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Krist V. Gernaey, John Woodley, Gürkan Sin

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Introducing mechanistic models in Process Analytical Technology education ((Research Highlight))

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6 **Research Highlight ((4411 words))**
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8 **Introducing mechanistic models in Process Analytical Technology**
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11 **education**
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16 Krist V. Gernaey^{1,*}, John M. Woodley¹ and Gürkan Sin²
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20
21 ¹Center for BioProcess Engineering, Department of Chemical and Biochemical
22 Engineering, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark
23

24
25 ²CAPEC, Department of Chemical and Biochemical Engineering, Technical
26 University of Denmark, DK-2800 Kgs. Lyngby, Denmark
27

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37 * Corresponding author: Krist V. Gernaey, Associate Professor
38

39
40 Postal address:

41
42 Department of Chemical and Biochemical Engineering

43
44 Technical University of Denmark,
45

46
47 Building 229
48

49
50 DK-2800 Kgs. Lyngby, Denmark

51
52 Fax: 0045 45 88 22 58; Phone: 0045 45 25 28 00; E-mail: kvg@kt.dtu.dk
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6 ((NO ABSTRACT BUT INTRO WITHOUT HEADING))
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8 The Process Analytical Technology (PAT) **guidance** of the Food and Drug
9 Administration (FDA) is designed to move pharmaceutical production away from
10 off-line product quality testing to ‘real-time release’ strategies supported by on-
11 line measurement of critical process variables. A successful PAT implementation
12 **primarily** requires in-depth process knowledge but also a number of tools and
13 methods **including** on-line analysis, process monitoring, as well as process
14 control. In order to achieve successful PAT implementation, the students and
15 professionals already working in the pharmaceutical industry will need more skills
16 particularly within the design, tuning and implementation of process control
17 algorithms. Based on reported experiences in other engineering disciplines such as
18 chemical and environmental engineering, we conclude that development of a
19 benchmark (mechanistic) modeling platform for pharmaceutical manufacturing
20 systems is needed. Supported by a team of experts from academia and industry,
21 **this** benchmarking effort can deliver documented and validated models of selected
22 case-studies from pharmaceutical industry. Such publicly available **and** expert
23 validated models could significantly contribute to educating students and
24 professionals with skills that are essential for implementing the Process Analytical
25 Technology **guidance** in **pharmaceutical manufacturing systems**.
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1. Process Analytical Technology (PAT)

Most pharmaceutical products today are small-molecule targets that are made using organic synthesis. In recent years the complexity of the molecules has increased in an attempt to improve selectivity and reduce side-effects. Higher molecular-weight molecules with multiple-chiral centers has also seen many processes now start to incorporate enzyme-based catalysis (driven also by environmental needs) [1]. Alongside these targets are also a growing group of biotechnology-based macromolecular targets, often referred to as bio-pharmaceuticals, such as insulin for example [2, 3]. Whether a small-molecule or a bio-pharmaceutical **target is required**, until a couple of years ago, all such manufacturing processes were fixed according to the specific production process description that was provided in the Drug Master File submitted to the FDA (or any other national regulatory body equivalent to the FDA).

It is common knowledge that there can exist considerable variation in raw materials, e.g. when switching from one batch of a chemical to the next batch, or when acquiring a chemical from an alternative supplier. Excessive variation in product quality – or in other words sub-optimal performance of the process – could be the result of having a fixed production process when confronted with unknown disturbances or variations in raw materials composition and/or properties, as schematically illustrated in the upper part of Figure 1. This does not affect the consumer (patient) directly, since time-consuming off-line laboratory testing of product quality is performed to ensure that every product batch **achieves**

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6 the required quality standards. The latter approach – also called the ‘lab-centric’
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8 approach – is characterized by minimal closed loop, real-time control and limited
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10 enterprise-wide data availability. However, since each product batch of inferior
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12 quality will lead to increased production costs of a pharmaceutical, the price of the
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14 final product becomes higher as a consequence of these inefficient production
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16 methods. An additional factor that might lead to inefficient production processes
17
18 is that there is usually very little time for production process development. Indeed,
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20 any delay in establishing a production process leads to decreased profit in view of
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22 the limited patent lifetime for each pharmaceutical, and thus process development
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24 by necessity is a compromise to ensure rapid time-to-market.
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32 However, with the publication of the Process Analytical Technology (PAT)
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34 guidance in 2004 (<http://www.fda.gov/cder/guidance/6419fnl.pdf>), the situation
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36 for the pharmaceutical manufacturing has changed significantly: One of the
37
38 central issues in the FDA PAT guidance is indeed the transition from a fixed to a
39
40 robust and adjustable manufacturing process by adopting innovative and new
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42 technology-based systems, as illustrated in the bottom part of Figure 1. When
43
44 implementing the PAT guidance on pharmaceuticals production, the process
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46 operation is adjusted as a consequence of upstream changes, such as changes in
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48 the properties of the raw materials. Instead of laborious off-line testing of product
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50 quality, the ‘real-time release’ concept is introduced in the PAT guidance, where
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52 product quality is now assessed in real-time based on the interpretation of on-line
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54 measurements. The focus of the PAT guidance is clearly on obtaining safe – for
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6 the consumer – and efficient pharmaceutical manufacturing processes, but for
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8 industry the PAT guidance is also an open invitation towards development and
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10 implementation of innovative manufacturing processes. Indeed, as long as the
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12 critical process variables are kept within the “design space” of the process, it is
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14 possible to perform process optimization, for example by introducing more
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16 advanced control combined with on-line measurement of critical process
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18 variables.
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24 During the past couple of years, the PAT guidance has slowly but consistently led
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26 to the change of an increasing number of pharmaceutical production processes
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28 (e.g. [4]). In addition, the implementation of the basic ideas of the PAT guidance
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30 by the pharmaceutical industry have also resulted in increased focus on this area
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32 in other regulated sectors, such as the food industry.
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38 This paper is an attempt to initiate a broader discussion within the biochemical
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40 engineering community on how the PAT guidance influences the required skills
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42 of scientists, engineers and managers involved in pharmaceutical process
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44 development and manufacturing. This of course also includes the current and
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46 future generations of biochemical and chemical engineering students. First, a
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48 concise literature overview is provided, to illustrate what is available in the
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50 literature with respect to PAT. This is followed then by a critical discussion and
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52 an outlook to the future.
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2. PAT in the literature

When taking a closer look at the literature, a substantial number of articles have been published already reporting PAT case studies or PAT-related work. The emphasis in many reported projects immediately following publication of the PAT **guidance** was on the analytical aspects: the papers either (i) report the development and implementation of on-line analysis techniques (e.g. [5, 6]) – especially spectroscopic methods – or (ii) report on the development and application of chemometric models to interpret the data generated by on-line analysis (e.g. [7]). The focus on analytical aspects in the early applications of PAT can be understood from a process control point of view, since development of on-line process monitoring tools is essential to provide on-line information about the process which can subsequently be applied by implementing suitable control strategies. On the other hand, Maes and Van Liedekerke [8] point out that this focus on analytical aspects in many cases can be explained also by a misunderstanding of the PAT concept, i.e. companies think of PAT in terms of current validation and quality control processes, focusing on the sensor and what it can measure rather than on the wider quest for process understanding. So, it seems that closing the loop, i.e. using the on-line sensors installed in the frame of a PAT project within a control loop, is a major challenge for industry. One explanation for this could be that people working on PAT projects in general do not have **sufficient** skills to design, tune and implement control loops.

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6 The most essential point when developing PAT applications is the availability of
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8 sufficient process knowledge, i.e. one has to know how a change in an input will
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10 influence the process output, for example the product quality. A number of
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12 authors have recently suggested that mechanistic modeling – a skill that most
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14 engineers possess – is an excellent way to represent the process knowledge [9-13].
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16 Indeed, the differential equations representing one or several unit operations in a
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18 production process inherently represent the input-output dynamics, which is
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20 precisely the type of information needed to pinpoint the causes of excessive
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22 variation of product quality or to select suitable actuators to counteract undesired
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24 variations in product quality. To this end, the model can be supplemented by a
25
26 modeling toolbox including uncertainty and sensitivity analysis to assess the
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28 statistical quality (read as reliability) of the simulated scenarios [14].
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34 Crystallization, a key operation in most pharmaceutical processes, is a good
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36 example to illustrate how process knowledge can be used. The increased
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38 understanding of the crystallization process has led to the use of first-principles
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40 based approaches for crystallization process design [15], and first-principles based
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42 models are increasingly used in the design of advanced control strategies for
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44 crystallization processes [16].
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51 Despite the fact that the use of mechanistic models for process knowledge
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53 representation increases steadily, it should be emphasized that data-driven
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55 modeling also plays a prominent role in the development of PAT applications.
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57 Chemometric models, for example, can be helpful tools in acquiring process
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6 knowledge, as discussed in detail by Kourti [17]. For complex operations, for
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8 example [18, 19], data-driven modeling is the only feasible alternative to
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10 represent input-output dynamics because our level of understanding is simply not
11
12 sufficiently high to formulate mechanistic models. One of the key advantages of
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14 data-driven models is that they can be solved extremely fast, and therefore this
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16 type of models is preferred if predictions are to be available in real-time, for
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18 example in a process control context.
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24 Last but not least, while on-line analysis is excellent and essential within a PAT
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26 application, it is not a goal in itself. On-line analysis methods should rather be
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28 perceived as useful tools. In a PAT context they are to be supplemented by
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30 continuous development of process understanding and by implementation of
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32 appropriate control strategies. Only then will PAT projects become a complete
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34 success.
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41 **3. Discussion**

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43 According to the PAT guidance, the following can be listed as PAT tools: (1)
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45 Multivariate tools for design, data acquisition and analysis; (2) Process analysis
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47 equipment and tools (e.g. including software sensors); (3) Process control tools;
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49 (4) Continuous improvement and knowledge management tools (e.g. artificial
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51 intelligence, supervisory control). The question is now how we can provide the
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53 necessary education for the scientists and engineers involved in pharmaceutical
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55 process development and manufacturing to allow them to develop PAT
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6 applications in an efficient way? Or in other words, how can we educate people to
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8 use the above-mentioned PAT tools? It is our thesis that education should not
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10 focus exclusively on the tools themselves – this too often appears to be the current
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12 approach (see above). Instead, learning should be based on detailed and realistic
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14 case studies, where the PAT tools are put to work to help create innovative
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16 manufacturing processes. Such an approach will help students to get a good
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18 feeling for the practical problems that will occur in any production process that
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20 needs to meet stringent product quality requirements, and in particular would
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22 assist in teaching problem-solving skills. Working with case studies should also
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24 appeal to professionals already working in the pharmaceutical industry, and would
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26 allow them to update their knowledge and skills such that they are better prepared
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28 for the task at hand: collecting relevant process knowledge and based on that,
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30 developing suitable control strategies to obtain consistent process performance
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32 and the requested high product quality.
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41 We are convinced that process modeling and simulation will play an important
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43 role here. Indeed, educating students in process monitoring and process control
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45 would arguably be easier through the availability of a number of realistic and
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47 industrially relevant modeling case studies that are validated by a group of experts
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49 from academia and industry, and made available freely for download. Note that
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51 the idea of using process modeling and simulation in pharmaceutical process
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53 development and production is not new. Petrides *et al.* [20] already demonstrated
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55 in 1989 how modeling and simulation can be applied to bioprocesses for
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6 estimation of process economics and to identify precisely those process points
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8 where optimization could be most rewarding. In 1995, Lonza demonstrated how
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10 process modeling and simulation can be used to shorten development time in the
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12 production process of a pharmaceutical intermediate [21]. Nevertheless, it would
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14 appear that the idea didn't completely catch up with the pharmaceutical industry
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16 in the nineties, probably because modeling often is considered as a time-
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18 consuming task or perhaps due to the "perceived" reluctance of regulatory bodies
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20 to accept such manufacturing procedures as pointed out in the FDA guidance
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22 (<http://www.fda.gov/cder/guidance/6419fnl.pdf>). The literature overview in the
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24 previous section of the paper demonstrates convincingly that there is a renewed
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26 interest in mechanistic modeling and simulation of production processes.
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34 Maes and Van Liedekerke [8] suggest that PAT project teams could learn from
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36 relevant experiences accumulated by other industries. To illustrate that the
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38 availability of the above-mentioned industrially relevant case studies is not an
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40 unrealistic dream, it is certainly worth mentioning a couple of initiatives that were
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42 taken in other research fields over the recent past to promote research in process
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44 control and process monitoring. In the chemical engineering field, the Tennessee-
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46 Eastman challenge was established in 1993 [22]. The Tennessee-Eastman
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48 challenge consists of a complete model of a chemical plant, including definition
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50 of control objectives, manipulated variables (including constraints), on-line
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52 measurements (ideal and non-ideal) and process operating constraints. In
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54 particular, the definition of the constraints and the fact that also non-ideal sensors
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6 are used allows a more realistic validation of process monitoring and control
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8 algorithms. The Tennessee-Eastman challenge – originally implemented in
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10 Fortran – has subsequently been implemented in other software packages (see e.g.
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12 <http://depts.washington.edu/control/LARRY/TE/download.html>), thereby
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14 extending the number of potential users considerably. As a consequence the
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16 Tennessee-Eastman challenge has been used extensively in research and teaching
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18 on process optimization, process control (e.g. [23, 24]) and process monitoring
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20 (e.g. [25-27]).
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27 Likewise in the field of environmental technology, the use of benchmark systems
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29 for assessment of process performance, control system evaluation and similar
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31 purposes is well established, especially for the evaluation of wastewater treatment
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33 plant control strategies [28, 29]. Originally started more than a decade ago,
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35 several benchmark plant lay-outs have now been developed, including a specific
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37 benchmark plant for testing of process monitoring algorithms [30] and a
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39 benchmark plant with a focus on plant-wide control (dynamic interaction between
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41 different plant units considered) [31]. Each wastewater treatment plant benchmark
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43 lay-out consists of a complete model representing a general treatment plant, an
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45 associated control system, a benchmarking procedure and a set of evaluation
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47 criteria. The inclusion of the benchmark wastewater treatment plant layout as a
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49 predefined software tool in several commercial simulator packages as well as in
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51 stand-alone Matlab, FORTRAN and C++ implementations has contributed
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57 considerably to their success. In addition, the simultaneous implementation of
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6 different unit process models in several software packages resulted in some
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8 unexpected “by-products”: it has for example led to a set of validated models (e.g.
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10 [32]) and modeling tools (e.g. [33]) which have become a standard in the
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12 wastewater treatment modeling community.
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17 With these successful experiences in mind, we suggest to start a similar modeling
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19 benchmark initiative for pharmaceutical manufacturing systems – biotech-based
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21 as well as chemical-based – similar to the above-mentioned Tennessee-Eastman
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23 challenge [22] and the wastewater treatment benchmark plants [30, 31]. The prime
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25 purpose of this pharmaceutical manufacturing system benchmark initiative would
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27 be to promote and facilitate the development and implementation of innovative
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29 PAT applications as well as the training of students at universities and staff
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31 involved in pharmaceutical production facilities. Specifically for the training of
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33 operators and engineers, one could for example use model simulations to illustrate
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35 the interaction between operating conditions in a crystallization unit (e.g.
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37 temperature, etc) and final product properties. Another example could be to
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39 demonstrate how the operating mode of a reaction unit (e.g. batch versus
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41 continuous process operation) influences the product yield as well as the choice of
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43 control and monitoring algorithms.
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52 Such a modeling benchmark initiative would require setting up an international
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54 expert panel. The expert panel should first agree on a number of suitable case-
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56 studies, for example one fermentation-based case-study and one based on organic
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6 synthesis. The expert panel should then reach a consensus on the dynamic models
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8 to be used for the unit processes, the sensors and the actuators that are part of
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10 these case studies. These models would then have to be implemented and
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12 validated – ideally in different software packages – and following validation the
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14 models could then be made publicly available for download. These publicly
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16 available validated models would be similar for example to the model repositories
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18 in the systems biology field (e.g. <http://www.biomodels.net/>). The model
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20 implementation and validation would undoubtedly be one of the most time-
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22 consuming parts of the simulation benchmark model development. Finally, the
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24 expert panel should decide on a number of reference simulation scenarios for each
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26 case study, such that the users of the simulation benchmark models have a
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28 reference point with respect to the process performance that is to be obtained. In
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30 fact, it could even be such that a competition could be organized where students at
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32 different universities could compete, for example to obtain the best process
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34 performance assuming that a limited number of on-line measurements can be
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36 introduced on the process.
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46 Note that the definition of the case studies should be such that they allow a
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48 realistic simulation of manufacturing systems for pharmaceuticals, which includes
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50 definition of unit operations, inputs and outputs, set points, sensors and actuators,
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52 recycle flows and process constraints, as well as a suitable set of performance
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54 criteria. The latter are a necessity to allow fair comparison of different operating
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56 scenarios and/or control algorithms in simulation. However, realism in the case
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6 studies should of course not mean that industry is required to give confidential
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8 product and process knowledge away when defining the case-studies. The case-
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10 studies could be defined on the basis of pharmaceuticals production processes of
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12 products that are no longer protected by a patent.
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18 The idea of having publicly available simulation tools is of course not new in the
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20 biotechnology field. There is for example a simulation model of β -galactosidase
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22 production by *Escherichia coli* available for download
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24 (<http://www.biotech.kth.se/bioprocess/enfors/index.html>). This model includes a
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26 detailed simulation procedure, and is intended for teaching about optimization of
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28 fed-batch fermentation and protein extraction in an aqueous two-phase system.
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30 However, what would be novel – in our opinion – is that we propose to use such
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32 case studies explicitly in a PAT context to test and compare different monitoring
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34 and control systems for innovative pharmaceutical manufacturing.
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42 If the research community in the pharmaceutical field reacts positively towards
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44 the ideas outlined in this paper, the only remaining question would be how to get
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46 started with the proposed benchmarking initiative. Which research groups are
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48 interested in developing and implementing mechanistic models that provide a
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50 sufficiently realistic simulation of a pharmaceutical production process? In
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52 Europe, for example, the European Federation of Biotechnology (EFB), and more
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54 specifically the EFB Section on Biochemical Engineering Science (ESBES),
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56 could be the driving force in launching such an initiative. Another alternative
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6 would be to apply for funding at the European level for setting up a network
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8 activity. Likewise similar organizations in the USA and Asia could also assist in
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10 developing the methodology and the tools. We would however strongly encourage
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12 industry (pharmaceutical production and software vendors) to be involved also,
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14 i.e. it should not become a purely academic exercise.
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20 Assuming that a benchmarking initiative for pharmaceutical manufacturing
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22 systems could be initiated, every participant in the initiative would clearly benefit.
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24 For academia, students confronted with realistic simulation-based case studies
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26 would receive high-quality training into monitoring and control problems that are
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28 highly relevant for industry. Pharmaceutical production companies could employ
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30 graduated students with improved PAT-related skills, especially with respect to
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32 increased understanding of process dynamics and process monitoring/control. The
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34 benefit for the software vendors is that such a collaboration would create a forum
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36 where modeling case studies are validated such that they could be used to
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38 demonstrate simulation packages to a potential customer. For the research
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40 community, the participation of software vendors and pharmaceutical companies
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42 would have the additional benefit of promoting the dissemination of the work
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44 done in the framework of such a benchmarking initiative.
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53 **4. Conclusions and perspectives**

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55 Process Analytical Technology has changed pharmaceutical production, but has
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57 also created a need for the development of new skills for the scientists, engineers
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6 and managers involved in pharmaceutical manufacturing process development,
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8 for example within understanding, design, tuning and implementation of control
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10 algorithms. Based on experiences in other engineering fields, we conclude that
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12 mechanistic modeling applied to a number of relevant case studies, and supported
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14 by experts from academia and industry, could form the foundation for a
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16 benchmark modeling effort of pharmaceutical manufacturing systems. The result
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18 of such a benchmarking effort – documented and validated models of selected
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20 case-studies, endorsed by experts and publicly available for download – could
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22 significantly contribute to educating students and professionals with skills that are
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24 essential for implementing the Process Analytical Technology **guidance** in
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26 practice.
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34 **Conflict of interest statement**

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36 The authors have declared no conflict of interest.
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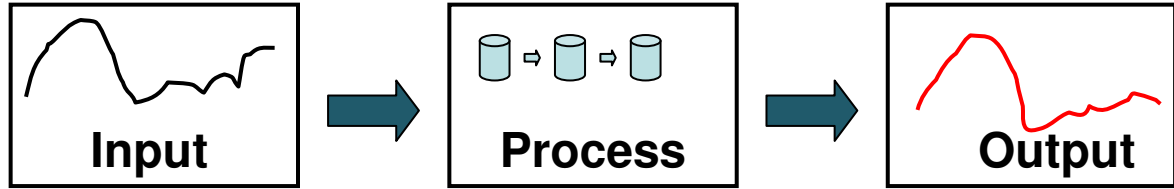
Figure Legends

Figure 1. Comparison between traditional 'fixed process' pharmaceutical production (upper part of figure) and the PAT-based approach leading to a robust and adjustable process (lower part of figure). (M = measurement; C = controller; FB = feedback; FF = feedforward)

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Fixed process



Robust and adjustable process

