From Quality by Design to Living Digital Twins

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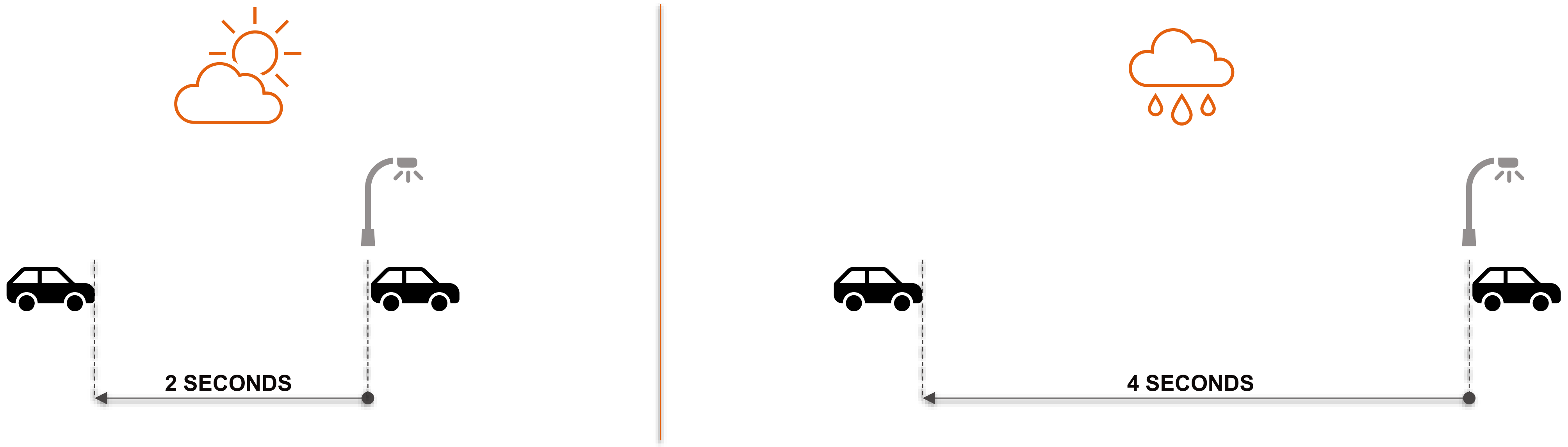
Khadija Mu’azzam [a,b], Francisco Vitor Santos da Silva [a], Jason Murtagh [b], Maria Jose Sousa Gallagher [a],

a Process & Chemical Engineering, School of Engineering & Architecture, University College Cork, Ireland
b DPS Group Cork, Arcadis, Netherlands

Agenda

Safety Moment Keeping a Safe Distance



Two second rule: to keep a safe distance from the vehicle in front, the two second rule can be followed. For dry conditions 2 seconds should be measured from a fixed point or 4 seconds in wet road conditions (icy conditions require larger gap).

2 seconds can be measured Saying **“only a fool breaks the 2-second rule”** which takes 2 seconds to say at a normal rate.

Agenda

01 Health and safety moment

02 Why QbD still matters

03 The modelling toolbox

04 Data infrastructure: PAT, soft sensors & instrumentation

05 Digital twin readiness: model (static) → shadow (live) → twin (interactive)

06 A staged roadmap

Why QbD Still Matters

- Quality is embedded in the design and control rather than end-of-line testing.
- Core elements include QTPP, CQAs, design space, control strategy, and continual improvement.
- Models link CPPs to CQAs, to explore and operate within the design space, and prioritise experiments and control actuation.

Design Space & Uncertainty

UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

ARCADIS

DoE & empirical, mechanistic, or hybrid models

Account for nonlinear regions via shape reconstruction and feasibility analysis.

Use black-box approximations to keep computation practical for expensive simulations.

Combine frequentist & Bayesian approaches to estimate prediction intervals and the probability of meeting constraints.

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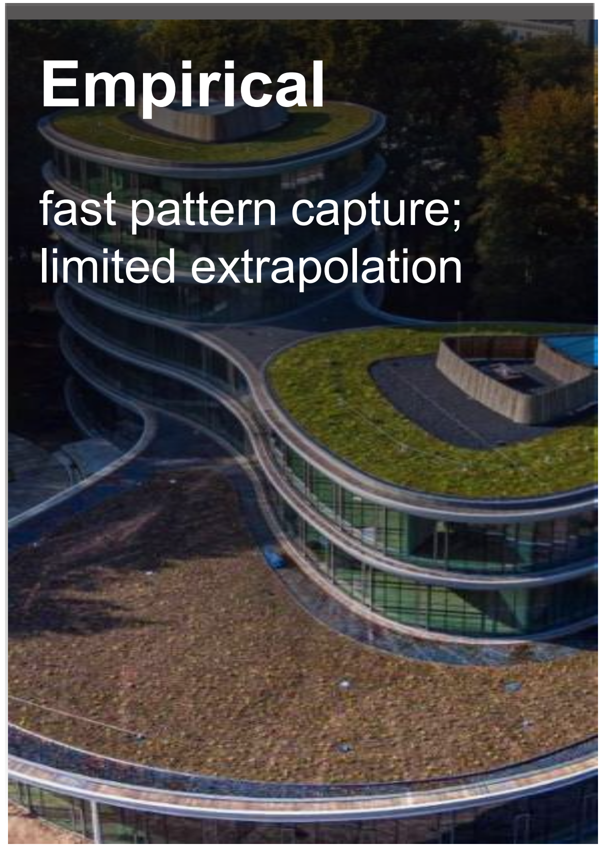
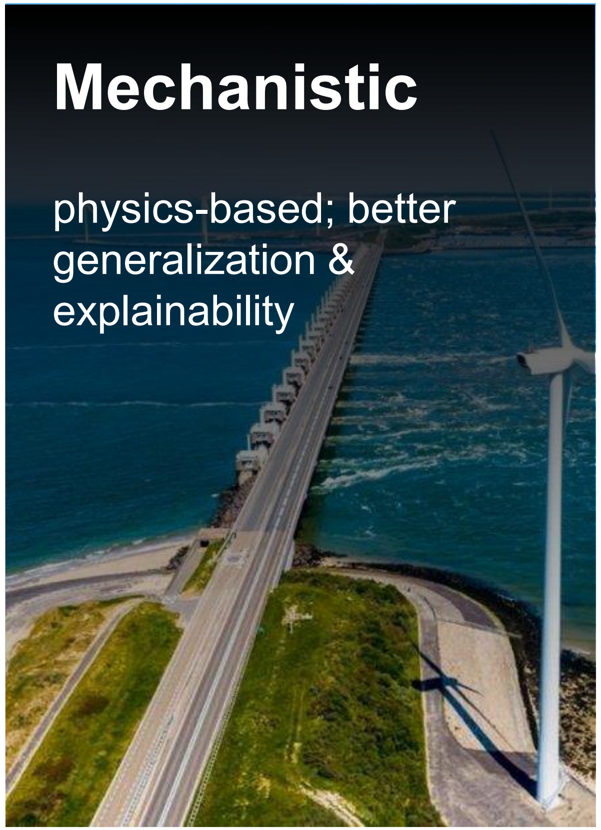
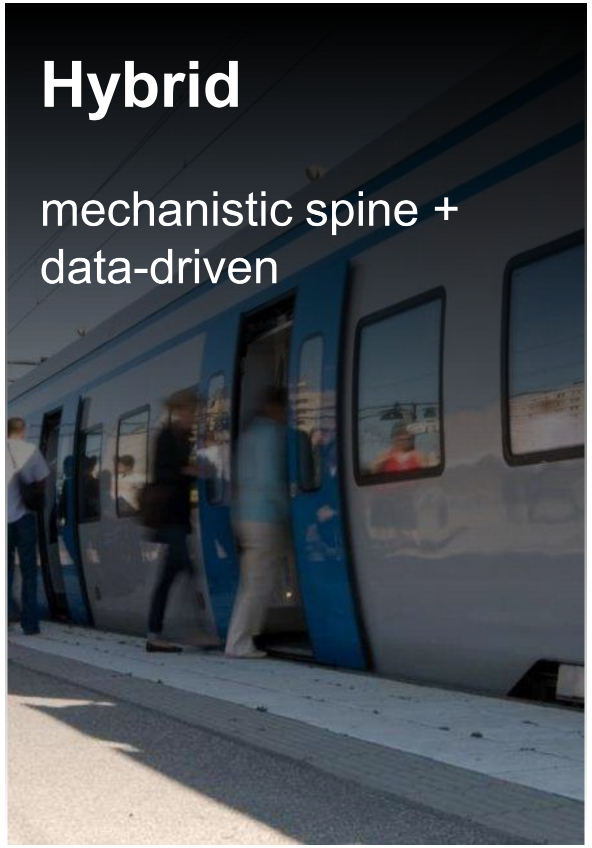
The Modelling Toolbox

Model selection should be determined by the intended application and by the level and quality of data and process understanding that can be sustained







Design & Control Across Bioprocess

- **Upstream**: Kinetic, population-balance models; heterogeneity → CQAs.
- **Downstream**: Transport limits, thermodynamic consistency; purity–yield trade-offs set separation guardrails.
- **Model Predictive Control**: Robust/Stochastic MPC, constraint tightening; explicit uncertainty handling → effective control.
- **Estimation**: State estimators (e.g., Kalman filters); noisy/missing data → soft sensing.

Agenda

Data infrastructure: PAT, soft sensors & instrumentation

Soft sensors: mechanistic, empirical (ML), and hybrid approaches used to infer unmeasured states and CQAs.

Spectroscopy: UV–Vis, mid-IR, Raman, and fluorescence paired with chemometrics for rapid estimation of key analytes.

Data engineering: rigorous cleaning, time alignment, dimensionality reduction and drift detection to sustain model performance.

Process probes: free-floating sensors deployed to reveal mixing non-uniformities and shear gradients.

Agenda

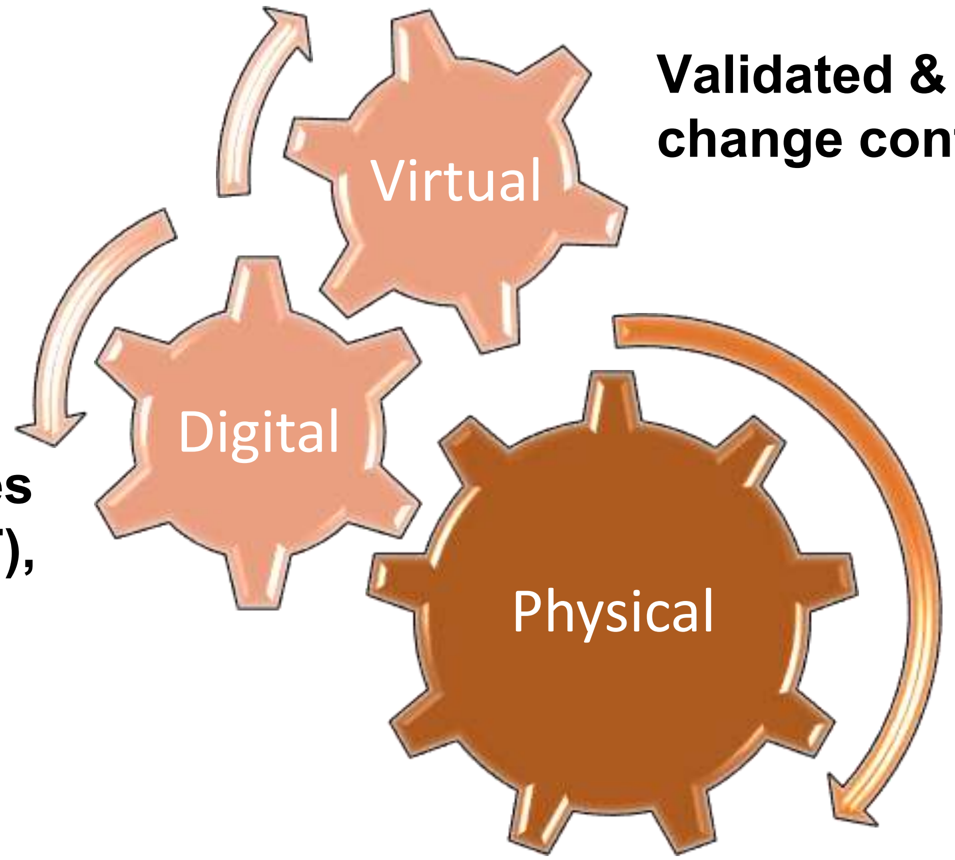
Digital Twin Maturity

Model maturity is selected according to purpose and data readiness, and deployed where benefits outweigh cost.

Digital Twin Requirements

Bake governance into the digital twin by using secure, standards-based communication (e.g., OPC-UA/MQTT with encryption/SSL) and strong data management to protect IP while enforcing rigorous model validation that assesses uncertainty and consistency between model and data.

Validated & under change control



Historians, interfaces (e.g., OPC UA/MQTT), cloud/edge options

Reliable sensors/ actuators for CQAs & CPPs

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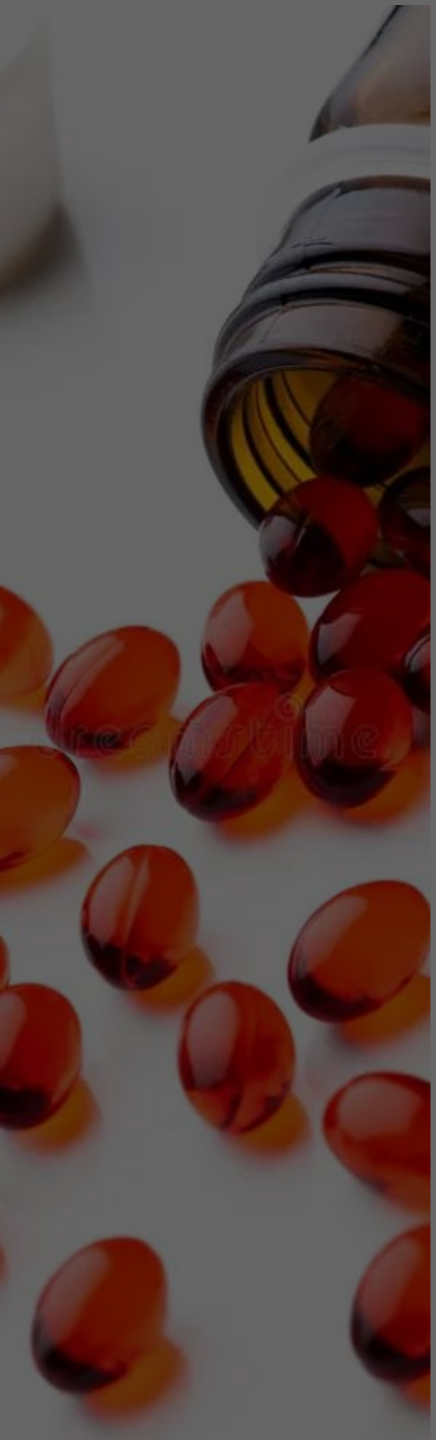
A staged roadmap

Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
1 & 2 **QTPP → draft CQAs & Build first model** The QTPP is used to draft CQAs, and a first mechanistic and empirical model is built and validated with explicit uncertainty.		**3** **Instrument for Information** Soft sensors fused via Kalman, targeted spectroscopy, and free-floating probes may be added, supported by a lean data pipeline and model registry.	Live operation is connected as a digital shadow to enable forecasts. **4** **Shadow → Selective Twin**	Integrate with plant systems (SCADA/ DCS, PI historians) and live data streams, standardize secure comms (OPC-UA/ MQTT with encryption. **5** **Industrialise & Scale**



Spotlight: Cell Therapy

- Heterogeneous starting material; limited sampling; single-use systems
- Non-destructive sensing is key (e.g. Raman)
- Hybrid soft sensors often the only viable real-time path
- Discipline in data/drift management is non-negotiable

What "Good" Looks Like

- Traceable line: QTPP → CQAs → CPPs → Design Space
- Living model registry with versions, data, and uncertainty bounds
- Operational twins where it counts; shadow-assisted decisions elsewhere
- First-class data engineering: alignment, drift, simple visuals
- Human-in-the-loop excellence (Industry 5.0 mindset)

Risks & Mitigations

- Model error → bad decisions
- Security / IP exposure
- Integration fatigue (heterogeneous / legacy systems)
- Validation burden

Resulting Advantages

Speed

Fewer experiments; more learning per run.

Robustness

Earlier detection; tighter variability.

Trust

Auditable link from design to manufacturing

Key Takeaways

- QbD provides the roadmap
- Data reality demands discipline
- Soft sensing & fusion are central
- Uncertainty & drift must be explicit
- DT maturity levels matter

Thank you

Khadija Mu’azzam

Senior Process Engineer at Arcadis | PhD research at University College Cork

Francisco Vitor Santos Da Silva

Senior Lecturer at University College Cork

Jason Murtagh

Lead Process Engineer & SME at Arcadis

Maria Jose Sousa Gallagher

Professor in Process & Chemical Engineering, School of Engineering at University College Cork