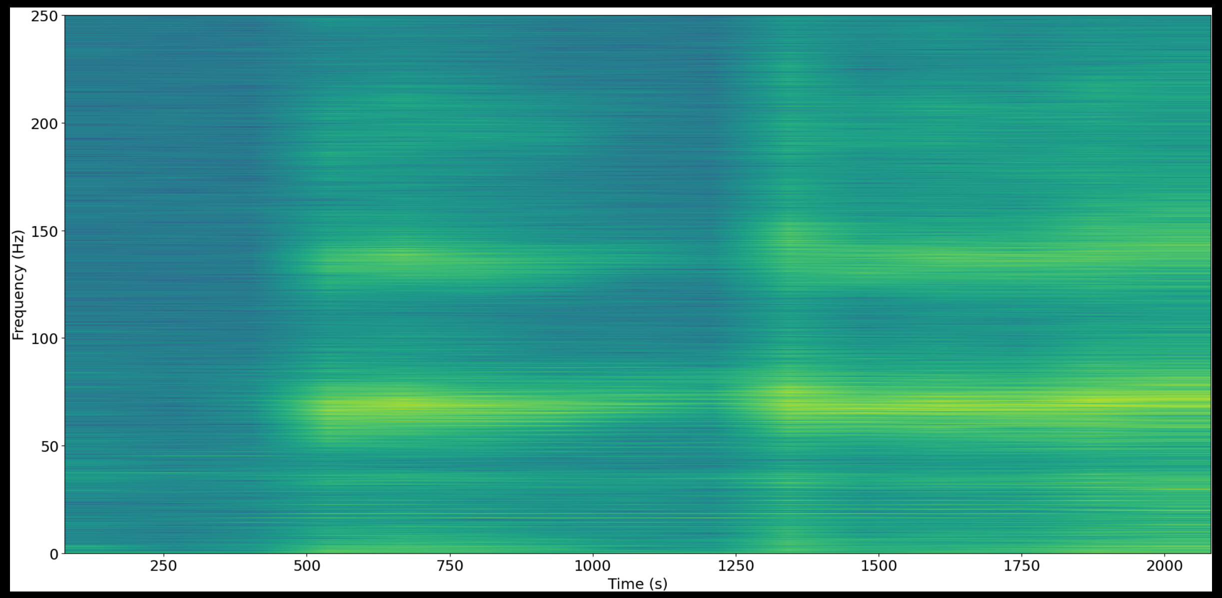
DATA-DRIVEN METHODS

RNN

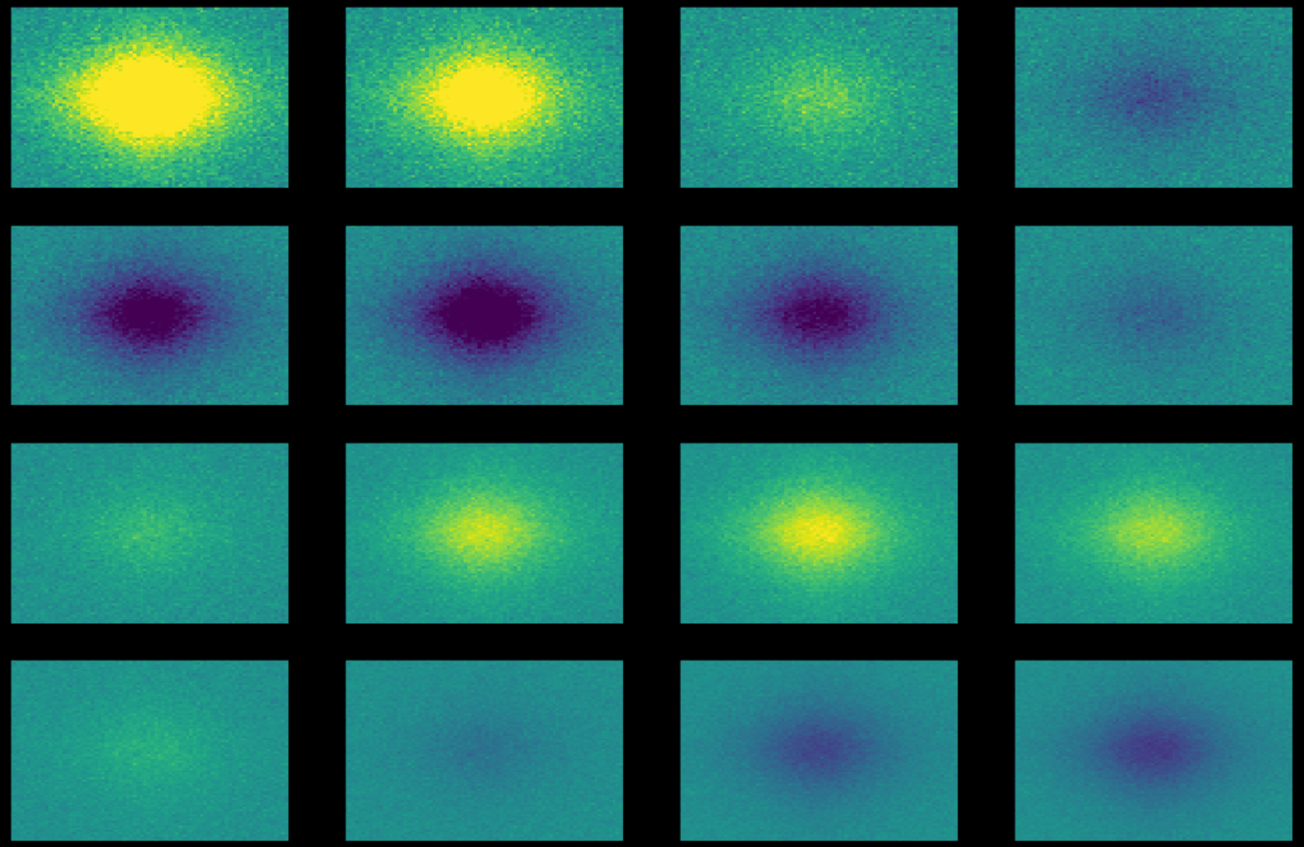
# DATA FUSION




NIR → Granulation PATTERN




Haptic sensor → Energy



Like an eye inside the granulator!

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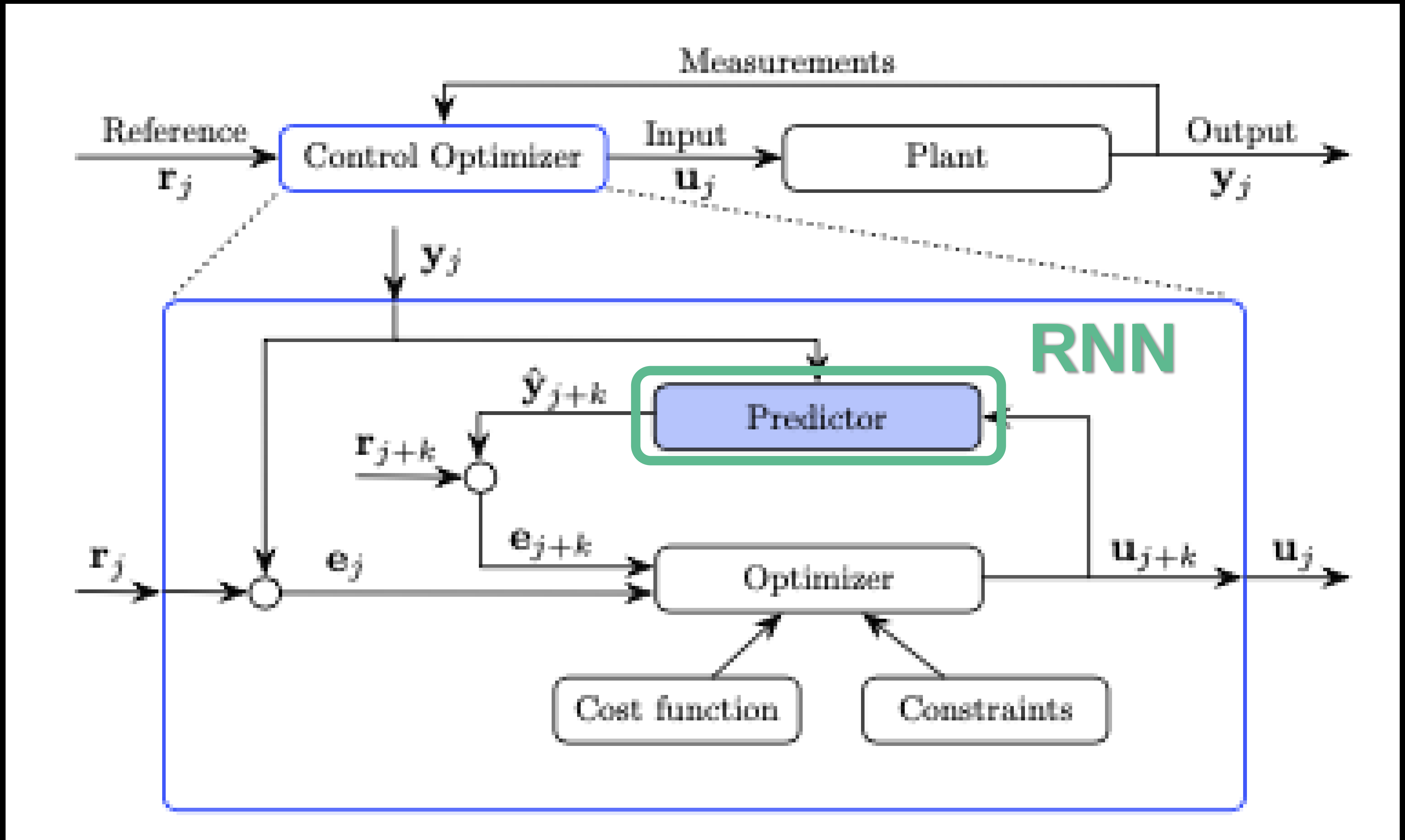
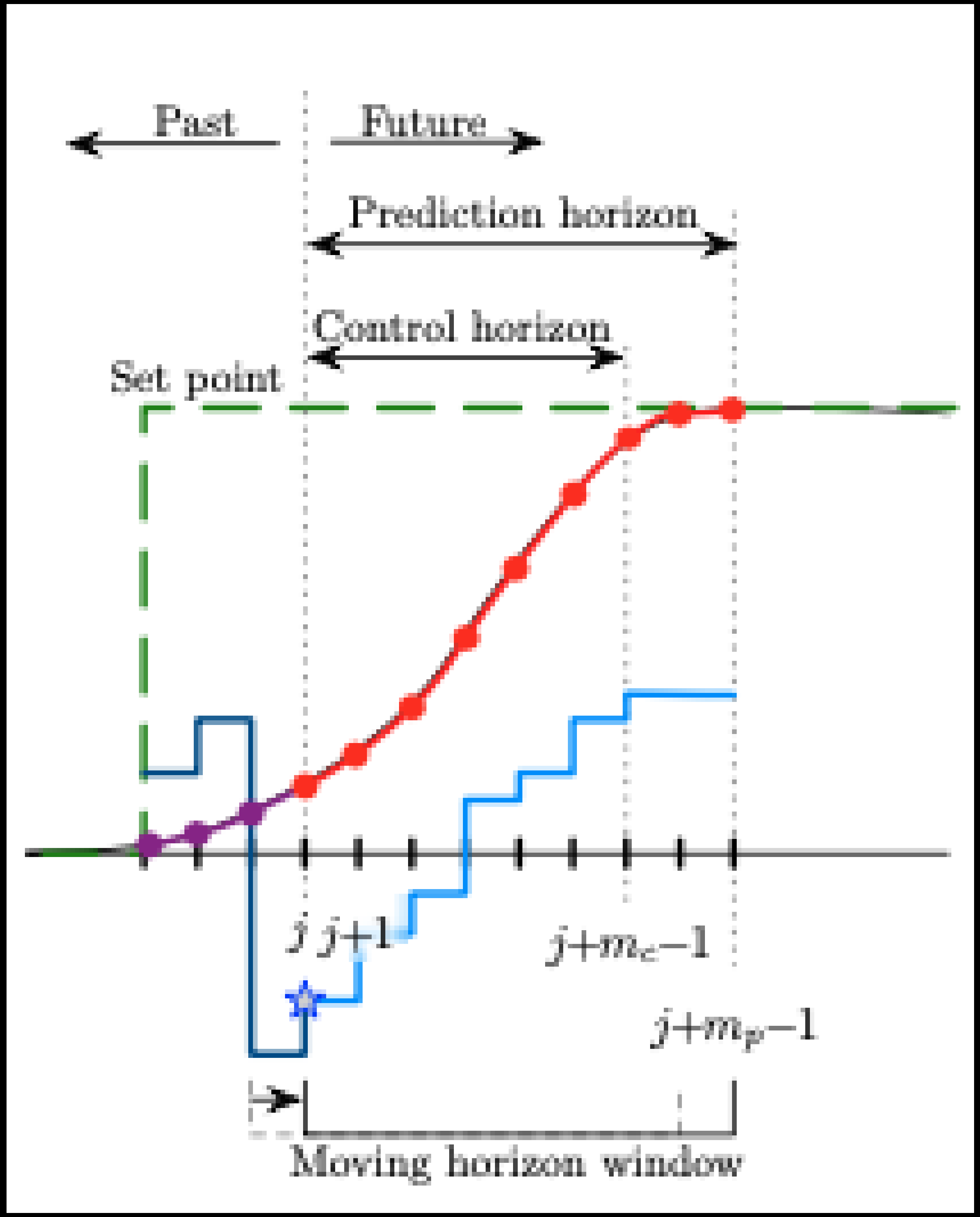
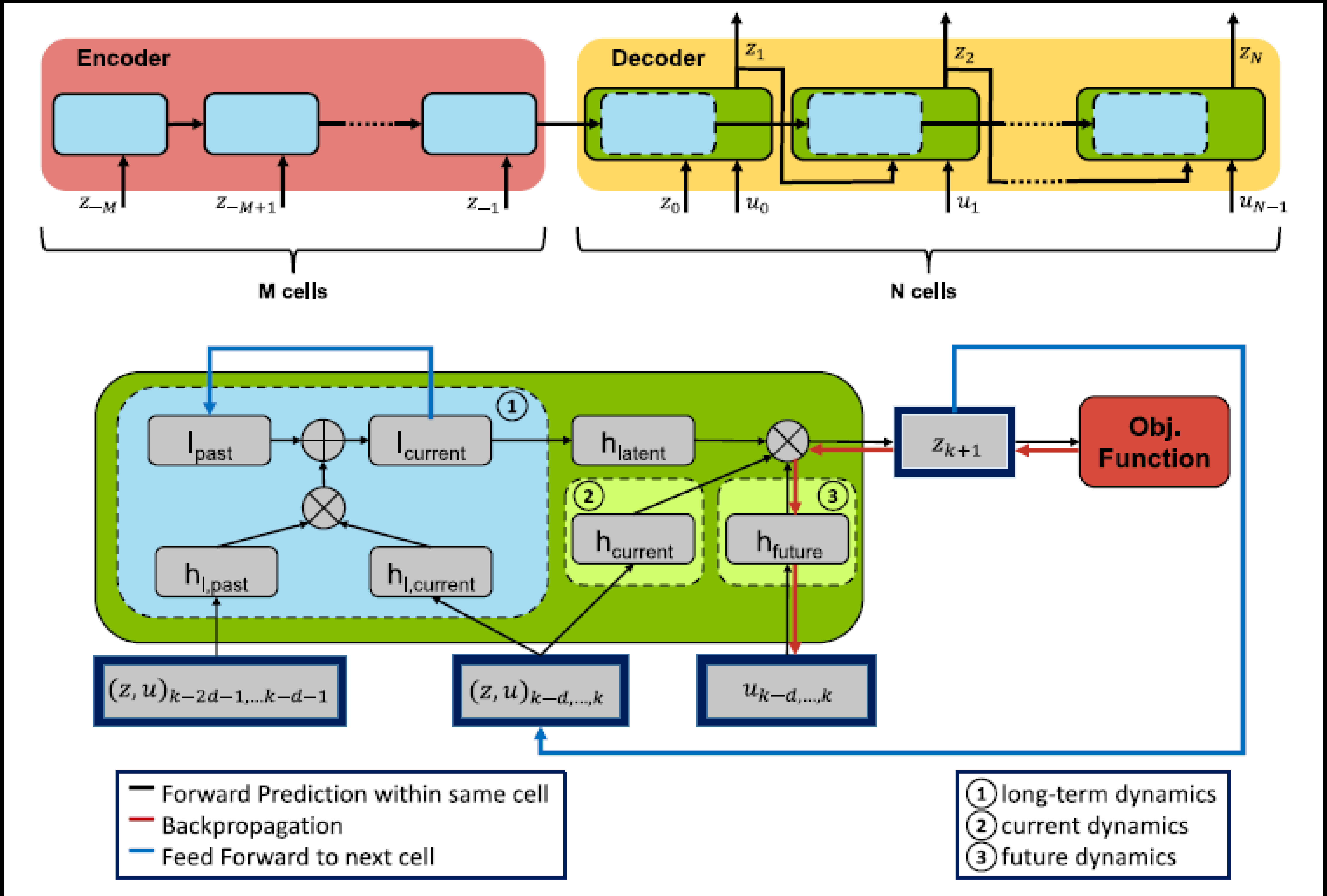
# MODEL PREDICTIVE CONTROL



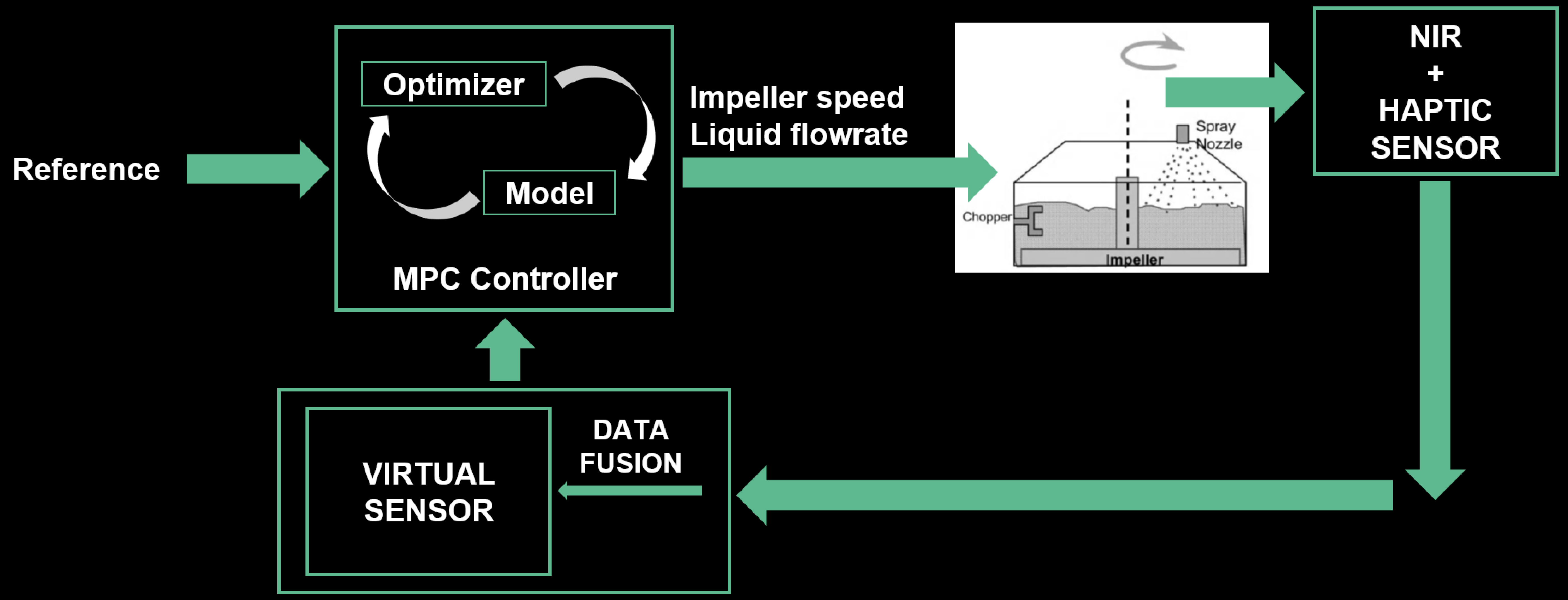

$$\min_{u \in \mathbb{R}^N} \sum_{i=0}^{N-1} \|f(y_{i+1}) - z_{i+1}^{\text{ref}}\|_2^2 + \alpha |u_i|^2 + \beta |u_i - u_{i-1}|^2 \qquad s.t. \quad y_{i+1} = \Phi(y_i, u_i)$$

# RNN




From: **Deep Model Predictive Control with Online Learning for Complex Physical Systems**
*Katharina Bieker, Sebastian Peitz, Steven L. Brunton, J. Nathan Kutz and Michael Dellnitz*

# OUR APPROACH




Offline **Reinforcement Learning** to obtain a more robust model

***A very large data set is needed to obtain a robust model!***

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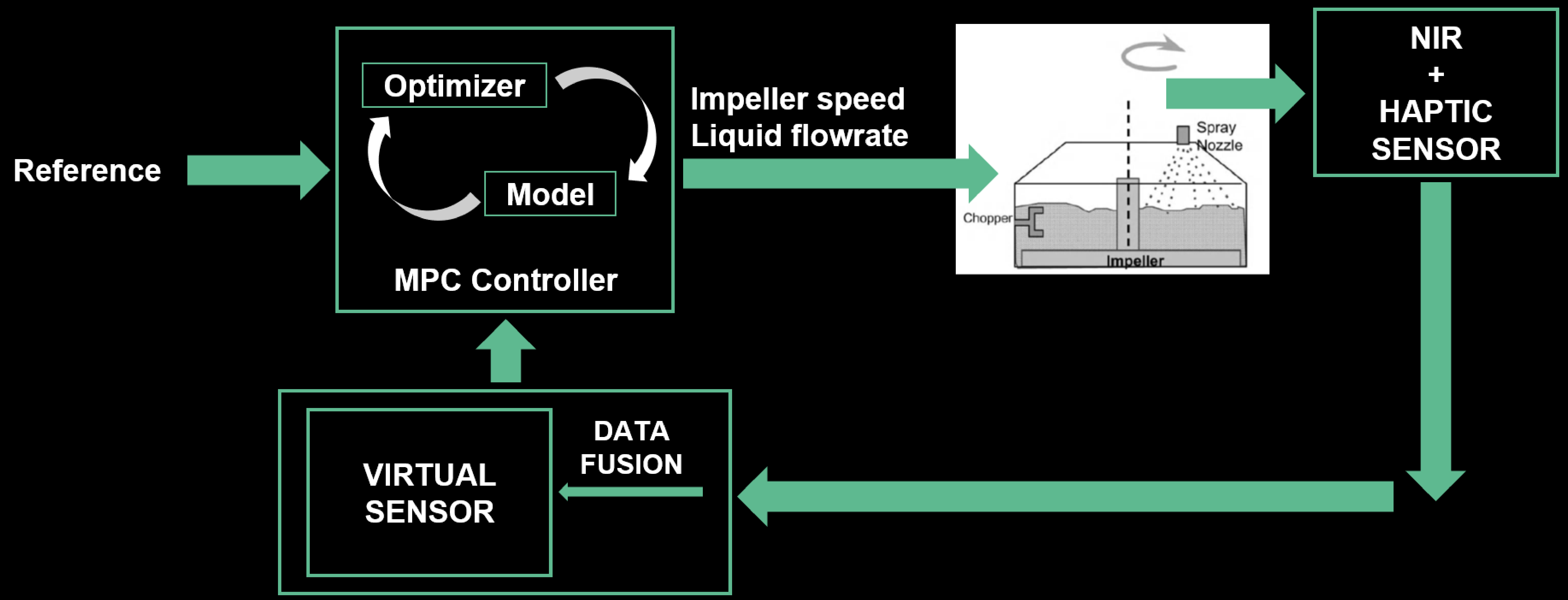
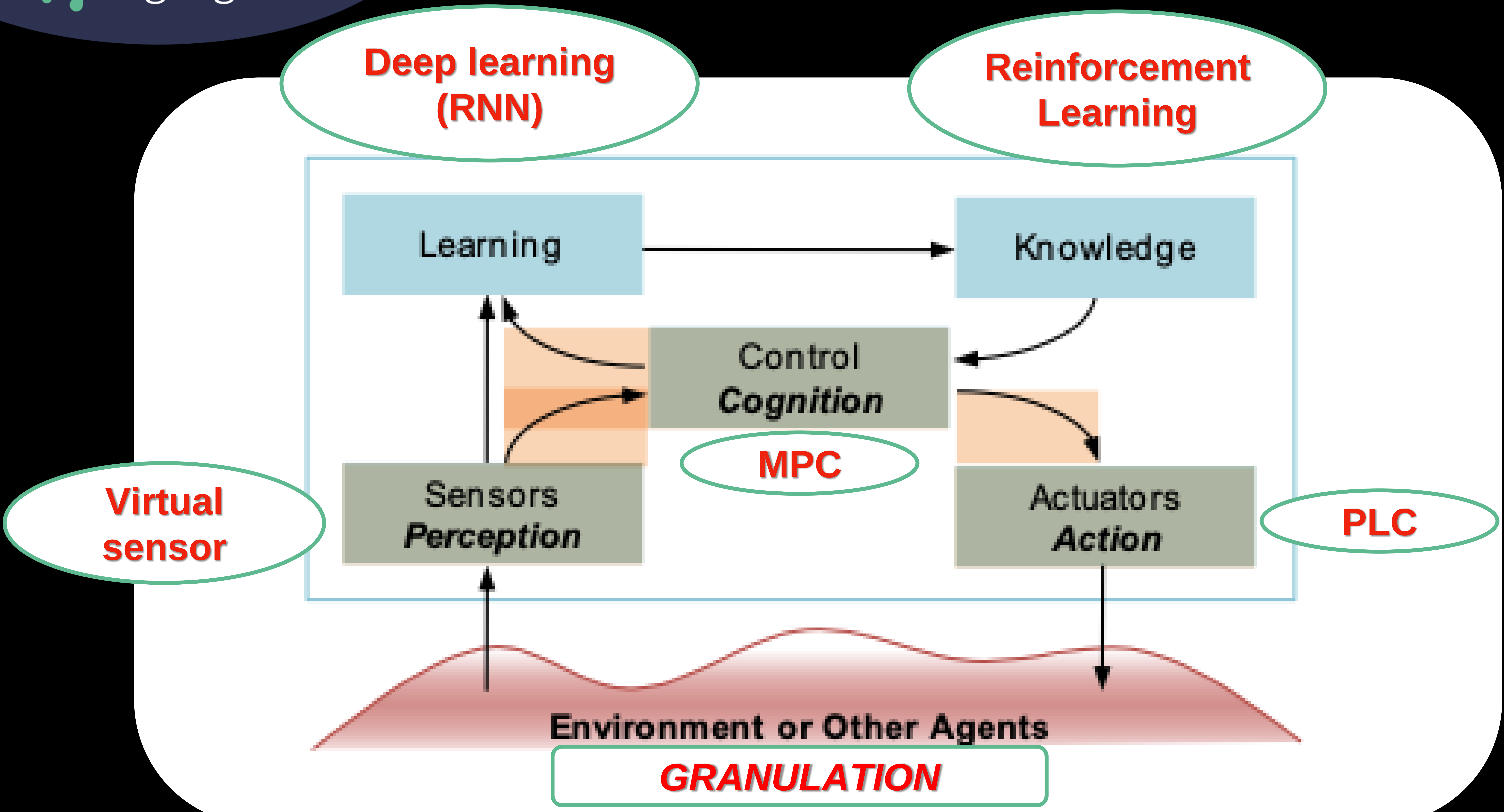



**We transform PAT in a control system!**

**We put quality control into the process!**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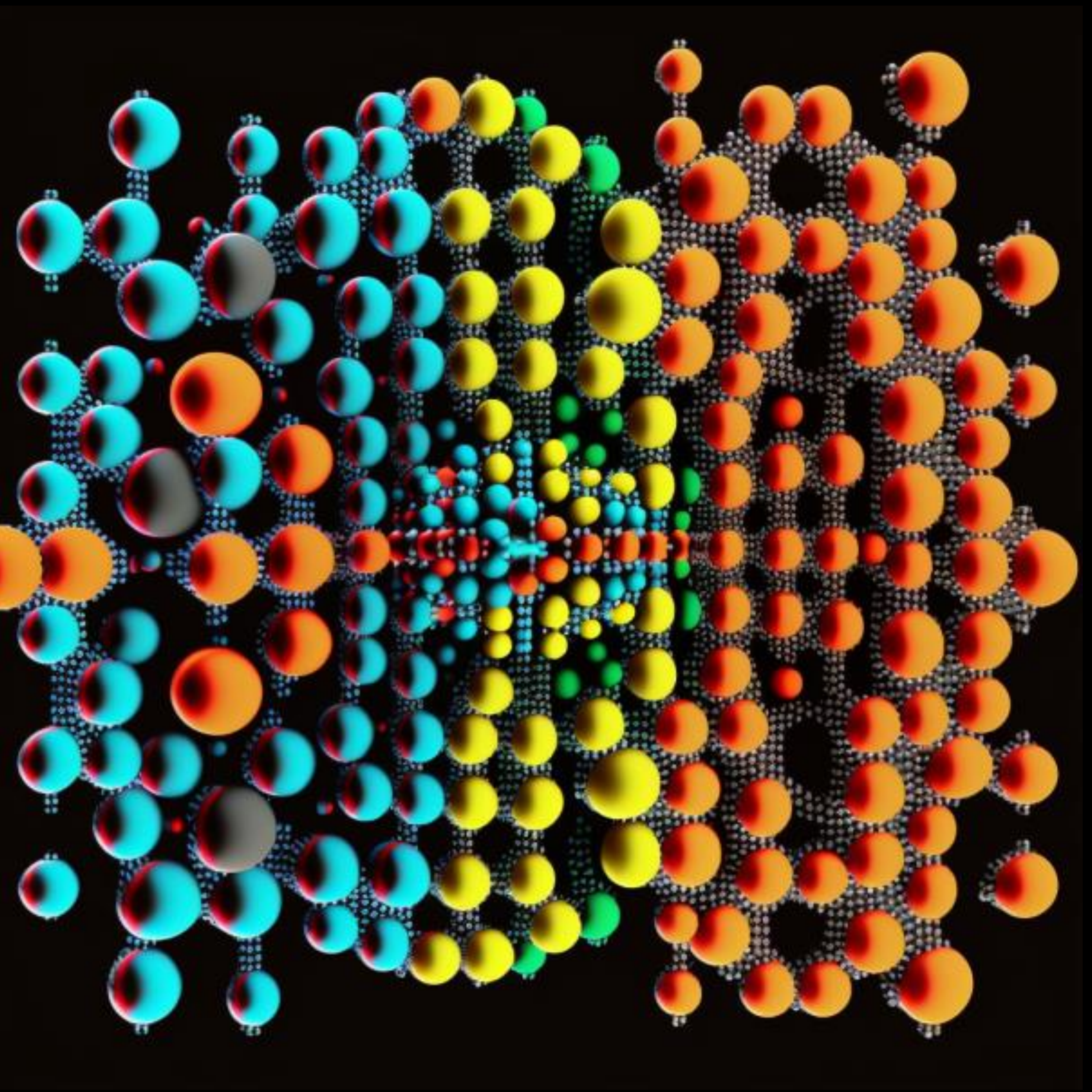
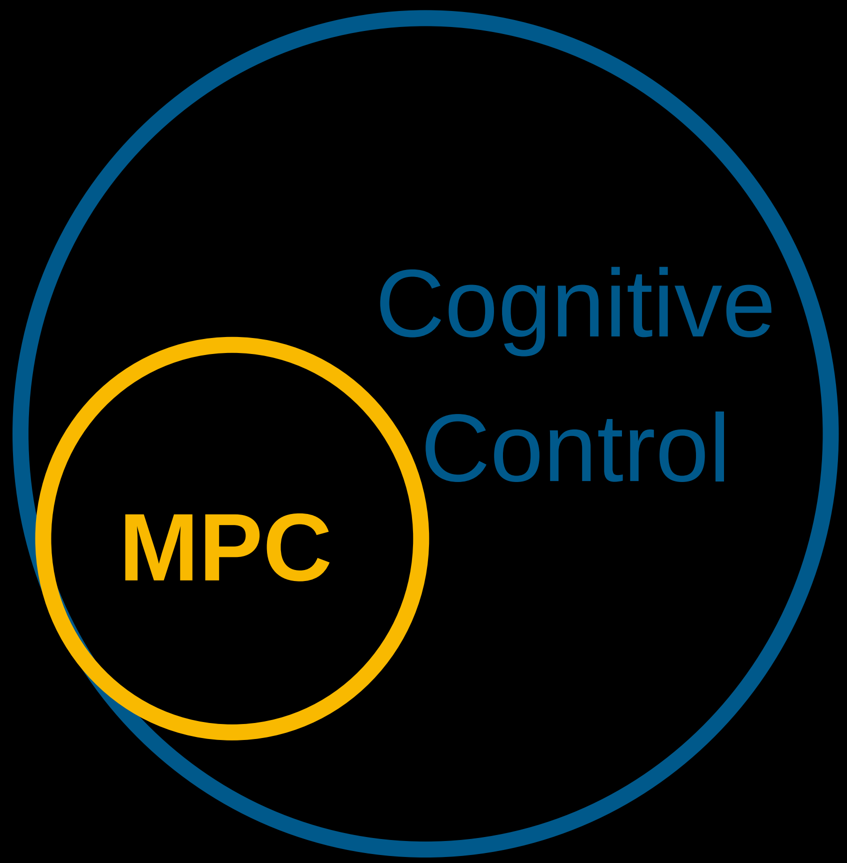
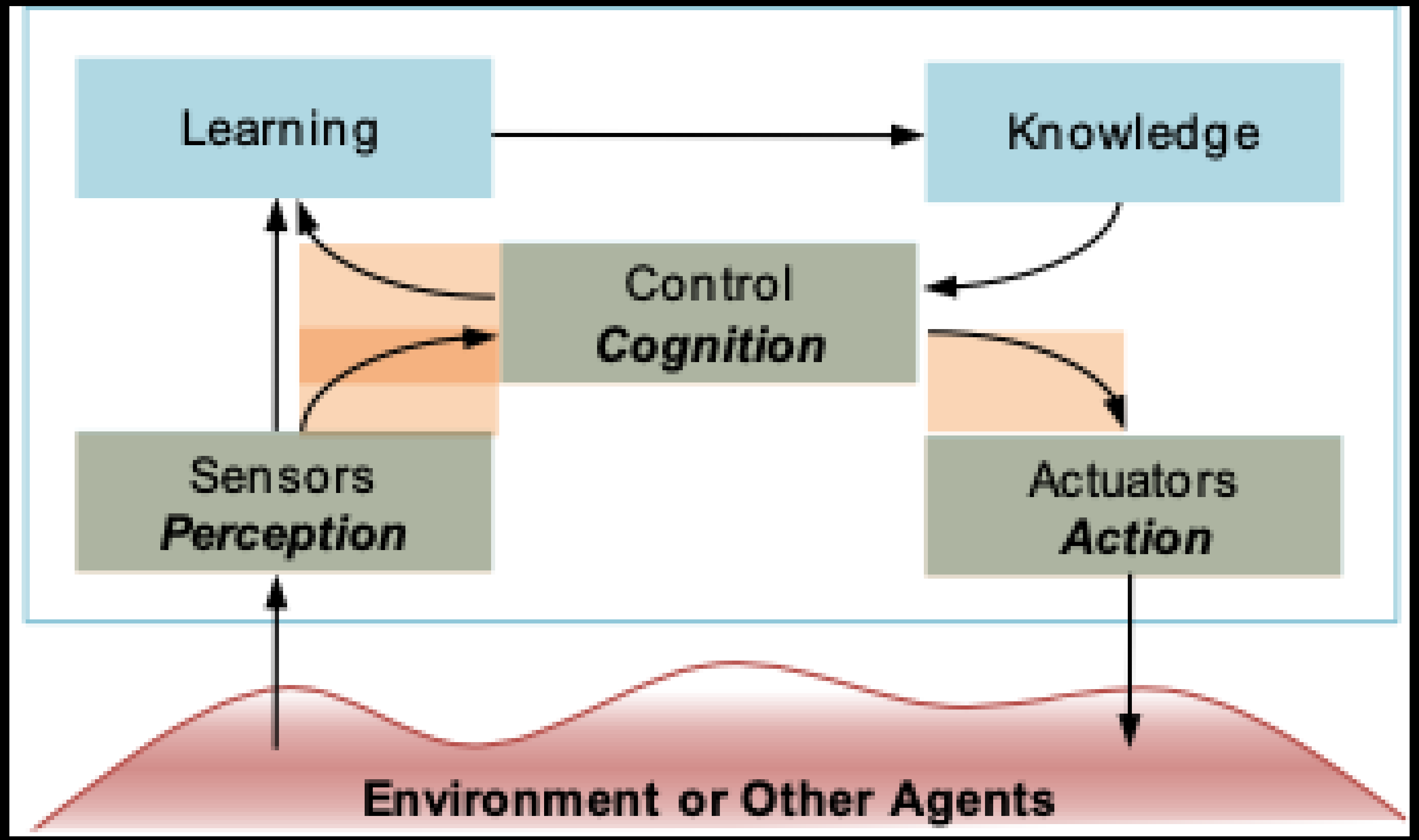
Deep learning (RNN)
Reinforcement Learning
Learning
Knowledge
Control
Cognition
MPC
Virtual sensor
Sensors
Perception
Actuators
Action
PLC
Environment or Other Agents
GRANULATION

# COGNITIVE CONTROL

Cognitive control is a branch of artificial intelligence (AI) that deals with the development of algorithms and techniques that enable machines to learn from experience, reason about complex situations, and adapt to changing environments.





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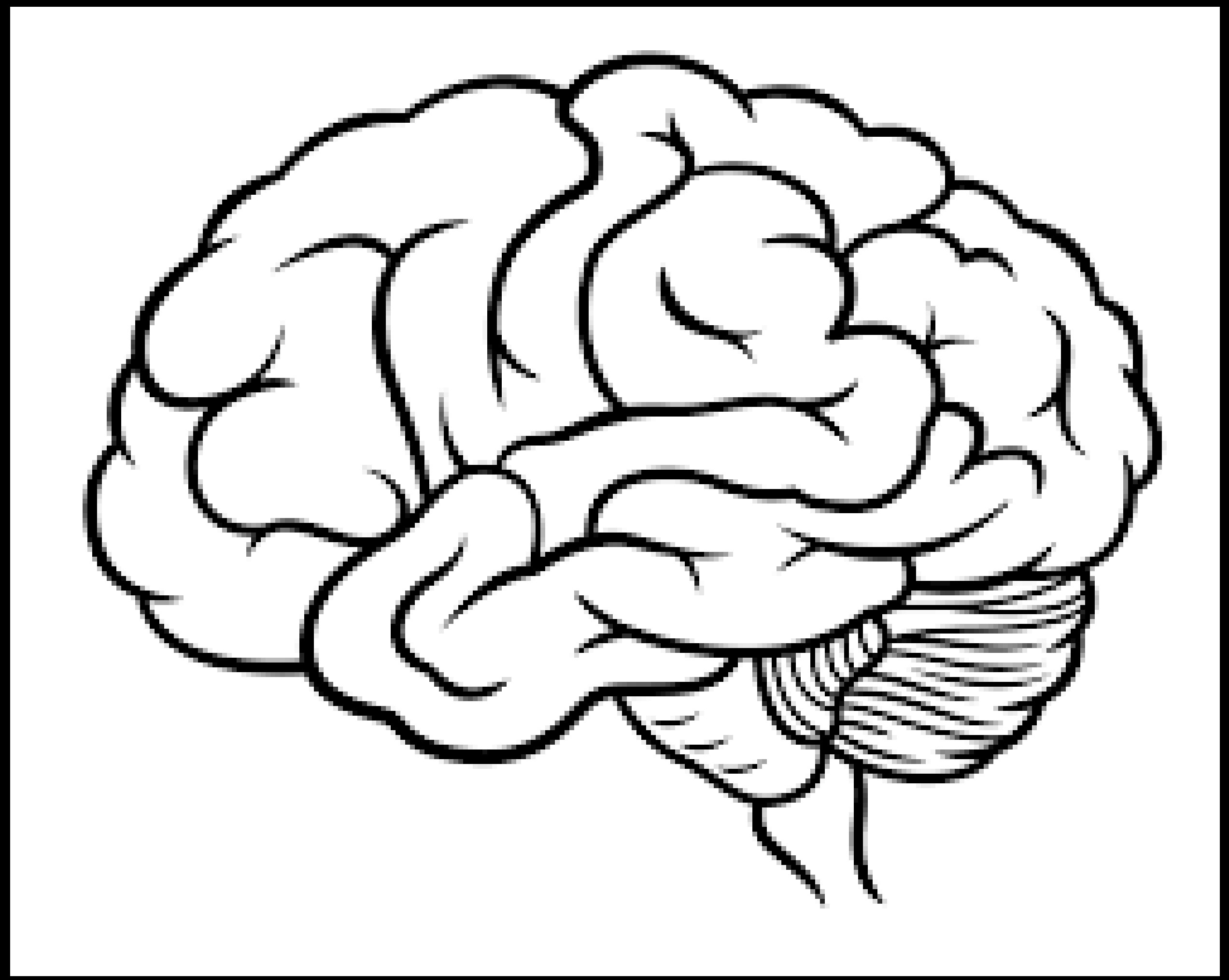
# COGNITIVE CONTROL AND MPC



- ← sense its environment
- → make decisions
- ← learn from experience
- ↔ adapt to changing circumstances

Similarly, cognitive control uses active sensing, decision making, learning, and adaptation to achieve better performance in control applications.

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# GEM

GRANULE EX MACHINA

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# 4. Data-driven discovery: 21st century Renaissance

Data-driven discovery is revolutionizing how we model, predict and control complex systems.

These systems are typically nonlinear, dynamic, multi-scale in space and time, high dimensional, with dominant underlying patterns that should be characterized and modelled for the eventual goal of sensing, prediction, estimation, and control.

Driving modern data science is the availability of vast and increasing quantities of data, enabled by remarkable innovations in sensors, increases in computational power, and virtually unlimited data storage and transfer capabilities. Such vast quantities of data are affording new opportunities for data-driven discovery, which has been referred to as 4th paradigm of scientific discovery.