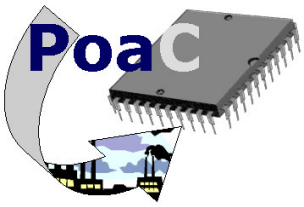

Process on a Chip

2007
Call for full proposals

1. Introduction

The quest for *smaller, faster, better* allowed computers with the dimensions of a living room to shrink to a size that fits into a cell phone, which itself is only slightly larger than a match box. Notebook computers, portable medical systems and airbag sensors are other examples of the enormous impact of miniaturisation on today's society.

The incredible power of miniaturisation is not limited to electronics. Chemical synthesis performed on a chip will allow for faster and more selective reactions, thereby reducing waste and eliminating expensive separation steps. If a complex chemical reaction can be successfully performed on a single chip, industrial scaling up might become relatively easy, by placing thousands of these chips in parallel. Researchers around the world dream of such miniaturised, clean processes producing chemicals, drugs and nutrients. Eventually these portable modular factories with capacities scalable from milligrams to tons will replace today's large-scale industrial plants.

The first step towards realisation of this dream was the application of micro fluidics (10 µm and up) technology in chemical systems concepts. Smaller volumes, higher flow rates and massive parallel designs brought the "Lab-on-a-Chip" within commercial reach. Nowadays, protein biochip sensors and desktop-sized systems for high throughput nanolitre-scale screening of biological samples are already widely available. These first applications indicate the viability of the "Process on a Chip (PoaC)" concept.

The "Analysis Lab on a Chip" described above is the starting point for the ambition set out in the PoaC research programme. A complete process on a chip should offer integrated circuits of micro channels, reaction junctions and finally characterization and work-up steps. One could imagine that on a single chip potential pharmaceuticals may be synthesised, analysed and screened on a nanolitre scale. In this manner several conventional development steps can be bypassed: only the most effective compounds need to be prepared in higher quantities, and scaling up has to be performed only once. This will substantially shorten the time to market of new products.

The Process on a Chip programme is now open for applications of researchers in the Netherlands. In this brochure the scope and aims of the PoaC programme are outlined and the conditions for research full proposals within the framework of the PoaC programme are set. Furthermore, a time schedule for the funding process is provided. Documents pertaining to this PoaC 2007 call for full proposals are available for download on the PoaC website: www.nwo.nl/acts/poac.

2. Scientific Background

The basic idea of PoaC is to construct an integrated circuit of microchannels, microreactors, characterization and work-up elements. A total production process is then assembled onto a microprocessor, which allows computer-assisted control of operation of the different elements. A process on a chip has several advantages when compared to traditional production procedures.

- By performing reactions in micrometer channels, *very efficient* mass and heat exchange processes will take place, due to miniaturisation. Reactions can be performed in a fraction of the traditional reaction times. Side reactions will be suppressed, which will result in an increase in *selectivity*.
- The high levels of control, as well as the application of small reaction volumes will result in a *much safer* use of inherently toxic or explosive compounds.
- Because a multitude of reaction channels and connections can be assembled on an integrated circuit, a change in reaction conditions can be applied very quickly. This results in a very *flexible* production process.
- Besides the flexibility in reaction conditions, PoaC is also very well suited for performing *combinatorial chemistry*, via parallel synthetic procedures.
- An increase in production volume from synthesis in a research environment to production scale can be carried out with PoaC by a *scaling out* procedure. Using an array of parallel operating chips, there is no need for extensive pilot plant studies. An increase in production volume is easily achieved by an increase in number of microreactors.
- The high level of dimensional control on (sub)micron scale allows very well defined production of micrometer-sized morphologies, as applied in *e.g.* food textures.

The multidisciplinary PoaC programme combines knowledge on physical processes on a nanoscale, nanofluidics and process design with synthesis and biotechnology. A scientific relationship exists with the ACTS programmes IBOS and B-Basic (see www.nwo.nl/acts for more information).

3. Programme Objectives

The Process on a Chip programme should lead to the following results within a period of approximately eight years:

- a large number of generic building blocks for chips (*e.g.* micro reactors, mechanical components, coatings, catalysts and measuring units) will be developed and integrated into larger working devices;
- novel synthetic routes, processing methods and analytical techniques will be designed and applied, leading to extensive expertise in the field of microreactor technology;
- companies will implement the results of the PoaC programme in set-ups ranging from test facilities to commercially viable production process;
- new technological SME's will result, possibly as direct *spin off* from university research, that will enter the chip component market and/or (chemical) product markets;
- circa 25 PhD students have been trained. Their interdisciplinary education, mutual contacts and interaction with the Dutch (chemical) industry will assure a strong basis for future development and application of PoaC technology in the Netherlands;
- participating research groups have strengthened their position. They will receive new impulses from neighbouring fields and from the participating companies. A strong cluster will be developed on the boundary between nanotechnology, micro system technology and bio-organic chemistry.

4. Research Themes

This 2007 call for full proposals focuses on three research themes, which are described briefly below.

A. Basic Expertise

The goal of this cluster is the development of fundamental and generic concepts for processes on a chip.

Within the research theme basic expertise new technologies and concepts are developed that allow a more efficient use of microreactor technology. This includes

i) the design and production of microreactor modules and the development of new scaling out principles. In addition, the collaboration with industrial partners for the construction of generic microreactor systems is desirable. This will eventually allow easy comparison of results between different research groups active within PoaC and will make a modular approach possible.

ii) better understanding about manipulation of fluidics in microchannels. Special attention should be paid to biphasic systems and the application of organic solvents. In addition, a thorough fundamental understanding of the principles underlying chemical processes that are performed under flow conditions in a confined environment needs to be obtained.

iii) Functionalized microchannels. To increase the scope of PoaC, microchannel coatings and surface modifications should be developed that for example introduce specific catalytic activity and allow control over fluidics

B. Analysis on a Chip

It is the aim of this cluster to develop methods for on-line monitoring of (syntheses) processes on a chip.

The Analysis on a Chip cluster does not want to compete with the already mature field of µ-TAS. Analysis techniques should be developed that allow on-line monitoring of the progress of synthetic processes. Information that is generated can be used as feedback to optimize reaction conditions. On line characterization of conversion, chemical structure, enantiomeric excess are all desirable and require both highly sensitive and reliable methods. Examples are miniaturised IR and fluorescence spectroscopy, NMR and mass spectrometry. Furthermore, combined separation and analysis modules are required for determining product purity.

C. Synthesis on a Chip

This cluster intends to stimulate the development of reactions on chips.

The cluster synthesis on a chip will focus on several aspects. First the possibilities of using microreactor technology for reaction optimization can be evaluated. The benefits of miniaturisation will carefully be evaluated, and the possibility of translating reaction parameters to batch scale processes will be examined.

As a second topic new synthetic procedures in microreactor technology will be investigated. This comprises reactions that are normally not possible in batch scale reactions (because e.g. of inherent safety issues) or that require highly controlled conditions with respect to temperature and diffusion rates. The complexity of the system will be increased by the introduction of catalysed reactions, or even cascade reactions. Another topic will deal with parallel synthetic approaches on a chip, which will lead to methods for combinatorial chemistry.
Mixing and separation are crucial elements of many production processes. Miniaturisation of mixing and separation technology can create huge benefits by obtaining higher levels of control.

Some examples (not limiting) are: fluorous / organic phase reactions; cascade reactions; combinatorial reactions; biotechnology on a chip; nano structures for storage and (controlled) release of chemicals; nano membranes of separation purposes.

Innovation projects
Projects within the PoaC programme should be innovation driven. The themes within PoaC are complex and far reaching, and have therefore frequently a long time horizon. Still, also shorter-term projects (1-2 years), which are focused on development of inventions or innovative techniques towards implementation, can fit very well in the PoaC programme. These short-term innovation projects can be based on promising results from earlier research (either in PoaC or other research programmes) and are given the chance to be further worked out in, for example, *Innovation Labs*. Innovation projects should be carried out in close collaboration with the industrial partners or SME's that are participating in PoaC. Note that the pre-competitive nature of the PoaC programme should be taken into account and that only academic institutes and GTI's can apply for support from PoaC.

5. Coherence and interaction

The expertise needed for the PoaC programme covers a broad range of disciplines. Multidisciplinary co-operation adds value to adequately address the challenges of this programme. Applicants are encouraged to seek collaboration with other research groups, within the same university or outside. To ensure coherence, applicants are specifically requested to link up their research proposals with the currently running projects, industrial interests, device development of the enabler platform, or a combination thereof.

Running projects
A description of the running projects from the first call of the PoaC programme can be found on www.nwo.nl/acts/poac (menu item "projects").

Industrial interests
To ensure a direct link with industry and to provide a pathway for innovation, the applicants are invited to indicate which (Dutch) companies may be interested in the proposed research (and to what extent they have been contacted). The companies that are currently involved in the PoaC programme have indicated the following interests:

A. *Basic Expertise*
In collaboration with industrial partners, the construction of a generic micro reactor system and peripherals such as pumps, sensors, actuators and software which can be standardised should be investigated.

B. *Analysis on a Chip*
The on-line analysis techniques should be developed and should be made available as generic building blocks. The techniques will include building blocks for all typical process analysis, including spectrometric (*e.g.* NMR, MS, (N)IR, Raman and UV), physicochemical parameters (*e.g.* temperature, viscosity, pressure) and chemical analysis (electrophoresis, chromatography and titration). Through the combination of several process analytics into a sensor module and including process analysis demands *a priori* in the reactor chip design, optimal process sensing can de accomplished. This will enable comprehensive analysis, and provide detailed process knowledge of reaction mechanisms and synthetic routes. These on-line analysis techniques will allow real-time measurement and allow closed-loop control of critical reaction parameters.

C. *Synthesis on a chip*
Synthesis on a chip should start with investigating optimal reaction conditions of (simple) reactions in a micro reactor environment. In order to accomplish this, micro reactor systems should be able to perform (automated) process development with the aid of statistical methods such as factorial designs and/or multivariate data analysis. The complexity of the system will be increased by the introduction of catalyzed reactions and

high pressure reactions. Ultimately, a micro reactor system should be able to produce large quantities (100-1000 g) of a chemical compound. With respect to purification of reaction mixtures, extractions are commonly used in organic synthesis and continuous flow extraction should be investigated. Since crystallizations are commonly used for purification or generation of a stable crystalline form, the use of micro reactors for crystallization should also be investigated.

Enabler platform
A unique feature of the PoaC programme is that the group of SME's have formed an enabler consortium. The platform aims at the organisation of communal interests of the PoaC programme with respect to realisation, use and development of hardware. In practice, the enabler platform provides (advice for) the development of specialised equipment that can directly be used by the researchers in the programme. This allows for a direct feedback from the "end users" to device development and, on the other hand, gives the researchers a head start with fully operational equipment. More information on the implementation plan of the platform can be found in the report "Uitvoeringsplan PoaC platform", which can be downloaded from the website www.nwo.nl/acts/poac (menu item "download").

6. Approach

Given the integrated approach, ACTS will stimulate the formation of discussion and knowledge exchange platforms for each research theme. Moreover, networking between the research themes will be stimulated via PoaC Work Conferences (closed setting), to be held yearly. On a project basis close interaction between university researchers and interested industrial partners will be actively brought about. Participants in the PoaC programme will be given the opportunity to communicate their results at open (inter)national conferences.

Besides the funding of excellent scientific research, the PoaC programme strives to serve as a national platform for research and related activities in the area of process on a chip. Ultimately this platform should provide an efficient academic and industrial research link to similar activities at an international level.

7. Organisation

In 2003, the NEW Foundation, established by the universities of Nijmegen, Enschede and Wageningen, received M€ 4 from the Ministry of Economic Affairs for the PoaC research programme. To ensure a truely national platform, recently the responsibilities for the complete PoaC programme have been handed over from the NEW Foundation to ACTS.

To oversee the PoaC programme activities, a PoaC Programme Committee has been appointed by the Executive Board of ACTS. The members of the PoaC Programme Committee are representatives from academia and industry. Presently, the composition of the PoaC Programme Committee is as follows:

Prof.dr.ir. J.C.M. (Jan) van Hest (RU Nijmegen)*, director PoaC*
Dr. ir. G.J. (Gerard) Kwant (DSM), *president programme committee*
Prof.dr.ir. R.M. (Remko) Boom (WUR)
Dr. J.G.E. (Han) Gardeniers (UT)
Dr. C.M.P. (Claudia) Kronenburg (Organon)
Ir. H. (Henk) Leeuwis (Lionix)
Dr. ir. R. (Remko) Achten (ACTS), *programme manager*

8. Procedure 2007 Call for proposals

General
The selection and evaluation of research proposals for the PoaC programme is performed in two steps. In the first stage pre-proposals were selected by the Executive Board of ACTS (using information provided by the PaoC PC). An advice of the PoaC Programme Committee was sent to the applicants by early November 2007.
In stage two the authors of the selected pre-proposals are invited to work out their pre-proposals into full proposals, using forms that will be available on the Internet in due time. The deadline for submission of (full) proposals is **9 January 2008 (23.59 h)**. A submitted full proposal that is not based on a pre-proposal submitted before or on 18 September 2007 (23.59 h) will not be taken in consideration. Submission must be done through the NWO Electronic Submission System (IRIS) available on www.iris.nwo.nl.

Each full proposal received is sent for evaluation according to the standard NWO criteria to at least two internationally renowned experts in the discipline(s) under consideration. This process takes about eight weeks. The applicants will get the opportunity to write a rebuttal to react on the comments of the referees (which will be given in anonymous form).

The PoaC Programme Committee takes into account the proposals, the advice on the pre-proposals, the referee reports and the applicants' rebuttals to evaluate the proposals according to the criteria given below and to rank the proposals. Using this information, the Executive Board of ACTS decides on the granting and funding of projects. It is anticipated that applicants are notified about this decision in spring 2008.

Criteria
The criteria on which the full proposals will be judged are:
- scientific quality;
- track record of the applicant(s);
- competence of the research group;
- timeline of the proposed research;
- aims/deliverables.

It is the responsibility of the PoaC Programme Committee to find a certain balance between the lines of research of the programme. This implies that the research effort perpetrated in this programme will not necessarily be equally divided between the proposed research themes mentioned in paragraph 5.

Conditions and budget
The budget for this call is approximately M€ 3. After screening of the pre-proposals, the PoaC Programme Committee may advise the applicant(s) to integrate his (their) pre-proposals into one full proposal.

Each pre-proposal may contain budget requests for the following categories:

- **Personnel**. The proposal may contain a budget request for two kinds of personnel: PhD students ("promovendi") and postdocs.

  Next to the *number* of requested personnel, indicate the *total* costs in k€ for each category of requested personnel. Part of the evaluation of the pre-proposal is an evaluation of the requested personnel. Personnel costs are based on the VSNU tariffs (as of 1 July 2007, including benchfee):
  - PhD-student (4 years): ~k€ 182
  - Postdoc (1 year): ~k€ 59
  - Postdoc (2 years): ~k€ 120

- **Consumables**. Expenses for consumables can be budgeted to a maximum of 12 k€ (including VAT ("BTW")) per year per researcher. Clean room costs should be included under this heading.

- **Equipment**. The budget for equipment, needed for carrying out the proposed research, has no formal limit. The requested equipment should be essential for and dedicated to the proposed research.

- **Other project expenses**. As in the standard NWO funding rules, costs of supervision, housing, depreciation of existing equipment, etc., are considered the financial contribution of the university or institute to the research project. These costs will not be remunerated.

Non referees
A list of non-referees (maximum of three names) can be sent to achten@nwo.nl on the same day the full proposal is submitted. Please provide a reason why the proposal preferably cannot be reviewed by this referee.

Audit and responsibility
Every applicant has financial responsibility for his/her own project(s). Concerning all previous points: only real expenses, made in direct connection to the PoaC programme, will be covered, and might be subjected to full checking procedures, to be effected after the execution and conclusion of the audit procedure of the institute carrying out the project.

Intellectual Property Rights
The general ACTS rules for Intellectual Property Rights apply for the PoaC programme.

9. Time Line 2007 Call

The deadline for submission of pre-proposals was 18 September 2007. The advice on submission of full proposals was sent to the candidates early November 2007.
The deadline for submission of the full proposals is **9 January 2008 (23.59 h)**. Please note that submission of a full proposal requires prior submission of a pre-proposal (see above).
The granting decision by the Executive Board of ACTS is foreseen in spring 2008.

10. Funding

Funding for the PoaC programme is provided by the Dutch Ministry of Economic Affairs, by NWO, and by several large companies and SME's. Presently involved in the programme are DSM, Organon, Aquamarijn, Bronkhorst, Lionix, Micronit, Nanomi and TNO. The total budget for PoaC is circa M€ 8 including contributions by the participating universities.

11. Information

For more information, please contact the PoaC programme manager:

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