Extended abstract: Model-based computer-aided framework for design of process monitoring and analysis systems

Summary

In chemicals based product manufacturing, as in pharmaceutical, food and agrochemical industries, a well-designed process monitoring and analysis system (PAT system) plays a very important role. These PAT systems ensure that the chemicals based product is manufactured with the specified end-product qualities. Systematic computer-aided methods and tools provide the means to design the necessary process monitoring and analysis system and/or to validate any existing process monitoring and analysis system. In this work a generic model and data (knowledge) based computer-aided framework for including the methods and tools through which a process monitoring and analysis system for product quality control can be designed, analyzed and/or validated, has been developed. Corresponding software has been developed as well.

Two important supporting tools developed as part of the framework are a knowledge base and a model library. The knowledge base provides the necessary information/data during the design of the process monitoring and analysis system while the model library generates additional or missing data needed for design and analysis. The developed design methodology consists of nine hierarchical steps for design of a process monitoring and analysis system. These steps cover problem definition, analysis (process, sensitivity, interdependency), design and verification of the PAT system. The developed framework and methodology has been implemented into a software (ICAS-PAT) that has made the use of the PAT design procedure easy, consistent and fast. Some additional features have also been added to the ICAS-PAT software that has made it more useful and user-friendly. For example, the options to open and analyze stored solved examples, to find the different applications of any monitoring tools, to search the knowledge/data stored in the knowledge base, to draw the open and closed-loop process flow diagrams and to build reports in MS word for documenting the design of a process monitoring and analysis system. To demonstrate the wide applicability of the developed framework, methodology and corresponding software (ICAS-PAT) in pharmaceutical, biochemical and food production processes three case studies involving a tablet manufacturing process, a fermentation process and a cheese manufacturing process have been developed.

1. Introduction

Today a significant opportunity exists to improve product quality and to optimize the production process through the implementation of innovative solutions for on-line monitoring, analysis and system control. The U.S. food and drug administration have taken an initiative (FDA/CDER, 2005) for application of process analytical technology (PAT) in the manufacturing industries. Application of PAT systems (FDA/CDER, 2005) – also called process monitoring and analysis systems – in manufacturing paves the way for continuous process and product improvements through improved process supervision based on knowledge-based data analysis, 'Quality by design' concepts, and through feedback control (Gnoth et al., 2007). The primary goal of PAT is to better understand the manufacturing process, and to use that knowledge on-line to achieve better control of the process, and as a consequence of applying control, also achieve a more consistent product quality. PAT is therefore defined as a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality (FDA, 2004; FDA/CDER, 2005).

The production methods for most industries, for instance, the pharmaceutical industry have changed considerably during the past years. Growing emphasis has been given to real-time adjustment of process operations in order to consistently produce products with predefined quality attributes. Extensive off-line laboratory testing of product quality should, for example, be reduced considerably when introducing PAT by the implementation of the real-time release concept, where product quality is assessed in real-time based on on-line measurement of critical process variables. It can thus be concluded that significant opportunities exist nowadays for improving the efficiency of manufacturing processes and quality assurance systems in the chemical, biochemical and pharmaceutical industries through introduction of novel and innovative techniques for product and process development, process control, and process analytical chemistry.

Originally, the application of PAT was mainly focused towards the pharmaceutical industry. However, PAT applications are rapidly spreading towards other regulated industries also, for example, the food industry. The introduction of PAT can generally be considered as a landmark in the acceptance of process systems engineering tools in modern pharmaceutical manufacturing and quality assurance of food and drug production processes. In terms of process monitoring, the use of PAT represents a paradigm shift in the sense that sophisticated quality control moves from laboratory-based to process-based (i.e., in-process) approaches (Lopes et al., 2004). The availability of real time monitoring tools and its efficient utilization are two prerequisites to shift from the traditional lab-centric production approach to the PAT inspired approach. In the last decade, emphasis has been given towards the development of efficient innovative on-line monitoring tools. However, less attention has been paid towards the development of systematic methods and tools for efficient utilization of the existing measurement methods and accompanying control systems to improve the production process such that the end product quality can be achieved consistently with minimum complexity and optimum cost.

2. Objective of the project/problem addressed

The objective of this PhD project is to develop a systematic model-based computer-aided framework including the methods and tools through which a process monitoring and analysis system (PAT system) for product quality control can be designed, analyzed and/or validated. The *design of a process monitoring and analysis system* requires a hierarchical step-wise procedure involving the selection of critical process variables, followed by the selection and placement of suitable monitoring and analysis equipments, and finally, the coupling of the monitoring and analysis tools to a control system to ensure that the selected critical process variables can be controlled adequately.

3. Current state of the art: highlighting the gaps that have been filled through this work

The review of previous work done in the area of process monitoring and analysis (PAT) shows some gaps in the current state of the art, when already existing approaches are confronted with the problem of designing a PAT system. These gaps have been filled through this PhD work, and are summarized as follows:

- Most of the available literatures regarding SND (sensor network design) mainly focus on the minimization of the number of sensors in the process under constraints such as high reliability, precision, redundancy and low cost and variability of process operational conditions and product quality. The minimum number of sensors was achieved by assuming that the remaining variables can be predicted accurately by process models. However, the process models are often not sufficiently reliable for prediction. Much less attention has been given to the problem of sensor network design for placement of appropriate sensors at appropriate production steps for monitoring and control of critical process variables and thereby assuring end-product quality. Certainly, the monitoring and analysis system (PAT system) of any process need to be designed carefully to obtain the end product quality consistently. However, the complexity involved in the design and maintenance of PAT systems make its implementation a difficult, time consuming and expensive task. Therefore, there is an obvious need for systematic computer-aided methods and tools through which a PAT system can be designed and implemented easily, faster and economically.

- Proper selection of measurement methods and tools (sensors) is one of the important aspects for design and implementation of PAT systems. Attempts that have been made for sensor selection have a clear focus on the selection of sensors based on sensor specifications. Process knowledge needed to integrate the sensor selection within the design of the process monitoring and analysis system, however, is typically not taken into consideration. Therefore, a well-designed knowledge based system (KBS) consisting of the process knowledge as well as knowledge on measurement methods and tools is needed to support the selection of the appropriate process monitoring and analysis techniques/tools.
- One of the key issues in handling data/knowledge is how to develop and represent the knowledge base so that it can be used efficiently to provide the problem solutions. Ontologies have been considered to provide the means for systematic representation of the knowledge base. Knowledge based systems have been used extensively to solve general complex problems. Much less attention, however, has been paid to the design and development of a knowledge based system that can be applied systematically for selection of appropriate process monitoring and analysis techniques/tools. The development of such a knowledge system was one of the objectives of this work. An extensive literature and industrial survey is necessary to build the required knowledge base.
- One of the challenges for design of PAT systems is to generate the necessary data. Simulation with appropriate process operational models provides the means to generate the required data. However, much less attention has been paid to development of a systematic model library integrated with a simulation tool through which the required data for PAT system design can be generated. A generic and flexible model library consisting of the mathematical models for different types of unit processes, sensors and controllers is therefore needed, to utilize the developed models systematically and efficiently for design of process monitoring and analysis systems. A suitable simulation tool also needs to be integrated with the model library to solve the mathematical models.

4. Main results

In this work a model-based computer-aided framework has been developed together with the methods and tools through which the design of monitoring and analysis systems for product quality control can be generated, analyzed and/or validated.

4.1. Design framework and methodology (Singh et al., 2009a): The first main result of this work is the systematic framework and methodology for design of process monitoring and analysis systems. The overview of the proposed framework for design of process monitoring and analysis systems is shown in Figure1. The starting point for the design methodology is the problem definition in terms of process specifications and product quality specifications that can be provided by the manufacturer or PAT system designer. These specifications will be used as the input to the developed system for design of process monitoring and analysis systems. A model library and a knowledge base act as supporting tools for the design of the process monitoring and analysis systems. As shown in Figure1, the developed design algorithm relates the product and process specifications to the available supporting tools, and subsequently generates a design proposal for the monitoring and analysis system. If the obtained PAT system satisfies the requirements then it is selected as the designed monitoring and analysis system. A well-designed monitoring and analysis system can subsequently be implemented and used to obtain the predefined product quality consistently and viably.

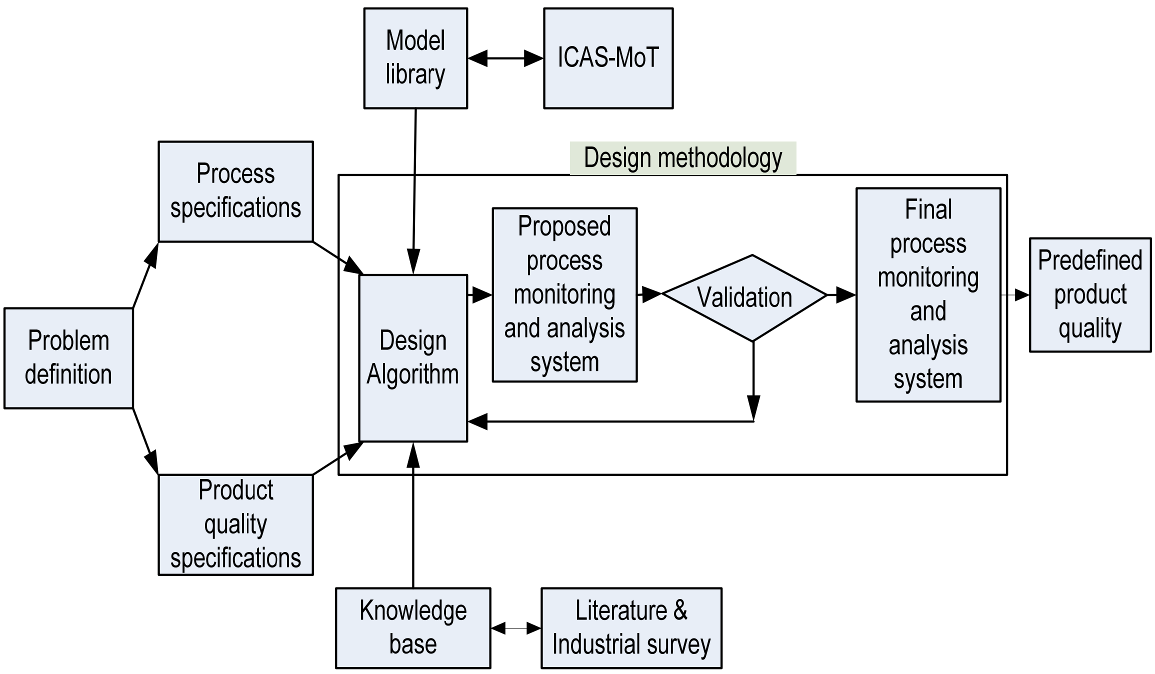

Figure 1: Schematic representation of the design framework

The overview of the design methodology is shown in Figure 2. The design methodology consists of nine hierarchical steps. The first step (product property specifications) is concerned with specifying the product properties that are desired (to be achieved) in the considered production process. The necessary process related information, such as, the raw materials, their composition and the equipments used in the production process are provided through step 2 (process specifications). The information provided through these two steps of the design methodology act as input data for the design problem. On the basis of the input data and with the consultation of the knowledge base, step 3 (process analysis) of the methodology generates a list of process points (in general, process equipments are considered as the process points) and a list of the corresponding process variables. The outcome of this step becomes the basis for subsequent analysis steps. The critical process points where monitoring and analysis equipments need to be placed and the corresponding critical process variables that need to be monitored and controlled in order to achieve the desired end product quality are then identified through step 4 (sensitivity analysis). The identification of the appropriate actuators and the selection of suitable on-line monitoring techniques and tools are necessary to successfully implement the control system in order to control the critical process variables obtained in step 4. The appropriate actuators for each selected critical process variable are identified through step 5 (interdependency analysis) while step 6 (performance analysis of monitoring tools) generates the list of the feasible measurement methods and tools for selected critical process variables. On the basis of the outcomes of steps 4 - 6, a process monitoring and analysis system is suggested in step 7. The proposed monitoring and analysis system consists of a list of critical process points, corresponding critical process variables, actuators, monitoring techniques and monitoring tools. The proposed process monitoring and analysis system is validated in step 8 and finally step 9 identifies a final process monitoring and analysis system.

The developed framework and the corresponding methodology are generic: its systematic approach to the design of a PAT system is complimentary to traditional process design, and should thus have a broad application range in chemical, biochemical, food production and pharmaceutical processes. The developed framework and methodology provide a clear opportunity to the manufacturing industry for moving from a lab-centric fixed type of process to a robust well-controlled and flexible PAT based process. This move is highly desirable in most of the regulated industries, for instance, the pharmaceutical industry, in an attempt to introduce more efficient production methods. The developed, systematic computer-aided methods and tools make the PAT system design procedure structured, simple, reliable and fast, that is, the design framework can *manage the complexity* of the PAT system design in a more efficient manner. Each step of the design methodology is quite clear in terms of calculations and generic in terms of application range. This makes the implementation of the methodology into a software quite easy.

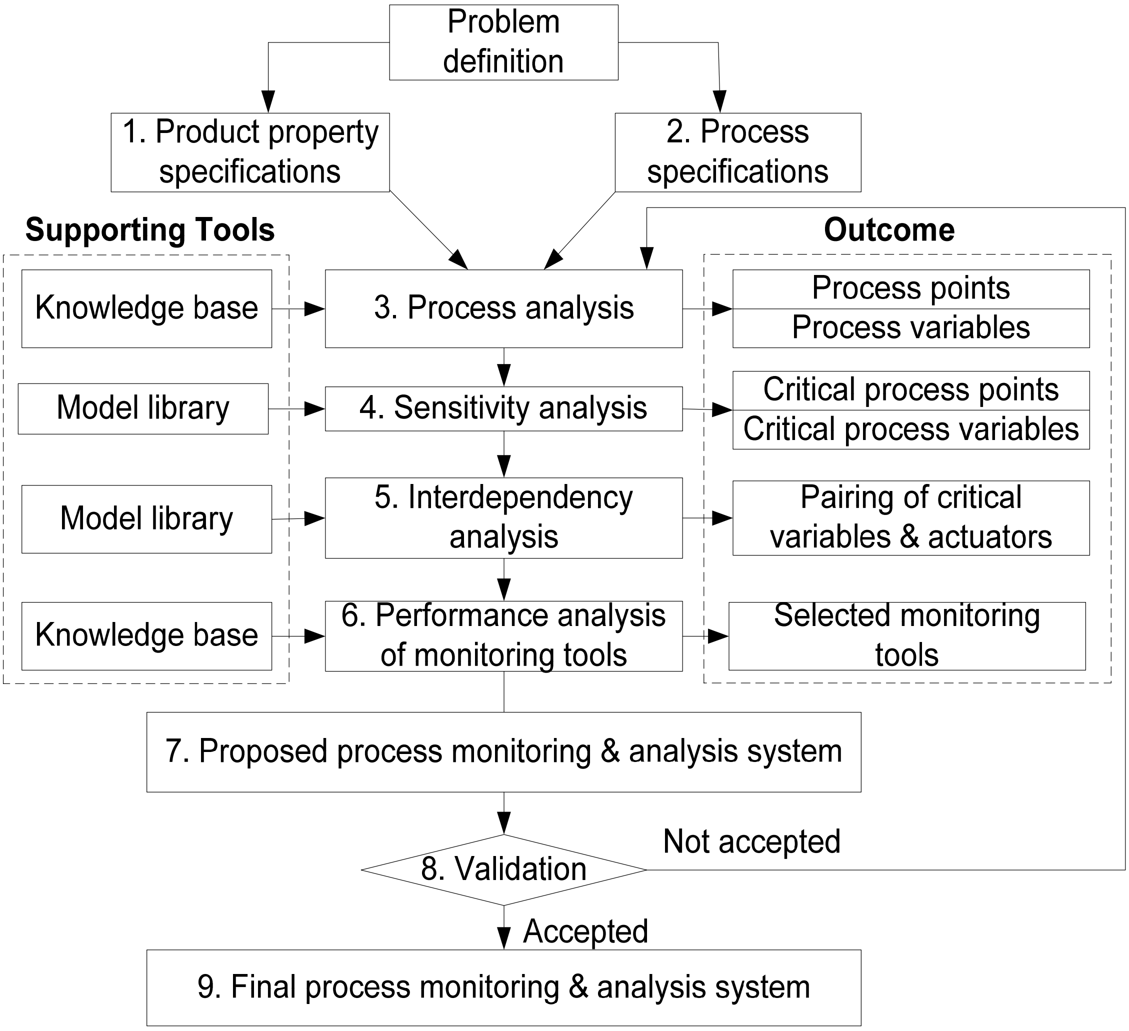

Figure 2: Overview of the design methodology, including the use of the supporting tools and the outcome of the individual analysis steps

4.2. Knowledge base on process monitoring and analysis systems: The second main result of this work is a knowledge base on process monitoring and analysis systems that has been developed to provides the necessary information/data during the design of the process monitoring and analysis system. The knowledge base consists of two sections. The first section stores the necessary process knowledge (type of processes, corresponding process points, process variables and actuators) while the second section stores the knowledge/data on measurement methods and tools (type of variables, available monitoring techniques and tools with specifications such as accuracy, precision, operating range, response time, resolution, cost etc.). An ontology has been designed for knowledge representation and management. The developed knowledge base has a dual feature. On the one hand, it facilitates the selection of proper monitoring and analysis tools for a given application or process. On the other hand, it also permits the identification of potential applications for a given monitoring technique or tool. An efficient inference system based on forward as well as reverse search procedures has been developed to retrieve the data/information stored in the knowledge base. The developed knowledge base covers a wide range of industrial processes, such as, fermentation, pharmaceutical tablet manufacturing, insulin production, cheese manufacturing, butter manufacturing, chemical reaction and a crystallization process. The structure of the knowledge base is generic and can be easily extended to include new processes as well as to include new objects (e. g., to add a newly developed sensor) within the existing processes. Moreover, the structure of the knowledge base can be adopted to build similar knowledge based systems for other applications. In particular, the developed knowledge base is by itself a useful tool because it provides the manufacturing industries an easily accessible and systematic option to compare the salient features of available sensors in order to select the best one that satisfies their requirements.

4.2. Model library: The third main result of this work is a model library that has been developed to generates additional or missing data needed for design and analysis of process monitoring and analysis systems. The model library contains a set of mathematical models for different types of unit processes, sensors and controllers. The structure of the model library is generic and can be easily extended to include new process models. A systematic and simple model development procedure has been suggested that when followed, leads easily to the development of new models for inclusion in the model library. Each process model is analyzed systematically to classify the equations (differential, explicit algebraic, implicit algebraic), to identify the variables that need to be solved (dependent, explicit, implicit) and the variables that need to be specified (constants, fixed by problem, fixed by system) and to build the incidence matrix (variable-equation relationships). This systematic procedure makes the application and solution of the model equations through a computer-aided system quite simple and straightforward. Furthermore, this systematic representation of the model equations has made the process models generic and applicable to a wide range of problems and systems. Therefore, the model library is considered a useful tool by itself that can be easily employed to study the process behavior for simple as well as complex systems.

4.3. Software (ICAS-PAT) (Singh et al., 2009b): The fourth main result of this work is that the developed framework and methodology has been implemented into a user-friendly software (ICAS-PAT) that made the use of the PAT design procedure easy, consistent and fast. As shown in the Figure 3 the general supporting tools (protected general knowledge base and model library) as well as the user specific supporting tools (specific knowledge base and model library developed by the user) are integrated within a general user interface. The system has built-in flexibility to either use the general supporting tools or the user specific supporting tools. This feature makes the software more generic and applicable for those industries where the models and data are to be kept confidential. The user specific supporting tools can be developed, extended and managed according to the user's needs while administrator rights are needed to edit/replace the general supporting tools. In either case a problem specific supporting tool (consisting of the problem specific knowledge and models) is generated and used for design of a specific PAT system. The use of problem specific knowledge/data and models reduces the data retrieval time since only a limited part of the knowledge base needs to be searched, and therefore the final PAT system is designed faster. As shown in Figure, the starting point for new problems is to provide the problem specifications, followed by the creation of problem specific supporting tools and then to design the PAT system according to the developed methodology (shown in Figure 2). For already existing case specific problems (saved earlier) the design methodology is used directly to generate new solutions, or, earlier solved case studies may be opened and consulted.

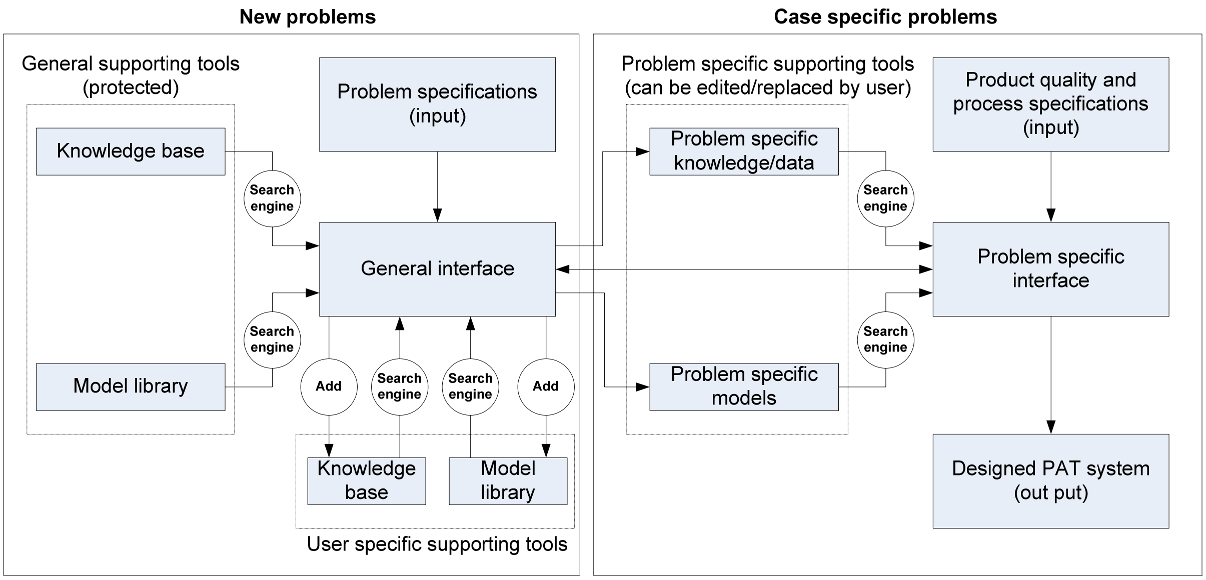

Figure 3: Implementation of the framework in a software

The objectives for developing the software have been to provide the user a means to quickly evaluate and/or design PAT systems and thereby, contribute to bringing a product to the market quickly, safely and at low cost. Some additional features have also been added to the ICAS-PAT software that has made the software more useful and user-friendly. These additional features of ICAS-PAT provide the options to open and analyze stored solved examples, to find the different applications of any monitoring tools, to search the knowledge/data stored in the knowledge base, to draw the open-loop as well as closed-loop process flow diagrams and to build reports in MS word documenting the design of a process monitoring and analysis system. Thus ICAS-PAT has a potentially wide range of applications in chemical, biochemical, food and pharmaceutical industries.

4.4. Case studies: Case studies have been developed to demonstrate the wide applicability of the developed framework, methodology and corresponding software (ICAS-PAT) in pharmaceutical, biochemical and food production processes. A tablet manufacturing, a fermentation and a cheese manufacturing process have been considered as illustrative examples.

5. Key innovations/achievements

- Generic framework and methodology for design of process monitoring and analysis systems (PAT systems)
- Software (ICAS-PAT) for design of PAT systems
- Dual natured "ontological knowledge based system"
- Model library (fermentation, tablet manufacturing, cheese manufacturing etc.)

6. Conclusions

In this work a systematic model-based computer-aided framework has been developed together with the methods and tools through which the design of monitoring and analysis systems for product quality control can be generated, analyzed and/or validated. The applications of the developed framework, methodology and corresponding software (ICAS-PAT) have been demonstrated through a tablet manufacturing, a fermentation and cheese manufacturing process. ICAS-PAT has a wide application range in chemical, biochemical, food and pharmaceutical processes.

7. References

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Refereed publications (International peer reviewed journal articles)

1. **Singh, R.,** Gernaey, K. V., Gani, R., (2009). Model-based computer-aided framework for design of process monitoring and analysis systems. Computers & Chemical Engineering, 33, 22-42
2. **Singh, R.,** Gernaey, K. V., Gani, R., (2009). ICAS-PAT: A Software for Design, Analysis & Validation of PAT Systems. Computers & Chemical Engineering, doi:10.1016/j.compchemeng.2009.06.021