Examples of ML and AI in manufacturing: Formufilling digital twin and automated visual inspection

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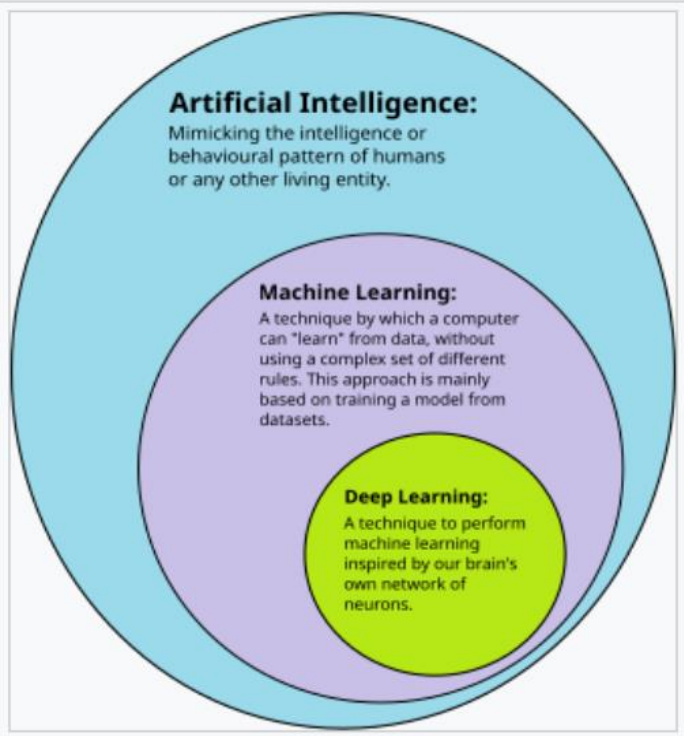
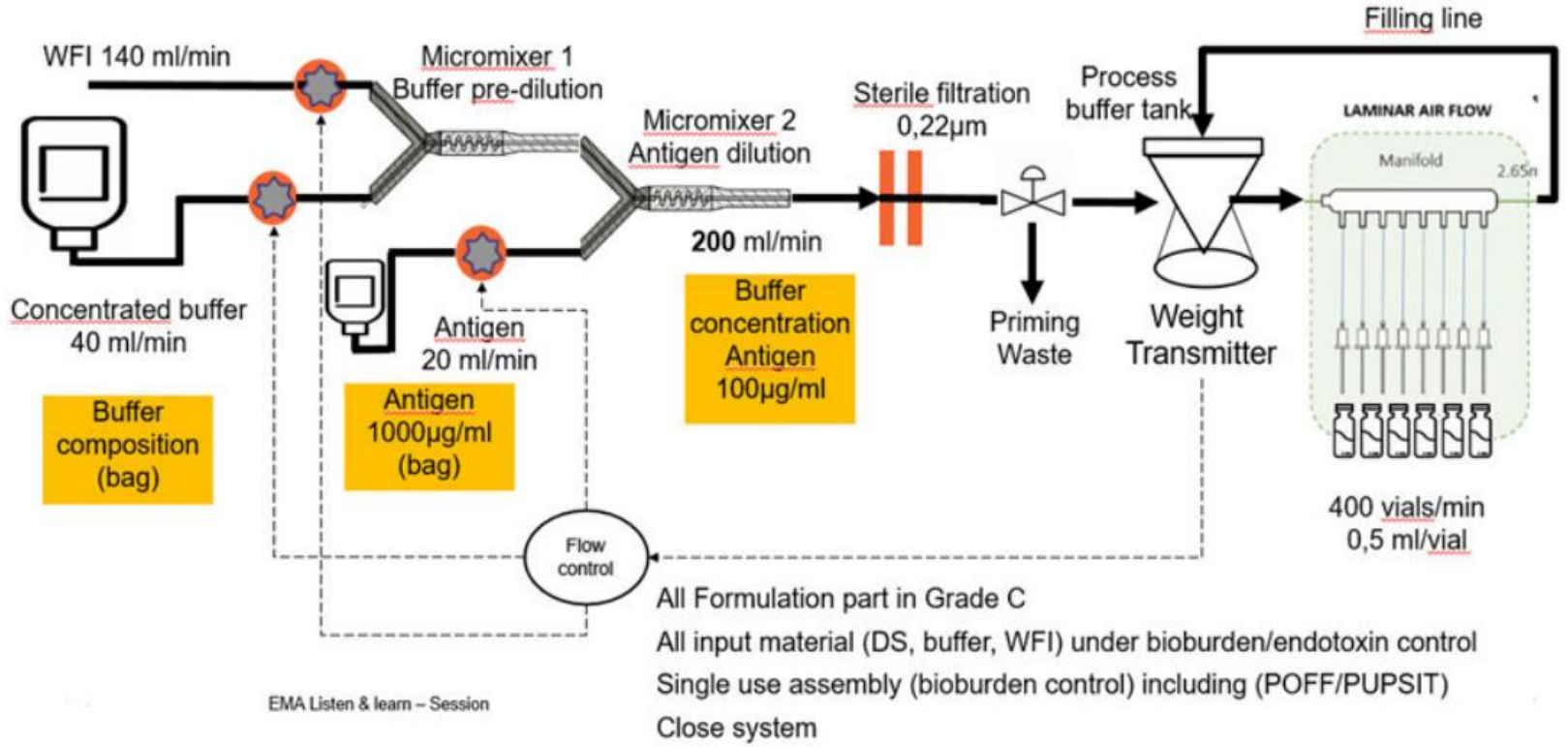
Overview



- Examples of the use of machina learning and AI
  - Machine Learning: Control of continuous formufilling as part of digital twin
  - Deep Learning: Automated Visual Inspection
- General Reflections on how to industrialise in a GMP environment

Continuous Formufilling

Digital twin control for continuous formulation and filling of a sterile product

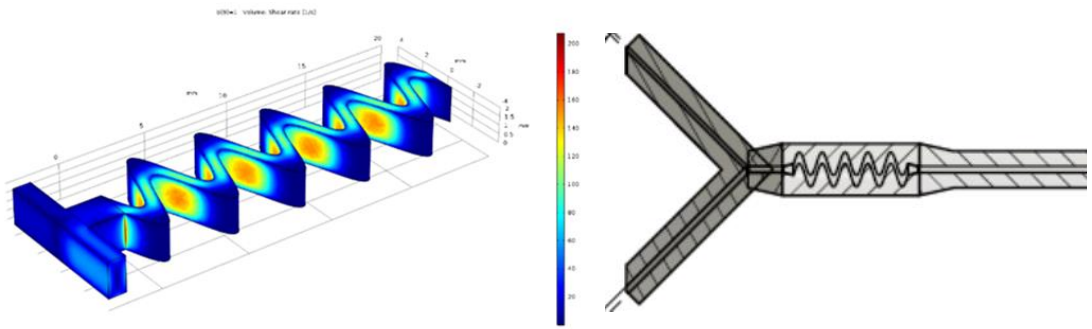


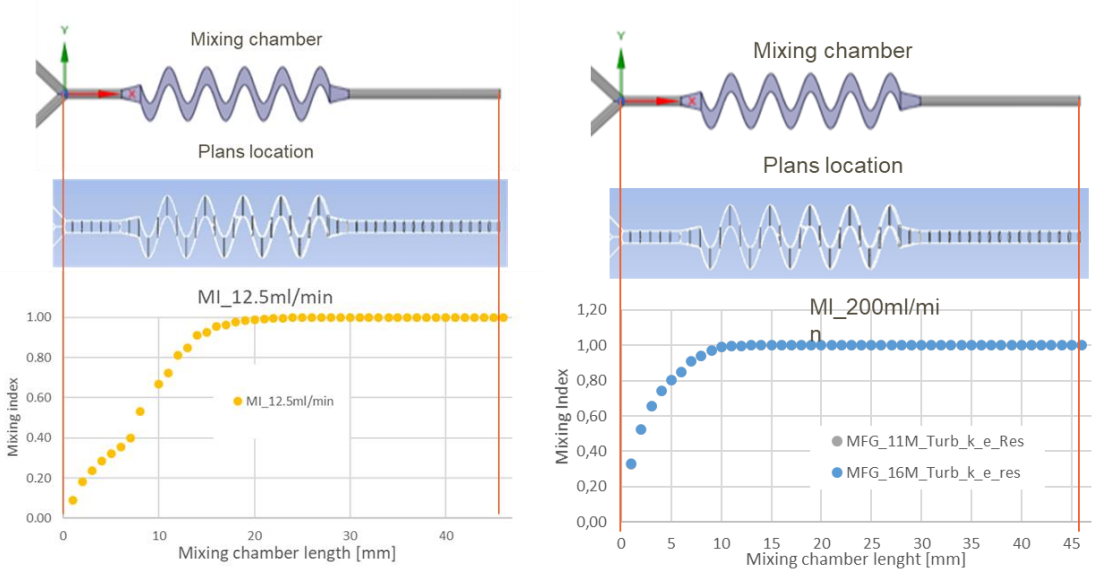
- ***Hybrid models comprising digital twin derived via empirical studies, CFD simulations, multiple sensor inputs ….***

- ***Control of CQAs eg concentration of antigen***

[2023 EMA QIG listen and learn: Link to Meeting Report]

Modelling Elements within the Formufilling Digital Twin





CFD models of mixing

PAT

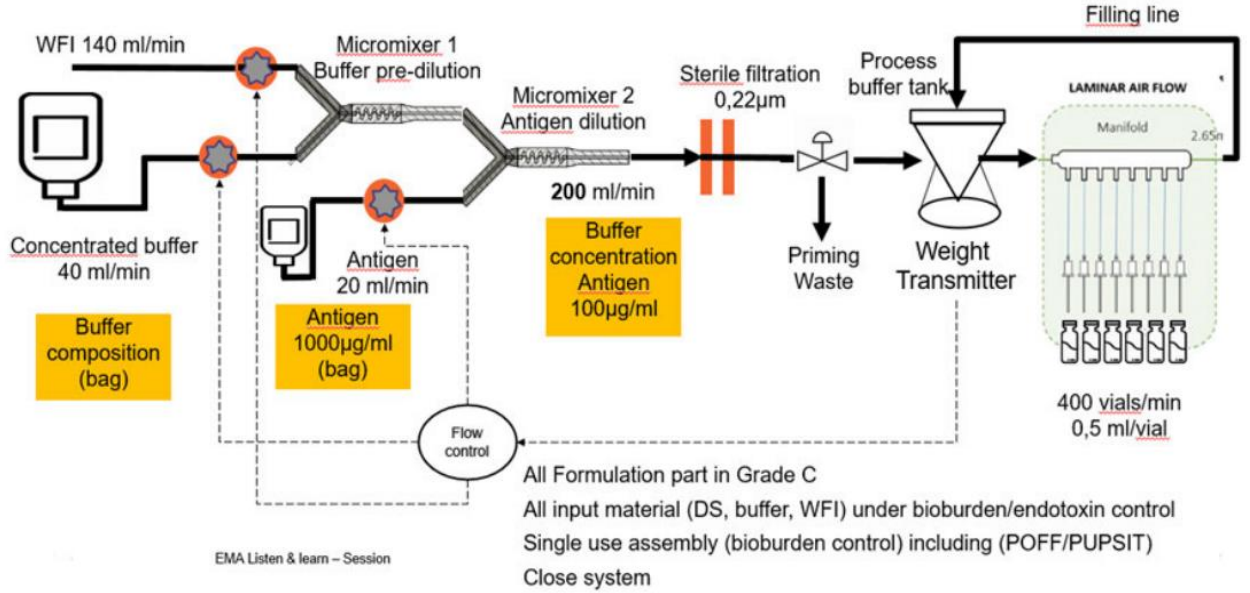
- flow-rate meters
- Balance
- Conductivity sensors
- UV detector
- Pressure

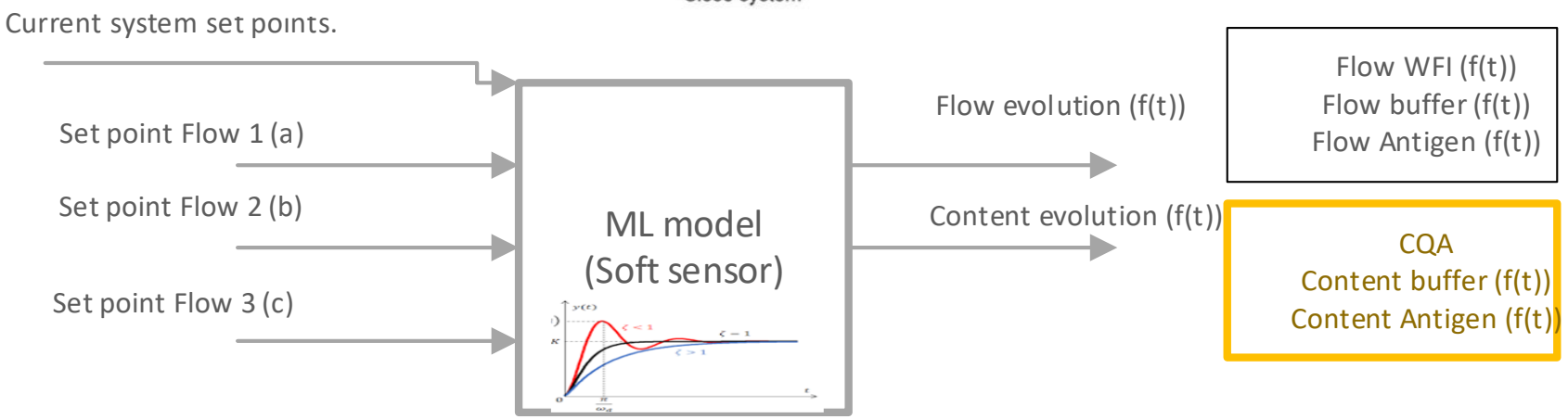
Soft sensors

- Antigen concentration prediction
- Flow-rate prediction

ML model training and assessment

ML model trained and tested via a stressed set of in-silico experiments
Process performance can be verified as part of PPQ Stage 1





Model Industrialisation

Increased model credibility

Increased model impact

Strategy for initial market supply

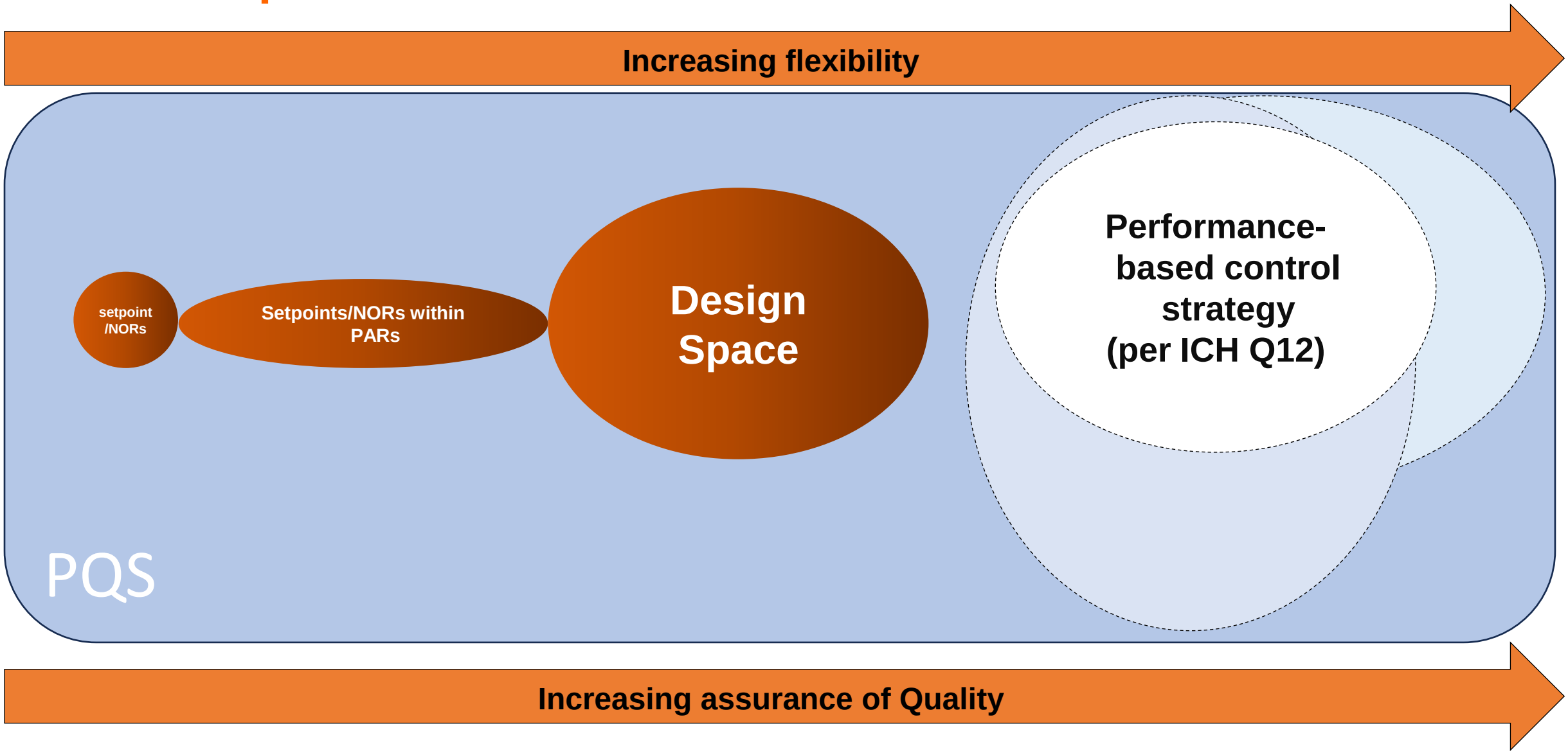
- **Release testing unchanged** (CQAs controlled as part of batch release)
- Fixed process boundaries (defined based on the model and then experimentally verified); no targets registered
- **ML can be active during manufacture to control the process within the defined process boundaries**
  - Based on maturity level of the twin, new set-points are proposed to the operator **or automatically activated in a closed-loop**
- **Model performance can be demonstrated in PPQ** where superiority of model-based-control can be demonstrated over classical (fixed parametric) controls.
  - Data from PPQ and subsequent CPV will show that the process is in a state of control
- **Full model validation should not be required and only limited data on model required in the dossier**

Future State?

- Process boundaries not fixed
- Performance-based control strategy
- Further model data provided in the dossier
- Increased focus on CPV
- **Increased reliance on machine learning and automation**
- **Model validation**

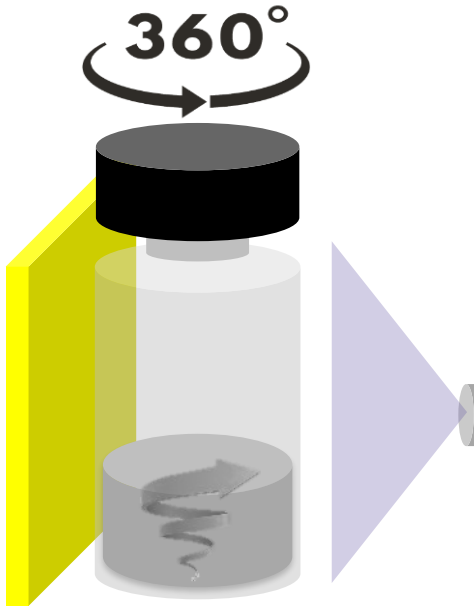
Framework to ensure that changes to models can be managed under the site PQS, without requiring prior approval

ML based process controls

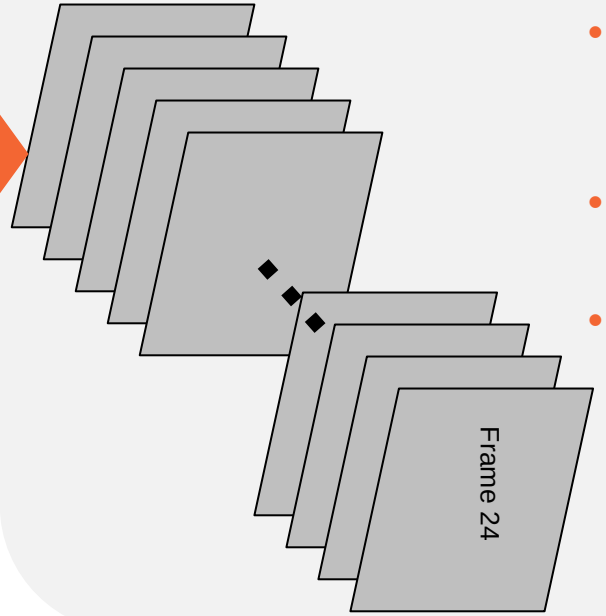


Automated Visual Inspection

Automated Visual Inspection Deep Learning Case Study



AVI machine takes
i.e. 24 frames
during vial rotation



For each of 24 Frames:

- Image aquisition and “pre-processing” (eg traditional image processing)
- Processing by Deep Learning model to classify defects
- Archive classification results in a register for each frame number

Pass / Fail

Automated Visual Inspection Deep Learning Case Study

Convolutional Neural Network (CNN) for Image Classification

Conform images

Crack images

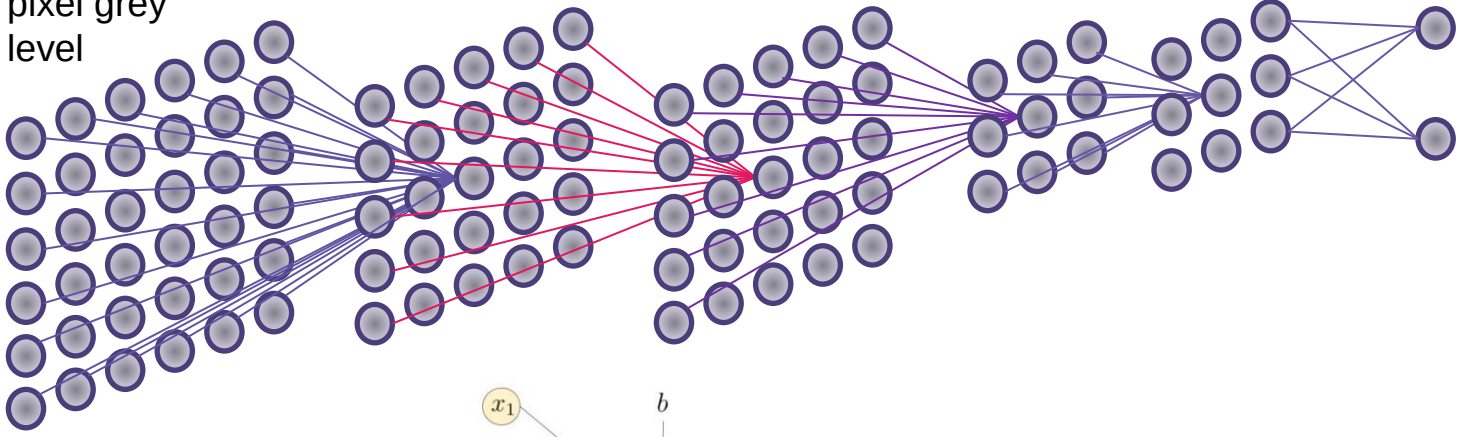
First layer to input each pixel grey level

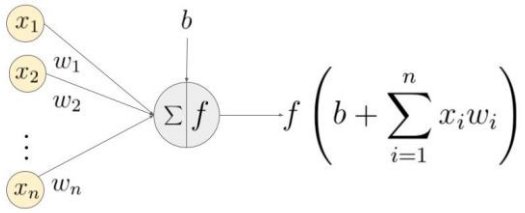
Early layers to detect big features

Last layers for final defect classification

Conform class

Crack class





Each neuron is a weighted sum of others with bias

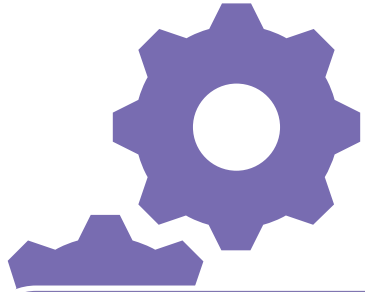
Many layers, designed to optimize image classification, containing from 3 to 50 million parameters to adjust

Automated Visual Inspection Deep Learning Case Study

Validation Strategy for Deep Learning Models in AVI

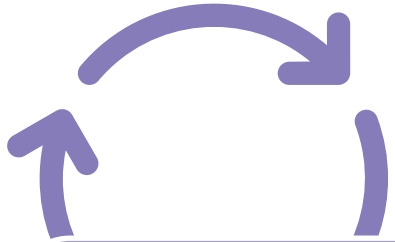
Desktop Qualification of Models

- Desktop OQ evaluation of AI DL model



On-line performance evaluation

- Digital Image testing OQ
- Real defect kit testing PQ to compare to MVI baseline
- Production Lots and trending



Life cycle Continuous improvement

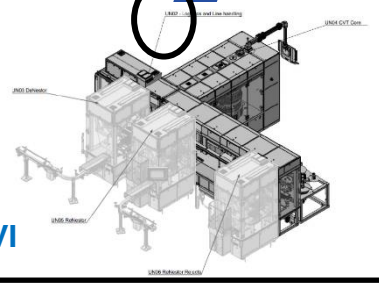
- Data gathering for improvement
- Continuous improvement under change control with continuous validation of performance

Exact approach will depend on how AVI is deployed

Lifecycle of Deep Learning Model

Active Learning Loop to speed up continuous improvement with real defects

Stream of new images from new batches



AVI

Validated & deployed AI models

Sample some unlabeled images from production

Labelling some saved images from production

Continuous improvement cycle for Model optimization

- Enabling GMP and regulatory frameworks

Retraining model offline

Transfer learning on existing model to refine performance

Validation with Change control of new refined model for new batches

Automated Visual Inspection Deep Learning Case Study

Considerations for industrialization

Deep Learning can significantly improve visual Inspection processes

- Use of Deep Learning may require new competencies and infrastructure
- Validation, lifecycle management should be based on quality risk management principles and characterization of risk
- Comparison of risks from human and automated visual inspection is a key consideration
  - Training, periodic review, documentation, acceptable false positive rate…
- AVI can fit within existing GMP and data integrity frameworks –need for manufacturers, regulators and QPs to understand the framework

What regulatory framework is needed for Digital Innovation?

No Regulation

Ultimate flexibility

Lack of clarity

No harmonisation

Strict regulation

Clarity

Lack of flexibility

Can be Harmonised

Goldilocks regulation?

Flexibility

Clarity

Harmonisation

Back-Ups

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Preliminary QIG Considerations regarding Pharmaceutical Process Models

Q2. What data is expected in the dossier in terms of model description and scope?

The level of detail regarding the model development and its description in the regulatory submission is dependent on the intended use of the model, its role in the control strategy, and the risk to material quality. This forms the basis for defining the degree of justification, and the extent of description, in an application. Requirements are defined as a function of the risk (see Table 1 in question Q3).

Q3. What data is expected to be included in the dossier in terms of model validation?

Risk	Example	Dossier location	Dossier requirements (see also question Q2)
Low	Process development, e.g. used to develop process understanding. Process optimisation (w/o change to registered process details). Mechanistic model used to speed up bioprocess scale-up/down. Digital Twin in shadow mode. Support batch release decisions based on QA predictions.	Dossier sections S.2.6/P.2.3 and S.2/P.3, as appropriate.	High level description of the model intent, type of model and how it is used. Manufacturing process validation data as described in the process validation guidelines.[4,5]
Medium	Process design (change to unit operation principle or setting of in-process control limits). RTD model in combination with in-line NIR process control. Support batch release decisions based on CQA predictions but [illegible] in combination with PA[illegible] release testing.	Dossier sections S.2.6/P.2.3 and S.2/P.3, as appropriate.	Detailed description of the model intent, type of model, how model is used and model operation, model assumptions, type of data used and model validation summary. Manufacturing process [illegible]idation data as [illegible]scribed in the process [illegible]alidation guidelines.[4,5]
[illegible]	[illegible]TD model w/o other related in-process measurement. Real-time release testing (reduced release testing).	Dossier sections S.2.6/P.2.3, S.2/P[illegible] and S.4/P.5, as appropriate.	As for medium risk above, plus model validation report (training/ validation/ test datasets, prediction metrics acceptance criteria, model validity space, *etc.*).

"*risk to material quality*" is a function of the control strategy

"*detailed description*" in "S2/P3" would be a significant concern - detailed established conditions should not be required for medium risk

"*validation summary*" a concern - appropriate verification is justifiable