PIPAc Production Intelligente de Principes Actifs

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Intelligent Production of Active Pharmaceutical Ingredients (APIs)

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The COVID-19 pandemic led to a drug shortage. The World Health Organization responded with strategies promoting local pharmaceutical production. This sparked the PIPAC project, a collaborative effort involving NovAliX, Alysophil, Bruker, and De Dietrich. The project, embodying Industry 4.0 principles, aims to produce APIs using compact units, marking a significant advancement in pharmaceutical production..

Fig. 1 Compact, mobile, autonomous and frugal production units

The goal is to create a compact, autonomous Artificial Intelligence (AI) powered unit for producing APIs (Fig. 1). This innovate solution combines flow chemistry, AI technology, Inline analytics (NMR and mIR) and Process Analytical Technology (PAT) (Fig. 2).

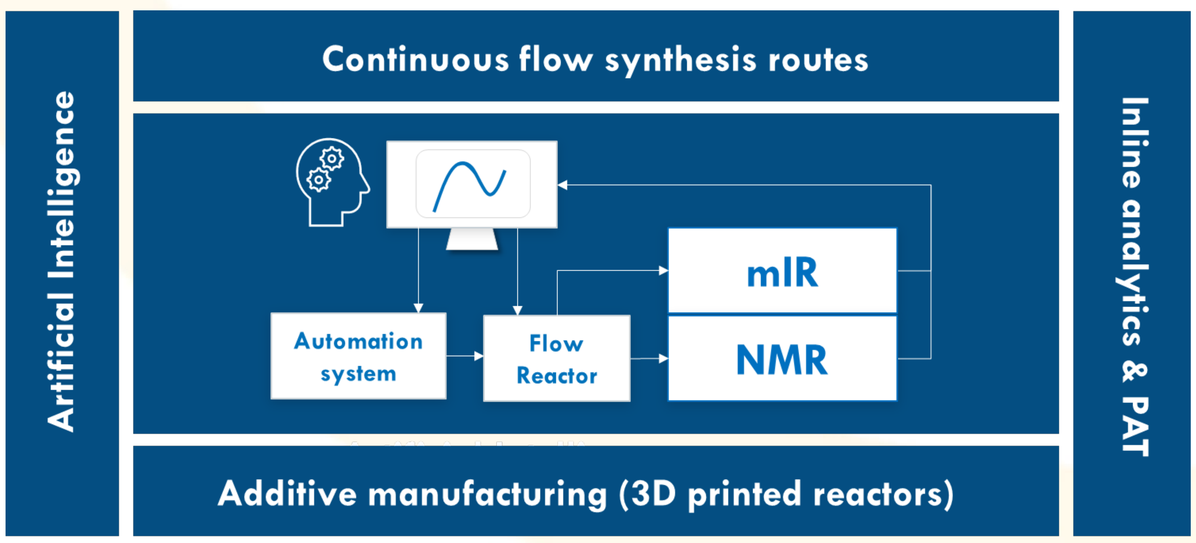

Fig. 2 Flow chemistry and AI enabled process control using NMR and IR as detectors

Real world reaction control

An autonomous chemical synthesis in continuous flow was demonstrated, piloted by a deep reinforcement learning (RL) agent. This was shown in a single-step dioxolane synthesis at 60˚C, adapting to temperature drops to 40˚C or below. The AI agent receives sensor data and influences controllable parameters like temperatures and flow rates.

Using deep reinforcement learning, the agent maximizes a reward signal for based on product conversion and adapts the sequence of decisions in response to the fluctuating environment (Fig. 3, 4).

Fig. 3 Synthesis of high potent API using NMR (left) and IR (right) sensing techniques

The AI agent receives information from various sensors (reactor temperature and conversion data, etc.) Then the agent provides a series of instructions to adjust controllable parameters (e.g., thermostat setting, flow rates, etc.)

Based the *reinforcement learning* concept, the method adapts ideas from psychology and neuroscience to the context of machine learning. The AI agent receives a reward signal compensating for its past performance. In order to limit waste of products and minimize the learning time, we develop a *digital twin*, which captures real-world chemistry. The agent discovers strategies to respond to ever-changing environment such that the conversion remains steady.

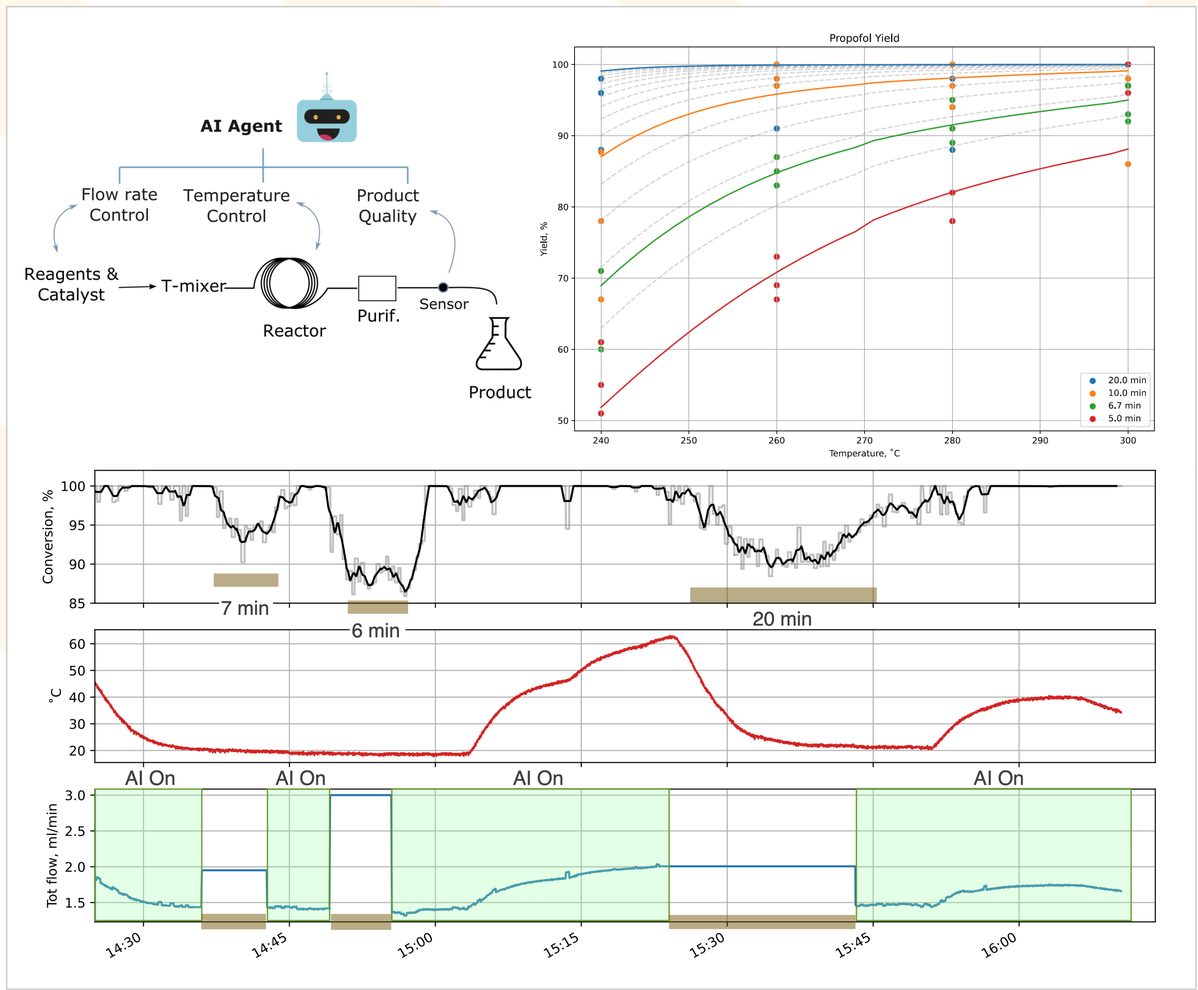

Fig. 4 AI agent controlling flow chemistry: The agent sustains a steady conversion (green highlights).

Conclusion

The method, with a history of success in Go and Chess, is a key component in ChatGPT's text-to-text engine training. Deep reinforcement learning is being applied to real-world challenges, including the development of multiple reaction chaining for API production. The AI agent's capacity to adapt reaction conditions in real-time proves invaluable for intricate or sensitive reactions. These lab-scale demonstrations pave the way for the first AI-autonomously piloted industrial chemical production demonstrator.

Milestones and Progress

- ✓ Optimized continuous flow synthesis routes for 3 high-demand APIs
- ✓ Development of reaction control in a virtual environment
- ✓ Proof-of-concept flow synthesis control powered by deep reinforcement learning
- ✓ Automated process control with In-line analysis and data acquisition
- ✓ Design and 3D-printing of a lab-scale system
- ▪ Automated continuous flow production at the lab-scale
- ▪ Implementation of a demonstrator and kg-scale manufacturing

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