



„A” Grant application form

1. Identification

Registration number	A/CZ0046/1/0008
Date and time of proposal submitting	09.05.2008 14:08

Full name of the proposal	Integrated tools and models for high-throughput and high-content analyses in food safety and quality - HCTFOOD				
Focus area of research	R&D in food safety and quality				
Starting date of the sub-project	01.11.2008	Closing date of the sub-project	30.04.2010	Duration of the sub-project	18
Value of grant asked	111118	Total budget of the sub-project	127458	Ratio of the grant in %	87.18

Legal name of the applicant	Jihočeská univerzita v Českých Budějovicích		
Abbreviation used	IPB		
Address of applicant	Branišovská 31, 370 05 České Budějovice Czech Republic		
Postal address if differs	Ústav fyzikální biologie Institute of Physical Biology Zámek 136 373 33 Nové Hradky Czech Republic		
Tax ID	CZ60076658		
Legal representative(s)	prof. PhDr. Václav Bůžek CSc., Doc. RNDr. Dalibor Štys CSc.		
Position(s)	rector, director of the Institute of Physical Biology		
Contact person	Doc. RNDr. Dalibor Štys CSc.		
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Eligibility
Justify eligibility of the applicant. You need to declare whether it is research institution or public/private institution of tertiary education. If it is business or not-profit organisation you shall describe its experiences in R&D (not older than three years)

The applicant is a public university - veřejná vysoká škola

2. Sub-project partnership

Partner A			
Legal name of the partner	Matforsk AS - Norwegian Food Research Institute		
Abbreviation used	MTF		
Address of applicant	Matforsk AS - Osloveien 1 - N-1430 Ås - Norway		
Postal address if differs			
Tax ID	NO885930522		
Legal representative(s)	Øyvind Fylling-Jensen, DVM, Ph.D.		
Position(s)	managing director		
Contact person	Ellen Mosleth Faergestad (Research Scientist)		
Phone	+4764970100	E-mail	ellen.mosleth.fargestad@matforsk.no
Skype		Web pages	www.matforsk.no
Eligibility			
Justify eligibility of partner in this application. You need to declare whether it is research institution or public/private institution of tertiary education. If it is business or not-profit organisation you shall describe its experiences in R&D (not older than three years)			
<p>Nofima Food /Matforsk is a research institution with 160 employees (63 research scientists), with extensive activities in microbiology, measurement technology and data modelling (see www.matforsk.no, www.specmod.org). It is an interdisciplinary research institute and has a number of relevant research projects going, also in health and food safety, with both national and international public and industrial funding. The institute has for 35 years held a high international position internationally in bio-chemometrics and high-throughput biospectroscopy, all the time with a high academic production and many years of experience in multivariate chemometrics. MTF has developed sophisticated integrative software for multi-block multivariate analysis.</p>			

Partner B			
Legal name of the partner	Centre for Integrative Genetics- CIGENE		
Abbreviation used	CIGENE		
Address of applicant	Norwegian U. of Life Sciences N-1432 Aas, Norway		
Postal address if differs			
Tax ID	NO969159570		
Legal representative(s)	Prof. Stig Omholt		
Position(s)	Director		
Contact person	prof. Harald Martens		
Phone	+4795075025	E-mail	harald.martens@cigene.no
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Eligibility			
Justify eligibility of partner in this application. You need to declare whether it is research institution or public/private institution of tertiary education. If it is business or not-profit organisation you shall describe its experiences in R&D (not older than three years)			
<p>CIGENE is a cross-disciplinary research organization within the Norwegian University of Life Sciences, with about 30 associated scientists from a number of fields in molecular biology, functional genomics, integrative genetics, bio-chemometrics and systems biology, and with a broad international network of cooperating laboratories (see www.cigene.no). CIGENE aims to contribute to a deep causal understanding of complex genetic characters in fish, plants and animals for scientific and commercial exploitation based on an integrative genetics approach. As a core facility under the Norwegian Functional Genomics Programme (FUGE), CIGENE is also responsible for providing a national service for detection, typing and interpretation of SNPs (Single Nucleotide Polymorphisms), and for systems-oriented computational biology</p>			

3. Aims

3.1. Main goal

Describe how the asked RF(CZ) grant can contribute to selected priority sector of EEA/Norway FM

Ensuring the safety and quality of food products, and developing innovative food products are two sides of the same problem. They critically

depend on the technical ability to detect and quantify biological, chemical and physical food components – to draw correct information from these data and to use this information to standardise and control the production process.

This project addresses the both technical and theoretical R&D aspects of the problem, in an integrative, holistic manner. Its goal is general and methodological, rather than focused on a concrete food product.

On the technical side, there is a steady influx of new measuring and data-modelling methods in food science and technology and other disciplines. This is in sharp contrast with the ability of primary food producers or food research institutes to constantly renew their laboratory capacity and detailed know-how.

The measurements must be rapid, relevant and reliable, cost-effective and covering sufficiently many aspects of the measured objects to allow high selectivity through multivariate calibration (i.e. Martens & Næs 1989: Multivariate Calibration. Wiley UK, Martens & Martens 2001: Multivariate Analysis of Quality. An Introduction. Wiley UK).

The present application concerns adaptation and refinement of some new, interdisciplinary techniques applicable for R&D on food safety and quality, as well as in other fields of the bio-sciences:

(1) Development of new data modelling methods and software tools:

The project partners have decided to refine our already advanced data modelling methods and implement them in software tools intended to help producers, control laboratories as well as research institutions to evaluate the food safety and quality,

(2) Innovative applications for food safety and quality:

The applications primarily concern metabolomic and spatio-temporal measurements of cells and cell cultures, e.g. for food-related micro-organisms (beneficial or non-beneficial), based on clear experiment designs, multivariate measurements and analysis by modern multivariate bio-chemometrics and process dynamic modelling.

(3) Common understanding. There is both complementary and partly overlapping expertise among the partners and adequate international courses have been established by IPB. The project shall contribute to achievement of higher quality of these courses, broader scope and improvement of the content. As part of the research, new insight in the experiment design theory and the biological object overall is obtained.

MTF and CIGENE have identified number of applications in the food research where the software tools can give novel ways of utilisation hardware to get more useful data in biological samples.

Two areas will be elaborated in particular - in part financed by this application – in conjunction with other, on-going projects, relevant for e.g. food safety and quality.

Contribution to basic research both in theory of multivariate stochastic systems and in theoretical systems biology is expected from the project.

3.2. Overall Objective

Describe the overall objective of submitted sub-project financed by the grant

Overall objective is to combine metabolomic and image data for objective analysis of food products for safety and quality. The research which partners performed so far, in particular over the last three years, identified some bottlenecks of contemporary technologies. There is a need for automated, robust and efficient analysis of metabolomic data and of microscopic and macroscopic images of e.g. microorganisms and other cell structures.

Better LC-MS metabolomic data: High-resolution LC-MS measurements are often affected by too much systematic and random noise. A robust analytical procedure was developed by IPB. The development of automated image analysis identified problems both on the side of data processing and of the hardware control.

Thus, integrated software tools will be developed combining the optimisation of analytical tools and hardware control tools:

Better image data: Improved information content from a high-grade RGB camera, to be used as a spatio-temporally resolved spectrophotometer. MTF has recently developed new methods, algorithms and software for model-based pre-processing of data, for cross-disciplinary interpretation of data and for analyzing proteomics images, and CIGENE has recently developed new methods, algorithms and software for self-modelling of non-linear dynamic systems based on multi-channel time series. These developments will be combined and further developed to meet the needs in this project.

These tools will then be applied to the following on-going research activities related to food safety and quality, as well as to modern integrative biology in general:

Improved spatiotemporal phenotyping of cells: Characterizing e.g. tissue culture or yeast cell morphology in various types of microscopy. The lab work will be done at IPB. Technically, the following elements will be used: IPB camera software; extension of MTF multi-image proteomics software, etc.

Improved metabolomics: Metabolic profiling is important with respect to sensory quality as well as food safety and health. Both IPB and MTF will seek to employ the IPB new 2-way software for improving LCMS metabolomics data in on-going food-health-quality projects. The LC-MS analysis tool and manual and semi-automatic tool for cell morphology analysis will be prepared.

All these activities are highly cross-disciplinary, involving low-level electronics and signal processing software, high-level multivariate pre-processing, calibration and multi-disciplinary statistical interpretation, and multivariate dynamic mathematics, as well as application-specific food science and technology, robotics and microbiological lab-work. Although we draw on many already on-going projects in which we are already involved, such cross-disciplinary activities are always difficult to fund explicitly. So the funding from the present application would greatly help our R&D work, in addition to stimulating our mutual research cooperation.

3.3. Rationale

Justify why you are asking for the RF(CZ) grant, why the sub-project application should be supported and how it relates to cooperation with EEA donor countries

The support is requested for a concrete project with broad application in food analysis. All three partners, Czech IPB and Norwegian MTF and CIGENE, are active in the field. MTF and CIGENE, where applicant partner prof. H.Martens works, have longer expertise and much broader scope in the field. IPB is a young institution and focuses on integrative mathematical description of object of interest. The three institutions complement each other both in terms of expertise and in terms of research attitude and approach. The proponents believe that the project shall substantiate (a) concrete results with concrete application within the framework of the proposal, (b) theoretical results of overall significance and (c) long term collaboration in basic as well as applied research for benefit of both countries.

IPB is running the science park associated with its campus where joint company-academic institution projects are being developed. This ensures immediate applications of developed products and procedures in company practice as well as best achievable communication between the academic and industrial sphere.

MTF is an interdisciplinary research institute and has a number of relevant research projects going, also in health and food safety, with both national and international public and industrial funding. The institute has for 35 years held a high international position internationally in bio-chemometrics and high-throughput biospectroscopy, all the time with a high academic production and many years of experience in

multivariate chemometrics. MTF has developed sophisticated integrative software for multi-block multivariate analysis. CIGENE focuses on innovative integrative genetics, theoretical systems biology and non-linear dynamic modelling, as well as high-throughput genomics and transcriptomics. CIGENE has an advanced research environment for merging non-linear systems biology and biochemometrics, in the context of yeast and mammal genomics. Several scientists have joint positions at MTF and CIGENE, and the present cooperative climate is very stimulating, see www.specmod.org.

3.4. Risks

Describe the principal risks of the sub-project successful implementation and the management issues for their minimizing

There is broad agreement on the subject and focus of the project and understanding between key proponents.

(a) Risks in technical part of the project are not expected and in case that they occur, they will be eliminated by utilizing complementary infrastructure at the site of the other partner.

(b) Organisational problems may occur in case that project activities shall conflict other projects at the respective institution. At IPB, the team of HCTFOOD will be completely independent from other activities. MTF is currently being integrated as an important part of a new national research organization NOFIMA, and organizational problems might arise, but are not anticipated. CIGENE is a coordinated center building on many different research grants, but its financial basis is secured for the application project period. CIGENE and MTF may be seen as one team, since several relevant researchers work both places. Both the CZ and N teams, however, rely on data and materials obtained in other projects. In the beginning of the project there will be organised two project meetings, one in Norway and one in the Czech Republic, at which procedures of data deposition and publishing will be defined.

(c) Personal problems may arise if members of the team shall leave the team. In the short time-span of the project these problems are not expected, however, most of the project tasks may be done by several team members. MTF and CIGENE although being different in financial basis and organization, are located close to each other, and work very well together in a number of projects.

(d) Conflict-of-interest may arise if different commercial or legal interests collide in the project. This is not seen as a problem, since the conditions upon entering the research cooperation are clear. At IPB, the relationship with the company Code Farm on the use of the LCMS software will be dealt. Harald Martens (together with E. Stark, New York) has patents on a certain multivariate pre-processing methods EMSC; to the extent it is used here, this will have to be dealt with. Matforsk is developing open-source multi-block multivariate and 2DGE software packages that will be used in this project – that should create no problems. CIGENE has no known commercial or legal issues in this relationship.

(e) The main technical leaders H. Martens and D. Stys, have been involved in several successful international projects. They are backed by stable teams of young investigators. IPB has developed project management team focused mainly on international and EU structural funds project both for academic institutions and third parties (over 30 projects of total financial size of over 15 M€). It is able to educate and methodically guide project administrative managers and, in case of problems, to replace them on temporary basis.

4. Sub-project description

4.1. Results

Describe predicted Results of the submitted sub-project financed by the grant. The Result indicators are meant to cover the main physical outcomes of the sub-project activities, and characteristics of the sub-project. Please note that there will typically be more than one indicator for each Result, and often more than one Result for each activity

The results within the project frameworks will be implemented software tools, technology transfers, publications and scientific meetings. The long term results will be establishment of research partnerships, teams and subsequent projects.

(a) The development of robust and generally applicable software is critically dependent on proper definition of variables and utilised mathematical procedures. It has been the experience of all partners that it is increasingly more impossible to define variables solely on theoretical basis of results obtained by the measurement. The technical setup, the background of experiment technical performance, needs to be included. The outcome of this novel approach is triple (i) the new software itself (indicator implemented software packages), (ii) new theoretical knowledge (indicator number of publications) and (iii) new technical knowledge from which technologies transferable to industrial partners arise.

(b) The team is composed of (i) investigators with long term international experience, (ii) Ph.D. students with backgrounds ranging from cybernetics and applied mathematics, through hardware development up to animal and human physiology and (iii) experienced administrators of international projects. Female team members participate in each of the categories. In this was respective indicators are fulfilled. Moreover, there is established and proven everyday communication between the three groups which ensures that problems arising in concrete technical or administrative part of the project will be anticipated and solved by the whole team, quickly and without the impact to project procedure.

Predicted numerical value of Fund's Results indicators

Number of publications of results in prestigious journals (impacted, indexed or reviewed)	4
Sub-project with innovative approaches	Yes
Sub-project lead by female expert (one of leading positions)	Yes
Sub-project lead by young expert (one of leading positions – not older than 35 y. at the moment of application)	Yes
Sub-project lead by regional entity (applicant with seat outside of Prague or regional partner in one of leading positions)	Yes
Number of organizations supported (applicant and partners)	3
Number of R&D events supported (active participation at public seminars, conferences, exhibitions)	2
Other values - please specify	
Implemented software packages	2
	0
	0
	0
	0

4.2. Purpose

Describe Purpose of submitted sub-project financed by the grant. Purpose in EEA Grants framework: direct and immediate results. For each Purpos define at least one indicator, please

Direct purpose of the project is solution of research and development problems of relevance to R&D on food safety and quality, which arose in parallel in both partner institutions and to which each of the partners has particular solutions. These will be expresses in technology transfers and software applications. The long term purpose is submission of new grant projects or research partnerships.

Predicted numerical value of Fund's Purpose indicators

Number of new grants / contract of partnerships between the Czech Republic and EEA EFTA countries	2
Number of products (e.g. methods, procedures, technologies) transferred (planned transfers)	2
Set up number of new patents, prototypes and/or industrial applications (planned number)	2
Other values - please specify at least one indicator and its value	
project meetings	2
courses	2
	0
	0
	0

4.3. Activities

Describe shortly individual activities necessary to reach projected results and purpose /incl. background of their financial estimations, and substantial planned supplies/. Please, describe also the role of partners in each activity. It is recommended to start title of each activity by its serial number (it helps to sort activities in tab 7. Time schedule)

Please add another record for max. 5 activities and max. 5 sub-activities to all activities

Experimental tools for multivariate description in microbiology and cell biology

Experimental data available for building of mathematical models in systems biology do not reach the level of comprehensiveness, reproducibility and precision needed for rigorous testing of the model. To reach the goal set up in the "Multivariate dynamic modelling of biological systems" the comprehensive assessment of data with objective analysis of their validity is needed. The problems in reaching this goal come from data analysis and instrumental setup. The goal of this activity is to develop software tools, both for data analysis and instrument drivers, that allow automatized and experimentally and mathematically correct assessment of biological data. Tools will be developed for morphological, metabolomic and metabolomic analysis. This sub-activity will focus on: A) The improvement of the signal processing in a LC-MS metabolomic data and state-of-the-art digital RGB camera of generic applicability once developed.. B) The use of these signals for monitoring variations in biological samples in various ongoing projects, in particular on genetically well characterized yeast cell lines The developed procedure under B) is by no means confined to this particular organism; it may be generally applicable in any analogous project: B.1) Quantitative cell morphology: Microscopy of cells of various types of cells under different conditions . B.2) Quantitative cell morphology (at CIGENE and IPB): Microscopy of cells of wild type and genetic knock-out lines of yeast (*Saccharomyces cerevisiae*) grown under different conditions BUDGET (52 258 €) In this activity will be employed researchers, students (MSc and Ph.D.) and laboratory assistants. Activity-specific administration, i.e. invoicing, organization of business trips, costs of scientific meetings etc. is also in adequate part included in the budget of this chapter The small budget for services will be used for service measurements. On the side of IPB this activity consists of extensive experimental work. For that, mainly materials for tissue cultures cultivation will be purchased, i.e. disposable laboratory material (i.e cultivation vessels, pipette tips etc.) and chemicals. The services are planned for service analyses, mainly metabolite analyses. The office costs cover general performance of the services of the institute. On the side of MTF the data shall be generated mainly in frame of other, ongoing, projects. The costs are requested for selected additional experiments needed to complete the data. Due to different type of budget construction in Norway, the office costs are included to the personal costs. The role of CIG in this sub-project is small. The rationale and distribution of costs is identical with that of MTF. In accordance with sub-activities: Metabolomic software ...: 30 % of activity budget Analytical tools and: 30 % of activity budget Microscopic characterization of cells ... : 40 % of activity budget

Sub-activities

The sub-activity describes logical part of the activity. At least one sub-activity shall be added to all activities (to enable check marks in Time schedule)

Metabolomic software analytical tools development (A.1)

Analytical tools and instrument drivers for microscopic time-lapse experiments (A.2)

Microscopic characterization of cells with different genetics, at different stages and environments (B.1), (B.2)

Multivariate dynamic modelling of biological systems

The ultimate goal of the modelling is to describe the development of cells on the basis of molecular transformations and signalling events in the cell. Among that metabolite pathways and cell morphology play the integrative role. Proteins and their regulatory states determine the metabolic fluxes and structural features in the cells. Some new mathematical methods and software tools will be developed, for the use of image time series as input to the characterization of latent state variables, and their causal control structures. This is part of an on-going activity in CIGENE for linking systems biology modelling to biospectroscopy and other high-throughput measuring principles via dynamic biochemometrics. Part of this work is rather theoretical - estimating local Jacobian matrices from time series data, and comparing eigenvalue properties and singular value properties of the local Jacobian matrices. But if successful, it may create an opening between the two disjoint cultures of dynamic non-linear modelling and multivariate statistics/chemometrics, thereby enabling new ways to use the future's massive streams of process measurement data to explore causal under-lying structures. BUDGET (25 492 €) This activity is based on intensive personnel activity and computer experiments. Material costs consists mainly of books and other literature, eventually software and hardware upgrade. Services shall include input to software development by third party. In other parts, the rationale behind the budget construction is similar to that included in previous sub-activity. In accordance with sub-activities: Pre-processing of data...: 50 % of activity budget Multivariate analysis...: 15 % of activity budget Attempts to rotate ...: 15 % of activity budget Attempts to estimate ...: 20 % of activity budget

Sub-activities

The sub-activity describes logical part of the activity. At least one sub-activity shall be added to all activities (to enable check marks in Time schedule)

Pre-processing of data for noise reduction, normalization and removal of systematic but undesired variations by EMSC and a new technique for replicate-correction, and domain-transforms to find optimal data representation

Multivariate analysis of pre-processed data in terms of relevant latent variables by PLSR, to reveal underlying systematic patterns of variation

Attempts to rotate the latent PLSR variables into estimates of causal state variables

Attempts to estimate control structure (local Jacobians $A(x)$) by nominal-level PLSR of ODEs $dx/dt=x^*A(x)+e$ and the search for correspondence between predicted emerging properties and experimentally observable values

Practical pilot assessment in selected advanced food products

The goal of this activity is to implement developed tools in two practical tasks which relate to ongoing advanced food product development, (a) microalgae-based food additives (Nové Hrad science park) and (b) international in-vitro meat consortium (Cigene). In the project (a) the product is the active compound enhanced microalgal biomass. Strains are selected from natural strains and the growth condition for production of active compounds are often sub-optimal for the production strain but may be optimal for other strains including toxic cyanobacteria. A fast, reliable, and sensitive method is needed for assessment of such contaminations in the production process as well as in

the final control. Basis of such test will be developed in the frame of this project. These experiments will be performed in project proposers technological laboratories. Proposer is co-owner of the patent CZ 13496 U1. 2003Closed solar photobioreactor for cultivation of microalgae under supra-high irradiance which is implemented in the scienc park and utiised by the company BP Medical s.r.o. for production of microalgae-based food additives. The real-life samples will be obtained from this production line. (b) Part of the in-vitro meat project is based on tissue culture growth. A high-content high-throughput method for monitoring multiple samples is needed in the consortium. Detail or the in-vitro meat consortium are availabel at partnet web site <http://www.cigene.no/archive/news/46-news/53-establishment-of-an-international-in-vitro-meat-consortium.html>. Numerous food test samples are available in partner laboratories and will be tested both in proposers and partners microscopic laboratories. BUDGET (26 766 €) This activity s based on implementation developed tools in two practical tasks. Material costs consists mainly of chemicals and other running costs of instruments. Other major costs are salaries of experts. In other parts, the rationale behind the budget construction is similar to that included in previous sub-activity. In accordance with sub-activities: Development of the test... 50 % of activity budget Development of the analytical tools...50 % of activity budget

Sub-activities

The sub-activity describes logical part of the activity. At least one sub-activity shall be added to all activities (to enable check marks in Time schedule)

Development of test for cyanobacterial toxin detection

Development of analytical tool for meat tissue development

Project management

Te purpose of this activity is project administrative management, meetings, deadlines etc.. There will be a part time project manager who will take care of administrative part of the project. Other administrative tasks will be carried on by partners existent administrators. BUDGET (7 647 €) The costs included in this chapters are solely those which could not be allocated to individual scientific and technical activities. For this reason, only personnel and office costs are requested.

Sub-activities

The sub-activity describes logical part of the activity. At least one sub-activity shall be added to all activities (to enable check marks in Time schedule)

Project management

Scientific meeting and joint education activities

Important activity essential for future development is formal and informal sharing of scientific knowledge. (a) The informal part will be achieved by scientific meetings. There will be the project launch meeting (N), and the conclusion meeting (CZ). The schedule has been chosen with respect to the fact that administrative tasks need to be fulfilled and this will be best achieved in lead partners location. (b) The formal part will consist of three courses, (i) Physical biology and (ii) Applied biospectroscopy and biochemometrics. These courses cover theoretical and technical basis of project activities. Lecturers from both partners and selected specialists will be included. BUDGET (15 295 €) In this activity will be covered mainly salaries of participants, lecturers and administration of meetings. The services consist mainly of rental of premises and organization. In accordance with sub-activities: Scientific meetings. 58 % of activity budget Courses: 42 % of activity budget

Sub-activities

The sub-activity describes logical part of the activity. At least one sub-activity shall be added to all activities (to enable check marks in Time schedule)

Scientific meetings

Courses

5. Sub-project team

5.1. Sub-Project management

Describe all management roles; add names of key persons and their responsibilities for sub-project management. Mark their gender and age if you are intended to apply an affirmative action focused to women experts and/or young scientists

The central, financial and administrative, management of the project will be performed by Dagmar Kaftanova (F) born 1976, has been the project leader of the sub-project e-clue4Mateo of the INTERREG IIIC program Mateo. She worked also as administrator of another EU structural fund projects and currently she works as administrator of the project funded by Czech ministry of industry and trade. The administrative procedures of EEA and Mateo seem to be similar at least from the general point of view and DK is not only a women under 35 working at regional institution, but she seriously is among the most qualified persons for this task.

Technical manager of the project will be Dalibor Stys (M), born 1962. DS is the founding director of IPB and has ample experience from coordination of international project including FP6, INTERREG III A and C and other structural funds projects. DS will be also responsible for IPB technical operations.

Main coordinator at Norwegian side will be Harald Martens (HM), born 1946. HM is a recognised international scientist and author of textbooks on core subject for the project. He has experience in both academic and industrial research. He will also be responsible for CIGENE technical operations.

For technical management in MTF will be responsible Ellen Mosleth Faergestad (F), who has two M.Sc (in both crop science and in applied mathematics and statistics), and a PhD in crop science.

In this way, the core management of the project is well balanced w.r.t. gender, age and nationality. It includes persons with major administrative focus as well as senior scientist. There is both recent and long-term experience in international team projects.

5.2. Experts (applicant & partners)

Describe all expert roles and their inputs for individual sub-project activities, results and purpose; add names of key persons and their experience, incl. their (co)authorship of solution or application used in praxis or patent. Add also their h-index or impact factor

IPB:

Technical leader and responsible for Scientific meetings and joint education activities: Assoc. Prof. Dalibor Stys Ph.D. (h-factor 9) is the founding director of the Institute of Physical Biology, University of South Bohemia. DS, born 1962, graduated in Physical Chemistry at the Charles University in Prague and obtained his Ph.D. in Biochemistry at Czechoslovak Academy of Science. He was a visiting scientist at Lund University in 1992-1995. Since his return to the Czech Republic he was responsible for numerous development projects which resulted in establishment of the Institute of Physical Biology, University of South Bohemia and of the Science park Academic and University Center Nové Hradky.

Experts for sub-project activities

Experimental tools for multivariate description in microbiology and cell biology

MSc. Ina Khrytankova, born XXX, is a Ph.D. student in the group of DS, graduated in animal physiology at the University of Minsk (Analytical tools and instrument drivers for microscopic time-lapse experiments)

Ing. Jan Urban, born XXXX, is a Ph.D. student in the group of DS, graduated in Cybernetics at the University of West Bohemia (Metabolomic software analytical tools development)

Ing. Jan Vaněk, born XXXX, is a Ph. D. student of Cybernetics at the University of West Bohemia and part time research technician in the group of DS (Proteomics analysis tools)

Ing. Tomáš Levitner, born XXX, is a Ph.D. student in the group of DS, graduated in Applied electronics at the University of West Bohemia (Analytical tools and instrument drivers for microscopic time-lapse experiments)

Multivariate dynamic modelling of biological systems:

Ing. Štěpán Papáček Ph.D., (M) born 1962, obtained his Ph.D. in Science engineering at the Faculty of Mechatronic and Interdisciplinary Engineering Technical University Liberec in 2005, research assistant in the group of DS (Dynamic modelling of bioreactors)

Norway (MTF,CIGENE):

Prof. Dr. techn. Harald Martens is the Norwegian lead scientist in the project. He works currently at three cooperating institutions at Campus Aas, Norway, - as senior researcher at Matforsk, senior researcher at CIGENE and professor II at the Norwegian U. of Life Sciences, Department of mathematical sciences and technology. In addition he is an adjunct professor at U. of Copenhagen, Department of Life Sciences.

He has a M.Sc. in biochemical engineering and a Dr.Techn. in chemometrics. He has previously in his research career worked as professor II in chemometrics at the Norwegian U. of Life Sciences (Aas), Department of chemistry, biology and food science, as professor II at the Norw. U. Science and Technology (Trondheim) at the Dept. physical chemistry, as guest professor in chemometrics at Technical U. of Denmark (Lyngby), Bio-Centrum, Denmark and as visiting statistician at U. of California Davis, department of enology and viticulture, as well as guest researcher in protein chemistry at Lund U., Sweden, in multivariate data analysis at Kyoto U., Japan and as protein analyst at Makerere U. Uganda.

He has also worked for 10 years as research entrepreneur in private business (multivariate process modelling, model-based video-coding) and has been instrumental in establishing two companies currently listed on the Oslo Stock Exchange (CAMO AS, DYNAPEL AS); in that connection he holds several international patents concerning model-based compression of video sequences (European patent EP 0 750 141 B1 ,US patent # 6,046,773 , US patent # 6,157,766 , US patent # 5,568,400, US patent # 6,157,766), and on mathematical separation of light scattering and light absorbance from individual spectral profiles. (US Patent 5,568,400, European patent 0415401).

He has published more than 150 scientific papers and several books (see e.g. Martens & Naes: Multivariate Calibration. J.Wiley & Sons 1989, current citation index: >2500), and received several international research awards, e.g. the Herman Wold gold medal of chemometrics from the Swedish Chemical Society. He recently chaired the 2007 international data modelling conference "Causalities Explored by Indirect Observation" (PLS'07).

His current research interest is in combining multivariate modelling of high-dimensional bio-data in terms of latent variables (biochemometrics) and non-linear dynamic ODE modelling; in this connection the use of RGB camera to monitor a) temporal and spectral development in 2DGE proteomics and b) temporal and spectral developments in high-throughput robotics of .genetic variants of microorganisms, grown under different conditions.

Prof. Martens is active in the inter-institutional Centre for Bio-Spectroscopy and Data Modelling (www.specmod.org), together with the other Campus Aas scientists in the project:

Matforsk: Dr. Ellen Mosleth Faergestad will head the proteomics gel monitoring task, prof. H.Martens will lead the yeast cell-culture monitoring task, in cooperation with Dr. A. Kohler, prof. Stig Omholt at CIGENE and a large team of yeast researchers at U. of Gothenburg, lead by prof. A. Blomberg.

Dr. Mosleth Faergstad has two M.Sc. educations and a PhD, and has extensive experience in crop science, cereal chemistry, proteomics and general multivariate bio-chemometrics.

Prof. Achim Kohler has a PhD in theoretical physics, and has worked extensively with and image analysis and with high-throughput FTIR-based biospectroscopy and microscopy with multivariate data modelling for linking transcriptomic metabolomic and genetic data in food-related systems such as pathogenic bacteria and genetic lines of yeast. He also works on synchrotron FTIR images of individual cells, and on software development for interdisciplinary multiblock multivariate analysis; this will be used in the current project. He is currently the head of the Statistics project at Matforsk, and is also an Amanuensis II at Norw. U. of Life Sciences, Dept of mathematical sciences and technology.

CIGENE: prof. H.Martens will lead the work to test image data as input for multivariate biochemometrics and high-dimensional non-linear ODE estimation, together with prof. Stig Omholt, prof. Erik Plahte and Dr. Arne Djuvslund. Prof. Omholt is the initiator and leader of the Centre for Integrative Genetics, and has, together with Prof. Plahte published a number of high-level papers on genetics, biological regulation and systems biology. Dr. Arne Djuvslund is now a post-doc, with a PhD in mathematical systems biology. Their insight into the theoretical properties of dynamic nonlinear models will be essential for the practical use of the camera input as high-dimensional dynamic phenotype in the current project applied for.

5.3. Publications

Please, include overview of relevant publications of experts listed within 5.2 (not more than 5 per expert, not older than 5 years).

Use structure according the standard ISO 690:1987 Bibliografic references - Content, form and structure or ISO 690-2:1997

Bibliografic references - Part 2: Electronic documents or parts thereof

DS:

Negative feedback regulation is responsible for the non-linear modulation of photosynthetic activity in plants dynamic light and cyanobacteria exposed to a environment (2003), Nedbal L., Březina V., Adamec F., Stys D., Oja V., Laisk A., Govindjee, *Biochimica et Biophysica Acta-Bioenergetics*, 1607.

A closed solar photobioreactor for cultivation of microalgae under supra-high irradiance: basic design and performance (2003), Masojídek J., Papacek S., Sergejevova M., Jirka V., Cerveny J., Kunc J., Korecko J., Verbovikova O., Kopecky J., Stys D., Torzillo G., *Journal of Applied Psychology* 15, 239-248.

Secondary structure estimation of recombinant psbh encoding a photosynthetic membrane protein of cyanobacterium sp. PCC 6803 (2005), Stys D., Schoeferberger W., Halhuber Z., Ristevejova J., Muller N., Ettrich R., *Photosynthetica* 43, 421-424.

Standard reporting requirements for biological samples im metabolomics experiments: environmental context (2007), Morrison N., Bearden D., Bundy J. G., Colette T., Currie F., Davey M. P., Haigh N.S., Hancock D., Jones O.A.H., Sansone S.A., Stys D., Teng Q., Field D., Viant M. R., *Metabolomics* 3, 203-210.

Bilinear system as modelling framework for analysis of microalgal growth (2007) Papacek S, Celikovsky S., Stys D. and Ruiz-Leon J., *Kybernetika* 43, 1-20.

ŠP: papers with DS plus i.e.

Rehak B, Celikovsky S, Papacek S , 2008, Model for photosynthesis and photoinhibition: Parameter identification based on the harmonic irradiation O-2 response measurement

IEEE TRANSACTIONS ON CIRCUITS AND SYSTEMS I-REGULAR PAPERS Special Issue: 101-108

HM: papers with EMF, plus

Martens, H., Pram Nielsen, J. and Balling Engelsen, S Light Scattering and Light Absorbance Separated by Extended Multiplicative Signal Correction. Application to Near-Infrared Transmission Analysis of Powder Mixtures. *Anal. Chem.*; 2003; 75 (3) pp 394 – 404.

Martens, H., Bruun, S. W., Adt, I., Sockalingum, G. D., Kohler A (2007) Correction for temperature- and salt- effects of water in FTIR bio-spectroscopy by EMSC. *Journal of Chemometrics* 20, 402-417.

Kohler A, Hanafi M, Bertrand D, Oust Janbu A, Møretør T, Naderstad K, Qannari M, Martens H, (2008) New concepts for investigating several sets of data in modern bioscience. In: *Modern concepts in biomedical vibrational spectroscopy*, Blackwell Publishing, USA, Editors: Lasch P, Kneipp J., in press.

Achim Kohler, Monika Zimonja, Vegard Segtnan and Harald Martens (2008) Model-based pre-processing in biospectroscopy. In: *Comprehensive Chemometrics*, Elsevier , Editors: Walczak B, Tauler Ferré R, Brown S., accepted for publication.

Martens, M, Tenenhaus, M., Vinci, V. and Martens M. (2007) The use of PLS methods in new food product development. In : *Hal MacFie, Consumer-Led Food Product Development*. Woodhead Publ. UK, Cambridge UK chapter 21; pp 492-523.

EMF:

Rye M.B., Færgestad E.M., Alsberg B.K. A new method for assigning common spot boundaries for multiple gels in two-dimensional gel electrophoresis. *Electrophoresis*, 29, 6, 1359-1368, 2008.

Rye M.B., Færgestad E.M., Martens H., Wold J.P., Alsberg B.K. An improved pixel-based approach for analyzing images in two-dimensional gel electrophoresis. *Electrophoresis*, 29, 6, 1382-1393. 2008

Færgestad E.M., Rye M.B., Walczak B., Gidskehaug L., Wold J.P., Grove H., Jia X., Hollung K., Indahl U.G., Westad F., van den Berg F. and Martens H. Pixel based analysis of multiple images for identification of changes; a novel approach applied to unravel proteome patters of 2D

electrophoresis gel images. *Proteomics*, 7, 18, 3450-3461, 2008.

Jacobsen S., Grove H., Jensen K.N., Sørensen H.A., Jessen F., Hollung K., Uhlen A.K., Jørgensen B.M., Færgestad E.M., Søndergaard I. Multivariate analysis of two-dimensional gel electrophoresis protein patterns - Practical approaches. *Electrophoresis*, 28, 8, 1289-1299, 2007.

Grove H., Hollung K., Uhlen A.K., Martens H., Færgestad E.M. Challenges related to analysis of protein spot volumes from two-dimensional gel electrophoresis as revealed by replicate gels. *Journal of Proteome Research*, 5, 12, 3399-3410, 2006.

6. Budget of the sub-project

Examples of sorting expenditures to budget chapters see at Annex 13 of the Implementation Manual (part 2)

6.1. Budget proposal	Share of partners (total eligible costs)			Predicted sub-project cost in €	Portion of total	€ Grant required
	Applicant	Partner A	Partner B			
I. Personal costs	65400	20000	17600	103000	80.81 %	89795.49
II. travel expenses	1300	1200	1200	3700	2.9 %	3225.66
III. Goods purchased	7404	1755	1550	10709	8.4 %	9336.12
IV. Services	4550	1284	715	6549	5.14 %	5709.42
V. Office costs	2500	500	500	3500	2.75 %	3051.3
TOTAL	81154	24739	21565	127458	100,00%	111118
TOTAL (%)	63.67 %	19.41 %	16.92 %	100,00%		87.18 %

6.2. Activity budget

Activity	TOTAL	%
Experimental tools for multivariate description in microbiology and cell biology	52258	41 %
Multivariate dynamic modelling of biological systems	25492	20 %
Practical pilot assessment in selected advanced food products	26766	21 %
Project management	7647	6 %
Scientific meeting and joint education activities	15295	12 %
Balance to TOTAL	0	

6.3. Advance payment

Justify the volume of needed advance payment from RF(CZ).

Justify the volume of needed advance payment from RF(CZ).			
The partner institutions are part of the public sector and only small part of their budget comes from services to third part. Their ability to pre-finance the project is limited, thus the lack of advance payment may cause needs of bank loan and generally sub-optimal use of public funds			
Sum required	55559	% of grant required	50 %

7. Time schedule

Month/Activity	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Experimental tools for multivariate description in microbiology and cell biology																		
Metabolomic software analytical tools development (A.1)	■	■	■	■	■	■	■	■	■	■	■	■						
Analytical tools and instrument drivers for microscopic time-lapse experiments (A.2)			■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Microscopic characterization of cells with different genetics, at different stages and environments (B.1), (B.2)						■	■	■	■	■	■	■	■	■	■	■	■	■
Multivariate dynamic modelling of biological systems																		
Pre-processing of data for noise reduction, normalization and removal of systematic but undesired variations by EMSC and a new technique for replicate-correction, and domain-transforms to find optimal data representation		■	■	■	■	■	■	■	■	■	■	■						
Multivariate analysis of pre-processed data in terms of relevant latent variables by PLSR, to reveal underlying systematic patterns of variation					■	■	■	■	■	■	■	■	■	■	■	■	■	
Attempts to rotate the latent PLSR variables into estimates of causal state variables					■	■	■	■	■	■	■	■	■	■	■	■	■	■
Attempts to estimate control structure (local Jacobians $A(x)$) by nominal-level PLSR of ODEs $dx/dt=x*A(x)+e$ and the search for corespondence between predicted emerging properties and experimentally observable values						■	■	■	■	■	■	■	■	■	■	■	■	■
Practical pilot assessment in selected advanced food products																		
Development of test for cyanobacterial toxin detection											■	■	■	■	■	■	■	
Development of analytical tool for meat tissue development											■	■	■	■	■	■	■	
Project management																		
Project management	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Scientific meeting and joint education activities																		
Scientific meetings	■	■										■						■
Courses							■					■	■					

7.2. Comments to time schedule

There is interplay between the two research based activities. The data collection and data analysis must somewhat precede the theoretical analysis, however, both the model of biological process and that of technical experiment will be included to in the data analysis. In this way, apart from core data measurement and core mathematical modelling, most of expected results may be assigned to several sub-tasks. Scientific meeting will be scheduled to enable also preparation of intermediate reports and their timing will be specified accordingly. Proposed courses correspond to respective lecture series of the IPB Ph.D. program Biophysics. It will also be sought coordinated with activities in the inter-institutional CIGENE/UMB Ph.D. programs (Forskorskole) and SPECMOD at Campus Aas on systems biology and on genetics. Their timing will be specified according to the academic calendar for the respective year (unknown to us yet).

It may seem that the amount of work planned to be covered by the current research application is unrealistic. But based on experiences in our related ongoing projects and on preliminary dedicated experiments, we can assure that the plans are indeed realistic, at least for bringing the highly innovative developments and applications to a level of first academic publication. But the grant will be most welcome, since cross-disciplinary research is more difficult to finance than very focused projects.

It should be understood that, if granted, this project will be integrated into a large conglomerate of on-going research activities already financed.

8. Disclaimer

Name of authorised representative	prof. PhDr. Václav Bůžek, CSc.				
Position	rector	E-mail	rektor@jcu.cz	Phone	+420 389032001

The authorised representative of the applicant, disclaim

1.	I am entitled by the representative of the Applicant to submit the application in this call	I agree
2.	All what is laid down in this application is based on proper information, and as I am aware it is true. I acknowledge that, should I provide any inaccurate or incomplete information deliberately in this application, the application could be rejected in any stage of evaluation or implementation.	I agree
3.	The Applicant complies with all its duties according tax, social security and health insurance laws of the Czech Republic; all its partners comply with all their duties according tax, social security and health insurance laws their home country.	I agree
4.	All partners included in this application are willing to participate in the sub-project. All of them are prepared to sign a partnership declaration, which I shall deliver to the Intermediary upon request (in case that the application will be recommended to the final selection).	I agree
5.	All partners included in this application participated in the preparation of this application and are informed about its final (submitted) version.	I agree
6.	The Applicant and all its partners will cofinance expenditures of proposed budget as stated within the part 6 of this application, in the case the application is awarded by a grant.	I agree
7.	The Applicant and all its partners are not in any other situation excluding it from participating in RF(CZ).	I agree
8.	In the name of the Applicant I agree with publishing the Application within the information systems of RF(CZ) and FMs EEA/Norway and selected data (incl. financial) at web pages of RF(CZ) and FMs EEA/Norway and using them for other publicity purposes of RF(CZ) and FMs EEA/Norway.	I agree
9.	Logical framework is attached to the Application. (optional)	No
10.	In the name of the Applicant I am prepared to submit any document asked by the Intermediary to prove information included in this application.	I agree