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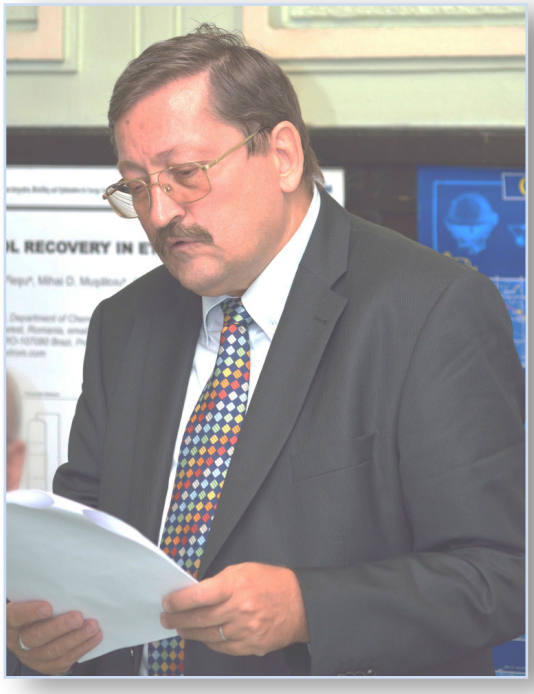
ANNIVERSARY: PROFESSOR DR. ING GHEORGHE MARIA AT 65 YEARS OLD TEACHER AND SCIENTIST

CURRENT TRENDS IN BIOMEDICAL ENGINEERING & BIOSCIENCES

Anniversary: Professor Dr. Ing Gheorghe MARIA at 65 Years Old Teacher and Scientist



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Department of Chemical and Biochemical Engineering

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Note: papers referred in the text can be found in the complete list of G. Maria publications onhis WEB-site [2], and in the attached ANNEX. Most of them cam be downloaded via its ResearchGate page

Abstract

Prof. Dr. Gheorghe Maria from University Politehnica of Bucharest (UPBuc.), Department of Chemical and Biochemical Engineering is a valuable scientist in Romania, being the successor and the continuer of the Romanian school of (bio)chemical reactors and (bio)chemical reaction engineering, and the creator of novel courses in the (bio)chemical engineer curricula at UPBuc., that is: "Model-based safety assessment of chemical processes and plants" (2004), "Metabolic Engineering" in the Food engineering and Bioengineering (2004), "Statistical treatment of experimental chemical data, and kinetic model identification" (1998), "Biochemical engineering" (2015). His research interests include a wide range of classic but also modern border fields, namely (bio)chemical reactors, kinetic modelling, bioinformatics, risk analysis of chemical reactors, modelling dynamics of cell metabolic processes, of gene expression, of gene regulatory circuits, and the drug release kinetics [2,13,16-18]. Following the large number of international cooperations (Table 10), its scientific productivity is impressive: he published more than 149 ISI papers (most of them as principal author, including more than 40 in top ranked chem. eng. Journals). Their publications are well cited (Hirsch index 20, I10 index 48). He reported high scores according to the Romanian ranking system (MEdC-OMs-2011). He authored a large number of ISBN books in Romania (6), and USA (5) (Table 4a-b). Also, he authored 5 teaching books, and 6 books chapters abroad [2,16]. In 2019 he joined (unanimously by votes) the Romanian Academy. as a correspondent member [35, 36](Fig.27).

Born	2-Oct-55	Nationality	Romanian
	village Fundeni, county Călărași, Romania.	Nicknames	Gigi, Mary (from highschool colleagues)
Residence	Bucharest, Romania	Spouse	Maria (Popovici) Cristina

Alma mater
1962-1970. Primary studies in Bucharest.
1970-1974. Secondary studies at Lyceum „Gh. Lazăr" in Bucharest (Baccalaureate 1974).
1974-1979. university studies (BSc and MSc) in chemical engineering at University Politehnica of Bucharest (UPBuc), major in organic chemistry, and chemical engineering (mathematical modelling & numerical calculus). Accepted at UPBuc. on 1974 without exams, due to the gold medal (Figure 3) obtained at the European Chemistry Contest (Olympiad) for High-schools (11 participant countries, among which Russia, Germany, Austria, Sweden, Czech Rep., etc.) [23a-b]. He graduated UPBuc as valedictorian on 1979, becoming a chemical engineer (Figure 4).
1981-1987. PhD student at UPBuc, Department of Chemical and Biochemical Engineering. Granted PhD in Chemical Engineering on 1987. (OM MEdC 7537/25.05.1987).
Command of foreign languages: French (very well), English (very well), German (basic level). Native Romanian.

Career (Institutions)
1979-1982. In-stage Chemical Engineer (Plant engineer) with Organic Chemical Enterprises in Bucharest, Romania.
1982-1990. Senior Research Scientist/Engineer with ICECHIM (Central Institute of Chemistry) - Chemical & Biochemical Energetics Institute Bucharest, (Bio)Catalysis Group.
1991-1992. Lecturer (Assistant Professor) with the Department of Chemical and Biochemical Engineering of University Politehnica of Bucharest (UPBuc.).
1992-1997. Asistant Professor with Swiss Federal Institute of Technology - ETH Zürich (Switzerland), Chemical Engineering Department, PSE group of late prof. David W.T. Rippin.
1997-1999. Associate Professor in Chemical & Biochemical Reaction Engineering with the Department of Chemical and Biochemical Engineering of UPBuc.
From 1999. Full Professor in Chemical & Biochemical Reaction Engineering with the Department of Chemical and Biochemical Engineering of UPBuc.
2002-2003. Senior Research Scientist (NIH fellow) with Texas A&M University (College Station, Texas, USA), Dept. of Chemistry, Biochemistry, and Cell Biology (2002-2003).
2019- He became a correspondent member of the Romanian Academy (unanimously by votes) [35]

Some honours and awards received by prof. Maria.
• 'N. Teclu' Prize of the Romanian Academy for kinetic studies on selective conversion of methanol to olefins, and for the design and scaleup of the industrial plant at Petrochemical Works Brazi (1985) (Figure 1);
• Diploma of excellence in research of the Romanian Federation of Biomedical Engineering, 2006[2] (Figure 2).
• included in "Who's Who in the World in Science & Technology" (1996 - in present);
• the gold medal (Figure 3) obtained at the Chemistry Olympics for highschools on 1974 (11 participant countries, among which Russia, Germany, Austria, Sweden, Czech Republic, etc.)[23a-b]
• EU Scientific Expert for EC-FP6 Programme - NEST Group (Safety engineering, and Bioengineering), 2003-2005.

• Swiss National Science Foundation Scientific Expert (Switzerland), 2005-2006.
• Scientific Expert for the Bioeng. RO Res. Program "Biotech", and those of Republic of Croatia, 2006.
• member in the Chemistry/Chemical Eng. Committee of the Romanian Council for Attestation of University Titles, Diplomas & Certificates CNATCDU (2011-2012).
• 12 awards for the best published papers granted by the Romanian Res. Agency UEFISCDI (2010-2019).
• correspondent member of the Romanian Academy (from 2019, unanimously by votes).


ACADEMIA REPUBLICII SOCIALISTE ROMÂNIA

ACADEMIA REPUBLICII SOCIALISTE ROMÂNIA

ACORDA

PREMIUL NICOLAE TECLU

TOV. MARIA GHEORGHE, G. MUSCA, GR. POP, ECATERINA POP, DOINA IVANESCU, N. IONESCU, ILEANA-JANETA IOSIF, M. RAUL, S. STRAJA, I. OLARU, I. GHEORGHE, LUCIA CREȚOIU, I. BELDEANU, GR. NICOLAE, RODICA BOERU

PENTRU Lucrarea "Catalizator și procedeu pentru conservarea metanolului la olefine"

DAT IN BUCUREȘTI LA 2 noiembrie 1985

PREȘEDINTE, Acad. Radu Voinea

SECRETAR, Prof. George Cățoiu, membru corespondent

Nr. 20

Figure 1: 'N. Teclu' Prize of the Romanian Academy for kinetic studies on selective conversion of methanol to olefins, and for the design and scaleup of the industrial plant at Petrochemical Works Brazi-Ploiesti (1985).


FEDERATIA ROMANA DE INGINERIE BIOMEDICALA

DIPLOMĂ DE EXCELENȚĂ

pentru calitatea lucrarii prezentate la

Conferinta Nationala de Inginerie Biomedicala INGIMED VII,

Bucuresti 9 - 10 nov. 2006

Se acorda ...dlui Gheorghe MARIA.....

Impreuna cu sincera apreciere a comunitatii nationale de inginerie biomedicala.

Director General FRIB
Prof. univ. dr. Bedros Petru Naianu

Comitetul de Organizare
Prof. univ. dr. Radu Negoescu

Figure 2: Diploma of excellence in research of the Romanian Federation of Biomedical Engineering, 2006.


REPUBLICA SOCIALISTĂ ROMÂNIA
Ministerul Educației și Învățământului

DIPLOMA

Se conferă PREMIUL I

elevei MARIA GHEORGHE

participant la cea de a VI-a Olimpiadă internațională de chimie a elevilor — București 1974

PREȘEDINTELE JURIULUI INTERNAȚIONAL,
prof. dr. FELICIA CORNEA

iulie 1974

Figure 3: Gold medal obtained at the Chemistry Olympics for highschools on 1974 (11 participant countries, among which Russia, Germany, Austria, Sweden, Czech Republic, Czech Rep., etc.).

1. Education and Acclaim (Early Life)

Prof. Maria was born in Fundeni (Călăraşi county, RO), a village which is very close to Bucharest, on October 2, 1955, being the middle child of a family with very old and strong roots in Oltenia (via his father) and Muntenia (via his mother). The grandparents on the maternal line, although with many children (6), have been quite wealthy, as his grandfather received a lot of land as a veteran of the battles of Marasesti and Oituz (WW1), as well as when he was decorated in high orders. As the Communist regime disposed of all their goods around 1950-1955, almost all his children had to shape their future by moving to Bucharest. So it's like, the family of dr. Maria lived exclusively in Bucharest. But, as the family material resources were extremely poor (with a domestic mother), after 1953, his family had to change their rented flat several times, by moving among various districts of Bucharest. Withal, Gigi (nickname of Prof. Maria) kept a close connection with the parent families in their home villages, during the wonderful summer and winter holidays spent there (Fundeni/ Călăraşi, and Baloteşti/Ilfov).

Over years, during primary school, Gigi received from his father, a border guard colonel, a very strong and strict education, based on seriousness, discipline, organizational skills, accuracy and fairness, also always open to new ideas and with a great love of his country to which he has always been proud to belong. Already in Bucharest during his primary studies, he reported exceptional top results, being an imaginative spirit, extremely curious, and with talent to exact sciences. He often read in advance the textbooks of his two-year older brother. After graduating secondary school, he attended Gh.Lazăr lyceum/highschool (1970-1974), which is one of the top high-schools in Bucharest, in a class specialised on Chemistry and Maths, led by late prof. Mariana Andrei, who knew how to channel his talent towards a rigorous study of Chemistry [5]. During his secondary studies in Bucharest, he reported exceptional top results, being an imaginative spirit, extremely curious, and inventive, particularly attracted to Chemistry and Mathematics. He quickly became noted for his original math approach to solving many chemical problems. He participated to a large number of high-school national competitions (so-called national Olympiads in Chemistry or Maths), by winning several awards. He was also a fervent supporter of Revista de Fizica si Chimie (Bucharest) for high-school peoples, where he contributed with problems to be solved, and where he published his first paper: Maria,G., Antiferromagnetism of magnetite, Revista de Fizica si Chimie B, 11(1), 6-10 (1974).

Due to their outstanding results, in 1974, he was included in the Romanian team to participate to the 6th IChO (International Chemistry Olympiad) for highschool peoples (11 participating countries, including Czechoslovakia, Poland, Hungary, Bulgaria, GDR, Romania, Soviet Union, Sweden, Yugoslavia, Austria, BRD)[23a-b]. At this esteemed and traditional contest, G. Maria won the Gold Medal by presenting original and ingenious solutions to several difficult chemical / computational chemistry problems. Being impressed by his success, writer Eugen Seceleanu, dedicated one chapter in his book to him [12]. Due to such an exceptional achievement, in 1974 he was admitted at UPBuc. without any exam, to study chemical engineering (Industrial Chemistry Faculty), where he chose to become BSc in Organic Chemistry, and MSc in Chemical Engineering, specializations to which he was particularly attracted. Later, this attraction will be materialized in a large number of innovative published studies on math modelling the kinetics of catalytic chemical processes, but also proposing kinetic math models of various metabolic (biochemical) processes in living cells. To achieve these ambitious goals, he was starting to study the theory of statistical estimation in depth. Later, during his doctoral studies, such extensive knowledge, allowed him to develop novel numerical algorithms for statistical estimation, and process optimization (for solving NLP, MINLP problems). Starting from these solid theoretical bases, later he reported lots of contributions in the area of multi-objective optimization of industrial chemical, enzymatic reactors, or bioreactors. During his university studies, he attended the courses of valuable professors, such as Prof. Ecaterina Ciorănescu-Neniţescu, and Prof. Margareta Avram for Organic Chemistry, Chemical reaction engineering with Prof. Raul Mihail, Chemical process optimization with Prof. Octavian Smigelschi, Transport phenomena with Prof. Octavian Floarea, and others. He graduated the UPBuc. in 1979 as valedictorian (Figure 4). During his college studies, he began to work already and publish several chemical engineering studies under the supervision of Prof. Raul Mihail and Prof. Octavian Smigelschi, being particularly attracted by the statistical estimation theory, numerical optimization rules, modelling (bio)chemical process kinetics.

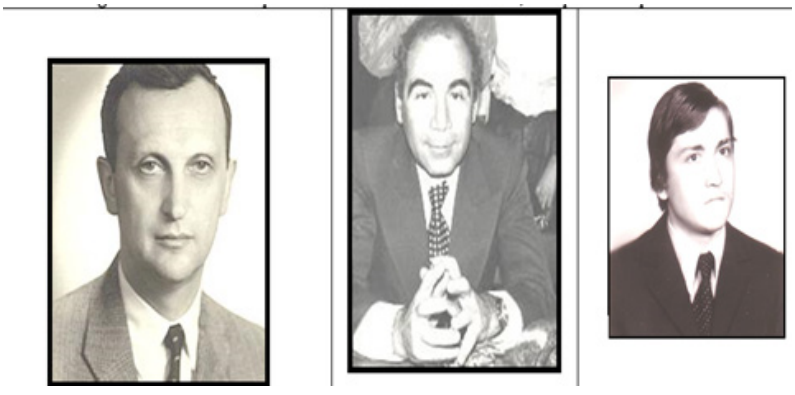

Figure 4: [left] Doctoral advisor late Prof. Raul Mihail. Diss title: Parameter Estimation of the Mathematical Models of (Bio)Chemical Processes (1987).; [center] MSc advisor late Prof. Octavian Smigelschi. Diss title: Modelling and optimization of a multi-cell sugar extractor (1979); [right] G. Maria MSc graduate of UPBuc as valedictorian (1979).

After MSc graduation, he began his career as an in-stage plant engineer (obligatory internship) for 3-years (1979-1982) with several state chemical companies in Bucharest, like Cosmetics Miraj co., "Chimica Dudesti" co. Despite of reduced spare time and tedious work over strict

industry shifts, he found time to activate as a teaching assistant at UPBuc., related to the course of "Chemical and biochemical reactors" (BSc, MSc applications in modelling, design, optimization, and control). In 1981 he started his PhD under the supervision of Prof. Raul Mihail, with the theme „Parameter Estimation of Chemical Process Models [19-22](textbooks no.1,3,5 of Table 4a), by approaching his preferred subject of modelling kinetics of a large number of catalytic chemical processes related to his parallel job with ICECHIM-IECB, including math modelling and simulation ofomplex chemical reactors, and publishing original numerical algorithms for kinetic parameter statistical estimation, and process optimization.

2. Research Engineer with ICECHIM (Central Inst. of Chemistry)-IECB (Chem. & Biochem. Energetics Inst.) Bucharest (Romania)

On 1982 he joined ICECHIM - Chemical & Biochemical Energetics Institute Bucharest, (Bio)Catalysis Group, being in charge with modelling the kinetics of a large number of catalytic processes, and with the technological design of the industrial pilot plant at Brazi-Ploiesti Petrochemical work / Refinery (PWB) [15]. Here are to be noticed their studies on kinetic modelling the catalytic processes of methanol conversion to olefins (MTO), or to gasoline (MTG), on zeolite / modified silica catalysts. Dr. Maria published these kinetic studies (in collaboration) in top chemical engineering journals (I&EC-Research, USA; Chemical Engineering Science, Elsevier) [7-11]. Based on these kinetic models he had a major contribution to the design of the industrial pilot plant for MTO/MTG at PWB. The chemical plant was put into operation on 1985 (Figure 5) [6,15]. The industrial pilot plant, with the characteristics listed in Table 1, was put into operation at PWB on 1985. The plant includes two fluidized-bed reactors (FBR): one for conducting the desired reaction (MTO, MTG, etc.), and one for catalyst regeneration. The catalyst has a continuous circulation, by pneumatic transport, between the two reactors [15]. At that time, only one similar pilot plant of the Mobil Oil comp. USA, was operated in New Zealand, but of a simpler construction, that is without continuous recirculation and regeneration of the catalyst. Much later, other industrial pilot plants for the MTO process were built-up, including two inter-connected FBR offered by UOP/Hydro comp., Germany (2005), and Chinese Dalian Institute of Chemical Physics (2015) [15]. A detailed description of tested catalytic processes on the MTO/MTG industrial pilot at PWB over 1985-1992 was presented in his booklet [15].

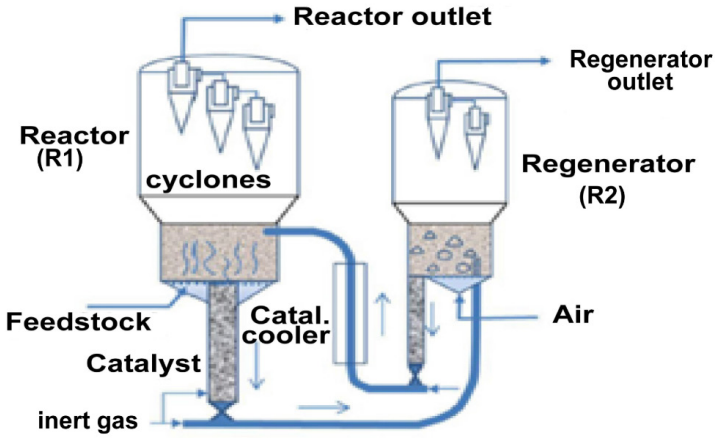

Figure 5: MTO/MTG industrial pilot at Petrochem. Works Brazi PWB (1985) [15].

Table 1: The Main Characteristics of the Industrial Pilot Plant for the MTO/MTG Process from PWB [15].

Industrial pilot with two catalytic reactors in fluidized-bed (FBR)	An FBR (reactor), and an FBR regenerator (for catalyst regeneration). The continuous circulation of the catalyst between the reactor and the regenerator is accomplished by pneumatic transport with an inert gas.
FBR Reactor (vapor phase catalytic reactions)	0.5m in diameter and 7m in height
FBR Regenerator (combustion of the coke deposited on the microscopic catalyst)	0.3m in diameter and 7m in height
LHSV; catalyst avg. size	0.4-2 1/h (for the MTG); 0.06-1 mm
Temperature range	280-450°C (reactor), and 480-560°C (regenerator)
Pressure	1-2 atm.
Observations	The pilot is equipped with gas-chromatograph analyzers and process computers connected "on-line" and "off-line". Approx. 50 process parameters are continuously recorded through appropriate equipment. A specific software is used for data treatment, with including data acquisition, numerical filtering, statistical calculations, mass and thermal balances, and kinetic evaluations.
Tested catalytic processes	MTO, BTX, MTG, EB, EtOH, OA, catalyst deactivation (see chap.2 abbreviations).

Following such an exceptional achievement, at both national and international levels, that is I) MTO-MTG process investigation, its development/scale-up, ii) industrial pilot plant design, building-up, and put into operation at PWB, and iii) testing various catalytic processes at the pilot-plant scale, Dr. Maria award the "N. Teclu" Prize of the Romanian Academy on 1985 (Fig.1). The developed kinetic models for the MTO and MTG processes become reference models with more than 150 citations on Googleschoolar. Beside testing the developed kinetic models and the catalytic processes for MTO/MTG on this industrial pilot plant at PWB, dr. Maria developed and published lot of kinetic studies and pilot tests for several others catalytic processes on zeolite catalysts, such as: i) selective alkylation of C4 olefins with methanol (OA), ii) Benzene or Ethylbenzene (EB) alkylation with ethene to get higher aromatics, iii) Ethanol conversion to olefins (EtOH), iv) Methanol to BTX (aromatic hydrocarbons). All these projects being developed with the ICECHIM-IECB Bucharest, (Bio)Catalysis Group. Industrial-scale tests by using the MTO/MTG pilot-plant were performed at PWB over the interval 1985-1992. More information on this realization in his textbook [15].

3. Tenure at ETH Zurich (Switzerland, 1992-1997)

Following the sociopolitical transformations of Romania after the collapse of communism in 1990, on 1992 he chose to follow an invitation and he came to Switzerland for working as Assistant Professor with ETH Zürich in the Process System Engineering group of the late Prof. David W.T. Rippin, part of the Chemical Engineering Department (Technische Chemie). Here he was involved in supervising several PhD/MSc. student projects. Besides, he actively participated as a senior investigator to several important research projects of the group, all in the (bio) chemical engineering area. In the first place, he was a key investigator in the Swiss Ministry of Energy project NEFF 505(1992-1997) "Saisonale Speicherung von Elektrizitat mit Chemisch Gebundenem Wasserstoff" (Seasonal Storage of Electricity with Chemically Bound Hydrogen), at ETH Zürich, and Paul Scherrer Institut Villigen (Switzerland). The project was experimental developed and tested at a catalytic pilot level at Paul Scherrer Institut Villigen (Switzerland) in cooperation with German DFG and French Vinci co. The project is aiming at transporting chemically stored hydrogen between continents. Thus, the hydrogen is stored by catalytic hydrogenation of toluene to methylcyclohexane (MCH), then the liquid MCH is transported to the beneficiary where it is catalytically dehydrogenated to toluene (liquid) which is back returned to the hydrogen source, and the cycle is resumed. Dr. Maria was in charge with development of kinetic models for the two hydrogenation-dehydrogenation catalytic processes, and with the pilot plant (fixed-bed) design and operation at Paul Scherrer Institut Villigen - PSI (Switzerland). The resulted key publication was [24].

Table 2: Teach Courses and Novel Courses Introduced by Dr. Maria in the Chemical Engineers Curricula at UPBuc, having as Support their Published Textbooks No. 1-5, and those Published in USA (Chap.6).

- (Bio)Chemical Reaction Engineering (BSc in Chemical Engineering, from 1987)
- Numerical and statistic methods for (bio)chemical data treatment and parameter estimation of (bio)chemical process kinetic models (BSc, MSc in Chemical Engineering, Food Engineering) (newly introduced from 1997)
- Metabolic Engineering and Bioinformatics (M.Sc. in Food Engineering, Biochemical Engineering) (newly introduced from 2004); UPB.11.S.09.O.0406
- Chemical Process Quantitative Risk Analysis and modelling of accident consequences (BSc, MSc in Chemical Engineering) (newly introduced from 2006); UPB.11.S.06.O.519; UPB.11.S.10.O.208
-(Bio) Chemical technology/engineering (BSc in Food Engineering, from 2015); (newly introduced from 2015) UPB.11.S.08.O.414

Figure 6: [Up-left]: ETH Rektorat; [Right]: Technische Chemie building on Universitatstrasse (1992-1997), and the ETH Polybahn; [Down-left]: Together with late Prof. D.W.T. Rippin at ETH Zurich (1993)

He was also involved in developing safety analysis of some industrial chemical reactors (i.e. the catalytic acetoacetylation of pyrrole with diketene at CIBA-NOVARTIS, Basel, Fig.22). Starting from this experience he later published lot of papers dedicated to multi-objective

optimization of risky chemical reactors by also considering a safety measure expressed in an original probabilistic way (see chap.7.3, Fig.15A-B). Their notable contributions in this area allowed him to write the first text-book in Romania dedicated to safety issues in chemical engineering/reactors, and introduced in the chemical engineers' curricula at UPBuc. a dedicated novel course (Table 2). At ETH Prof. Maria also developed and published KINEXP, an expert system for identification and estimation of kinetic models for given (bio)chemical processes, based on known experimental kinetic curves [25-28]. The software uses an own kinetic databank, that includes various kinetic models, and associated species kinetic curves, imported from solved case studies from literature. KINEXP uses a transfer of information original rules MIP [28], and a combination of direct and indirect methods to solve the NLP, MINLP problems, most of them being original ones (MMA, TFA)[2, 25-31](Table 6). Additionally, to help the kinetic model identification process of KINEXP, dr. Maria proposed an original statistical test ["lambda-by-sigma square", linked to target factor analysis TFA [29] for the analysis of parameter significance in a nonlinear regression models, by detecting the redundant parts of the model [29]. The resulted key publications are [25-31], with more than 1000 citations.

4. Tenure at Univ.Politehnica of Bucharest (U.P.Buc.) Commitment to Excellence in Teaching (Associate from 1981, Titular from 1991)

During his PhD stage (1981-1987), dr. Maria was also a teaching/research assistant with UPBuc. (chemical reaction engineering lab). On 1990 he joined UPBuc as a titular lecturer. With perseverance, conscientiousness, hardworking, and a tireless investigator and creative spirit he promoted all the university ranks until full professor with UPBuc. On 1997 dr. Maria returned from ETH Zurich to Romania (after a stay abroad of ca. 6.5 yrs. 1992-1998), becoming Associate Professor (1997), and then full Professor (1999) with UPBuc, by teaching courses in (bio) chemical reaction engineering, but also statistical treatment of (bio)chemical data, at BSc or MSc level. He approached classic fields, such as (bio)chemical reactors math (dynamic) modelling, optimization and control, (bio)chemical process kinetic modelling. But he also approached and introduced at UPBuc. modern teaching/research fields, required by the EU curricula, by writing 5 teaching manuals, and textbooks (Table 4a), being the promoter of several courses (Table 2), such as risk analysis of chemical plants, metabolic engineering, bioinformatics, (bio) chemical experimental data statistical treatment, biochemical engineering, kinetic modelling of (bio)chemical processes; math modelling of metabolic process dynamics in living cells aiming to design genetic modified micro-organisms (GMO) of industrial use, at BSc, MSc, or PhD level. Such novel courses, consistent with those developed in EU, derived from this large practical international experience over cooperative projects (Table 10), being a recognized expert on these topics for various EU (FP6) or national (Biotech) research programs.

The positive experience acquired when solving the international projects on bioinformatics mentioned in Table 10 (math modelling of metabolic process dynamics in living cells aiming to design GMO of industrial use) with Texas A&M university (chap.5), allowed him to write the first 3 text-books in Romania (published in USA, see chap.6) in such a subject, and to introduce a novel course on "Metabolic engineering and bioinformatics", and "biochemical engineering" in the curricula of biochemical engineering at UPBuc. (Table 2). Similarly, starting from the positive experience acquired at ETH when involved in developing safety analysis of some industrial chemical reactors (i.e. the catalytic acetoacetylation of pyrrole with diketene at CIBA-NOVARTIS, Basel), and from the large number of solved industrial case-studies dealing with multi-objective optimization of risky chemical reactors, he published lot of original contributions in this area [2,3] which, eventually, allowed him to write the first textbook in Romania in this subject (no. 2 in Table 4a), by introducing such a novel course in the chemical engineers curricula at UPBuc. (Table 2). **Academic and research interests**. Being focus on math modelling and CAPE (computer application in (bio) chemical process engineering), dr. Maria research interests cover a wide range of areas, including basic fields [(bio)chemical reactors, and reaction engineering], but also novel emergent of frontier fields as below mentioned: [2] Prof Raul Mihail (1920-1985) was the creator of the Romanian school of (bio)chemical reactors, by publishing the first course of "Chemical Reactors" (1971) in the country (and third in the world), and those of "Bioreactors" (first book in the country, 1987). This school was strengthened and continued by the brilliant textbooks of Prof. Ovidiu Muntean (1983-2003). Prof. Maria was one of their continuers making a bridge over years with the modern school of chemical and biochemical reactors and reaction engineering at UPBuc., by developing and promoting it through projects, publications (papers[2], and text-books of chap. 6), and through applications in academia and chemical industry, by approaching novel process engineering aspects, such as: advanced kinetic modelling, model-based design of (bio)chemical plants, safety engineering, reactor operation optimization, bioinformatics, and bioengineering.

Chemical engineering, chemical reaction engineering	Protein synthesis regulation (gene expression kinetics); simulation of the genetic regulatory circuits in living cells,
Metabolic engineering, computational biology	Systems biology, bioinformatics
Biochemical engineering, biochemical reaction engineering	Modelling the dynamics of genetic regulatory circuits
Chemical, biochemical and biological reactors (modelling, optimization, control)	Wastewater biological treatment (kinetic modeling)
Kinetic (mathematical) modelling of chemical, (bio)chemical, and biological processes	Risk analysis and ecological impact of risky chemical reactors (determination of critical operating conditions, simulation of the reactor run-away conditions). Optimized operating policies of risky chemical reactors.
Process identification, statistical estimation, data numerical treatment	Simulation of chemical accidents consequences and effects
(Bio) chemical process analysis and optimization	Chemical energetics (chemical storage of the hydrogen energy)
Enzymatic processes and catalytic process kinetic modelling	Controlled drug delivery (kinetics modelling; system delivery design).
Modeling the dynamics and regulation of metabolic processes in living cells (cell simulators)	

The teach courses, and novel courses introduced by Dr. Maria in the chemical engineers curricula at UPBuc. are those of Table 2. The support of these novel courses have been ensured by Dr. Maria with published Textbooks of Table 4a, and with 4 review ebooks published in USA (Table 4b). His involvement and publications in such research topics are coming from his vivid and very creative spirit, and tireless search in the vast domain of modelling, design, and optimization of (bio)chemical processes. Thus, many of their publications in such frontier fields are coming from his involvement over the past decades in a large number of international collaborative works/projects, by performing multiple stages abroad at various universities (Table 10), that is:

a) Germany [Ludwigshafen (1995), TU Erlangen (2000), Univ. Saarbrucken(1999,2009), TU Aachen (2004), TU Hamburg (2009), TU Braunschweig (2006)],

b) Switzerland [ETH-Zurich (1992-1998)],

c) Portugal (Univ. Porto, Univ. Coimbra, 1999-2000),

d) Canada (Queens'univ., Kingstown,1994),

e) USA (Princeton Univ, Texas A&M Univ, 2002-2003),

f) China (Tianjin, Inst. Ind. Biotechnology, 2010),

g) France [EP Grenoble (1996), EP Montpellier (1999)].

The scientific productivity (publications) of Prof. Maria in these research areas is impressive (see below chap. 7), including many original contributions. In short, Prof. Maria authored 11 ISBN books (6 in RO, 5 in USA), 5 teaching books (RO), 5 ISBN book chapters (abroad), over 150 papers in peer reviewed ISI international journals and univ. journals, and 80 in intl. conference proceedings, with more than 1400 citations (h-index 20 and i10 index 48 in Googleschoolar). According to the Romanian ranking system, he reported high scores signing NP= 130 ISI papers as principal author. The most cited first 5 papers (Googleschoolar) of prof. Maria are listed in Fig.7.


13.01.2020 Gheorghe Maria - Referințe bibliografice Google Academic

Gheorghe Maria

Professor, Dept. Chem. & Biochem. Eng., Univ, Politehnica of Bucharest

chemical and biochemical engineering mathematical (kinetic) modelling estimati… cell process modelling risk

CREAȚI-VĂ PROPRIUL PROFIL

	Toate	Din 2015
Referințe bibliografice	1413	563
h-index	20	12
i10-index	48	19

TITLU	CITAT DE	ANUL
A review of algorithms and trends in kinetic model identification for chemical and biochemical systems G Maria Chemical and Biochemical Engineering Quarterly 18 (3), 195-222	104	2004
Evaluation of multivalent dendrimers based on melamine: kinetics of thiol–disulfide exchange depends on the structure of the dendrimer W Zhang, SE Tichy, LM Pérez, GC Maria, PA Lindahl, EE Simanek Journal of the American Chemical Society 125 (17), 5086-5094	74	2003
Modelling and scaleup of the kinetics with deactivation of methylcyclohexane dehydrogenation for hydrogen energy storage G Maria, A Marin, C Wyss, S Muller, E Newson Chemical engineering science 51 (11), 2891-2896	55	1996
A Kinetic Model for Methanol Conversion to Hydrocarbons R Mihail, S Straja, G Maria, G Musca, G Pop Chemical Engineering Science 38, 1581-1591	52	1983
Kinetic model for methanol conversion to olefins R Mihail, S Straja, G Maria, G Musca, G Pop Industrial & Engineering Chemistry Process Design and Development 22 (3 …	38	1983

Figure 7: The most cited first 5 papers of prof. Maria in Google scholar.

Dr. Maria is a reviewer for many (bio)chemical engineering journals (25), and a member in the scientific/editorial board of "Chem. & Biochemical Eng. Q. (Zagreb)", "Revista de Chimie (Bucharest)", "The Scientific Bulletin of Univ. POLITEHNICA of Bucharest", "Bulletin of Romanian Chem. Eng. Soc.", "ECOTERRA Journal of Environmental Research and Protection" (edited by Romanian Soc. Environ. Sci. Eng., Cluj-Napoca, Romania). During his participation to scientific conferences, he co-chaired 16 national and international conferences, and presented more the 15 invited plenary lectures in various intl. Conferences [2]. At UPBuc. Prof. Maria was the promoter of several novel courses (Table 2), by also writing the supporting teaching manuals (Table 4a,4b) concerning i) safety analysis of chemical plants; ii) statistical treatment of data, and modelling the kinetics of (bio)chemical processes; iii) modelling metabolic processes in living cells aiming to design modified microorganisms of industrial use; iv) modelling the drug release from functionalized supports. Some of these teaching books are the first in Romania approaching such subjects, aiming to drive the national research toward such modern and update fields. From this point of view, Prof. Maria was the first in Romania who promoted at UPBuc. applications and projects of high complexity level, consistent with those developed in EU, referring to themes in the border areas of chemical and biochemical engineering, related to bioinformatics, genetic and metabolic engineering, simulation of metabolic processes in living cells, systems biology, and safety engineering, being an expert on these topics for various EU (FP6) or national (Biotech) research programs.

Table 3: PhD Subjects of Theses Supervised by Prof. G. Maria (2008-2019).

2008 -2011, Dragoş Nicolae ŞTEFAN, Analysis of thermal sensitivity and risk in the operation of chemical reactors.
2010 - 2013, Manuela Diana BUBOI (ENE), Studies on the kinetics of some oxidative-reduction enzymatic processes with importance in the sugar synthesis industry.
2010 - 2013, Anca DAN, Studies on the optimization of chemical reactors with the inclusion of safety operating criteria.
2011 - 2014, Ionela LUŢĂ, Studies of modeling the controlled release of biologically active compounds and the action of some microorganisms deposited on porous solid supports.
2013 - 2017, Hasan Hadi Salman KHWAYYIR (Najaf Technical College, Iraq), The risk analysis of industrial plants including highly sensitive chemical reactors.
2013 - 2019, Constantin MUSCALU, Studies on the optimization of industrial chemical reactors with high parametric sensitivity using multi-objective criteria in the presence of parametric uncertainty.
2014 -2019, Mara CRIŞAN, Studies on the optimization of some industrial enzymatic reactors with complex enzymatic systems
2017 - in progress, Marina MIHALACHI, applying some chemical engineering techniques to the modeling of essential stages of the central carbon metabolism in the cell cultures with application to optimizing the functioning of the bioreactors.
2019- in progress. PEPTĂNARU Ioana Mirela, MSC-diss., Optimization of the bi-enzymatic reactor to obtain mannitol from fructose with continuous in-situ regeneration of the NADH cofactor

These novel books and courses derived from his large practical experience with these subjects acquired from solved international projects. Thus, starting from the positive experience acquired at ETH when involved in developing safety analysis of some industrial chemical reactors (i.e. the catalytic acetoacetylation of pyrrole with diketene at CIBA-NOVARTIS, Basel), and from the large number of solved industrial case-studies dealing with multi-objective optimization of risky chemical reactors, he introduced a safety measure expressed in an original probabilistic way (see chap.7-3, Fig.15A-B). All these scientific activities in the safety engineering area, allowed him to write the first text-book in Romania on "Quantitative assessment of the chemical process and plant risk (650 pages, plus annexes)" (book no.2, Table 4a), and to introduce such a novel course in this topics in the chemical engineers curricula at UPBuc on 2006 (Table 2). The same positive experience acquired when solving the NIH project with Texas A&M university on modelling living cell metabolism dynamics, and bioinformatics, allowed him to write the first text-books in Romania (published in USA) in such a subject, and to introduce a novel course on "Metabolic engineering and bioinformatics" in the curricula of biochemical/food engineering at UPBuc. Such a huge computational/modelling effort to support the mentioned courses was accompanied by a novel dedicated course on "(Bio)chemical data statistical treatment and modelling the (bio)process kinetics" (books no.3,5 of Table 4a).

Table 4a: The Most Relevant Teaching Books in RO (With ISBN) Published by Dr. Maria (Complete List In [2]).

1. Iordache, O. Maria G Corbu S, Statistical Modeling and Estimation of Chemical Process Models, Rom. Academy Publ Bucharest, 1991, (300 pages), ISBN 973-27-0195-1.
2. Maria G, Quantitative risk assessment of chemical processes and modeling of accident consequences (Chemical Process Quantitative Risk Analysis and Modeling of Accident Consequences), Printech Publ Bucharest, 2007 (630 pages, with annexed routines), ISBN 978-973 -718-667-6.
3. Maria, G, Statistical analysis and correlation of experimental (bio) chemical data. Statistical data analysis and distributions (Statistical data analysis and correlations, Distributions and estimators), Printech Publ Bucharest 2008 (550 pages, with annexed routines) ISBN 978-973-718-886-1.
4. Maria, G, Luta, I, Kinetic modeling techniques and in-silico design of mesoporous structures functionalized upon controlled release of biologically active principles, Printech Publ Bucharest 2015 (p. 476), ISBN 978-606-23-0443-0.
5. Maria, G, Crisan, M, Maria, C, Parameter estimation of the (Bio) chemical process kinetic models, Printech Publ. Bucharest 2016 (528 pages), ISBN 978-606-23-0633-5.
6. Maria, G., Numerical methods to reduce the kinetic models of (bio)chemical processes, Printech Publ., Bucharest, 2019 (815 pag.), ISBN 978-606-23-1010-3, (in Romanian).

Table 4b: Relevant Ebooks Published in USA (With ISBN) by Dr. Maria in Bioinformatics [13,17,18], and Scale-Up of Various Novel Catalytic Processes [15].

[EBOOK1] [13] Maria, G, A review of some novel concepts applied to modular modelling of genetic regulatory circuits (O trecere în revistă a unor concepte noi de modelare modulară a circuitelor genetice de reglare), Series: Current Trends in Biomedical Engineering & Biosciences, Juniper publ California 91320, (USA) 2017, ISBN (USA) 978-1-946628-03-9. (50 pages).
[EBOOK2][17] Maria, G., Deterministic modelling approach of metabolic processes in living cells - a still powerful tool for representing the metabolic process dynamics, (Modelarea deterministă a proceselor metabolice celulare – Un instrument valoros pentru reprezentarea dinamicii proceselor metabolice), Series: Current Trends in Biomedical Engineering & Biosciences, Juniper publ., California 91320, (USA) 2017, ISBN 978-1-946628-07-7(USA).
[EBOOK3] [18] Maria, G, In-silico design of Genetic Modified Micro-organisms (GMO) of industrial use, by using Systems Biology and (Bio)Chemical Engineering tools, Juniper publ., California 93063, (USA) 2018(100 pages), ISBN 978-1-946628-12-1(USA).
[EBOOK4] [15] Maria, G, From residual biomass and inferior quality coal to the synthesis of methanol and then to hydrocarbons and gasoline – a Romanian project of high success, Juniper publ., California 93063, (USA) 2018, (50 pages), ISBN 978-1-946628-16-9 (USA).

On 2008 Dr. Maria became a PhD supervisor at UPB in the (bio)chemical reaction engineering area, with 7 PhD-s finalized, and 3 PhD-s in progress. The approached phd subjects are given in the Table 3. On 1986 he co-authored in Computers and Chemical Engineering, a novel numerical procedure, named MMA, that is a numerical algorithm performing a structured search of the global optimum of a multimodal (nonlinear) objective function. The MMA can solve nonlinear programming problems (NLP) by using an iterative adaptive random search with successive automated expansion/contractions of the search domain. The method can detect the global extremum for multimodal nonlinear objective functions, convex or neconvex, in the presence of complex constraints [30,31]. Later, Prof. Maria improved and extended the MMA performances leading to MMAMI able to solve mixed-integer nonlinear programming problems MINLP [31]. Later, Prof. Maria donated the right to use these routines to several universities: Univ. des Saarlandes (Technische Chemie, 1999); TU Erlangen / Karlsruhe (Germany)(2000), and Tianjin Inst. Ind. Biotechnology (China)(2010). On 1987 G. Maria finalized their PhD studies and got the PhD degree at UPBuc {see [19-22], and textbooks no.1,3,5]}.

In very short words, as a member of the Dept. of chemical and biochemical engineering of UPBuc. [3], Prof. Maria lead PhD and MSc studies in Chemical and Biochemical engineering, in a sustainable approach, leading the group of Biochemical engineering and Biochemical technologies (2006-2011) [4]. Also, he has laid foundation of the novel course on qualitative risk assessment of chemical reactors/plants, which was introduced in the chemical engineering curricula at UPBuc (Table 2). He developed a very large number of researches in modelling the kinetics of chemical, biochemical, and cell metabolic processes included in various national and international projects (Table 10). He was the key engineer in the research & design team that scale-up and design and put into operation the industrial pilot plant (Table 1) at Ploiesti (Brazi) Petrochemical Works (PWB), for testing the MTO, MTG, BTX, and other catalytic processes [2,6-11,15]. See details and abbreviations in the chap. 2, and their key publications on his WEB-page [2,15].

5. Senior NIH Fellow with Texas A&M Univ. (USA, 2002-2003)

On 2002 prof. Maria chose to follow an invitation and he came to USA for working as Senior Scientist / invited Professor with Texas A&M Univ (TAMU, College Station, USA), Dept. of Chemistry, Biochemistry, and Cell Biology in the framework of NIH projects of Prof. P. Lindahl, and Prof. E. Simanek. Here, prof. Maria was involved in supervising several PhD/MSc. student projects, but also in the research activities (two major projects of the group), being in charge with the (bio)chemical reaction engineering part (modelling the dynamics of lot of cell metabolic pathways). Basically, he was involved in two National Institute of Health (NIH) projects, that is: Fellow of PAL-GM63958 / 2002-2003: „Kinetic simulations of minimal living systems", and NIH Fellow of EES-GM64650 / 2002-2003: „Molecular recognition in dendrimers based on melamine - Kinetics of programmable drug release in human plasma", (Prof. E. Simanek). In the PAL-GM63958/2002-2003 project the theoretical studies focus on development of reduced kinetic models for representing the regulation of some protein's synthesis in living cells. Studies involved modelling the gene expression regulatory modules (GERM), and genetic regulatory circuits (GRC) in bacteria of interest. Researches have been developed at Texas A&M University, Dept. of Chemistry and Cell Biology, in the framework of a NIH grant (2002-2003). Dr. Maria proposed novel modelling approaches similar to those used in the chemical engineering and nonlinear systems theory. Some results have been published (iron metabolism dynamic model in mitochondria; Hudder et al., 2002[18]). Such dynamic simulators of the cell genetic regulatory circuits have been proved to be useful for in-silico design of genetic modified micro-organisms (GMO) with application in the biosynthesis industry, medicine, environ. engineering, etc. [13,17,18].

In the EES-GM64650/2002-2003 project the theoretical studies focus on development of extended and reduced kinetic models for representing the dynamics of successive chemically controlled drug release from multi-valent dendrimers based on melamine. Experimental reesearches have been developed at Texas A&M University, Dept. of Chemistry, in the framework of a NIH grant (2002-2003). Some results have been published [33], being later developed in successive theoretical publication [2,3].

Figure 8: Early activity with UPBuc., as a phd student and asstn. Professor (from 1980, and then as titular associate professor (from 1990). [Up-left]: my working office at UPBuc. (2007); [Up-right]: with my colleague C. Teodorescu, and my co-worker late dr. Liu Ching Tao (Nanjing, China). [Down]: in the chemical reactors lab. on 1982 together with (from left) (now retired) lector Iosif Nagy, late prof. C. Balaban, late prof. Raul Mihail, late dr. L.C.Tao (China), myself, (now retired) prof. O. Muntean, dr. S. Straja (now living in USA), and late lector M. Filipescu.

6. Textbooks

Based on his own research experience with industrial applications over lot of research projects (chap.4, Table 10), Prof. Maria published 11 highly influential ISBN textbooks (6 in RO, and 5 in USA) for teaching purpose (Table 4a-b). The impact of these textbooks has been attributed to the extensive background of Prof. Maria, acquired during the large number of solved case studies in the framework of the large number of national (27) and international (20) projects (see chap.4,7) to which he attended as a key investigator. Such a large work experience, provided him with the context into the connections between the macro- and micro-/nano-(cell-)scale of chemical and biochemical reaction engineering, and the large similitude in the dynamic simulation of metabolic processes in living cells with simulation of the dynamic macroscopic (bio) chemical / biological nonlinear systems. The most relevant published review ebooks in Bioinformatics (open access) in USA are presented in Table 4b. These textbooks are completed by 6 chapters included in books with ISBN published abroad [2]. The teaching books published in Romania by Prof. Maria (Table 4a) have been proved to be highly influential, as being the first written courses dedicated to the mentioned subjects. The books include theoretical aspects well balanced with solved case studies. Theoretical chapters are accompanied by a very large number of exemplifications completed by easy to access routines written in Matlab, or Excel codes. These textbooks are reference books used in the main universities of Romania to complete the instruction of chemical reaction engineering with novel courses within chemical engineering curricula (Table 2). Also, the mentioned review booklets published in USA are the first in Romania providing a novel perspective of biochemical engineering in border areas, such as bioinformatics, and systems biology.

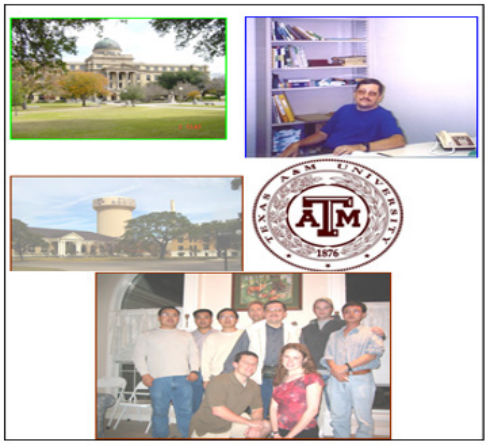

Figure 9: NIH Research activity at Texas A&M University (College Station, USA)(2002-2003). [Down]: The dedicated group of prof. Lindahl (middle). [Up-left] The faculty of chemistry and cell biology, and a view from campus [middle]. [Up-right] My working office at TAMU.

These textbooks are completed by 6 chapters with ISBN included in books published abroad [2]. In Romania, the above teaching books published by Prof. Maria have been proved to be highly influential, as being the first written courses dedicated to the mentioned subjects. The books include theoretical aspects well balanced with solved case studies. These textbooks are reference books used in the main universities of Romania in the instruction of chemical reaction engineering within chemical engineering curricula (see Table 2). Also, the review booklets published in USA (Table 4b) are the first in Romania providing a novel perspective of (bio)chemical engineering in border areas, such as bioinformatics, and systems biology, aspects included in their teach courses at UPBuc. (Table 2). The impact of these textbooks has been attributed to the extensive background of Prof. Maria, acquired during the large number of solved case studies in the framework of various international projects (see chap. 7). Such a work experience, provided him with the context into the connections between the macro- and cell-scale chemical and biochemical reaction engineering, and the large similitude in the dynamic simulation of metabolic processes with simulation of the dynamic macroscopic (bio)chemical / biological (living cell) nonlinear systems.

7. Commitment to excellence in Research

Over his long career of over 40 years, Prof. Maria published an impressive large number of contributions in the (bio)chemical reaction engineering, and related areas, as below summarized.

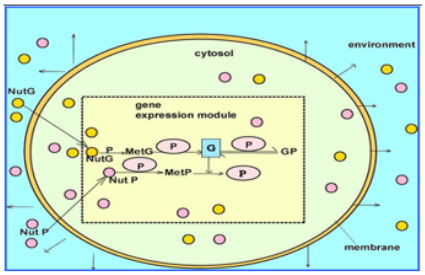

Figure 10A: The simplest reduced schemes of a generic gene expression regulatory module GERM in the holistic approach of [13].

149 papers in ISI / Scopus indexed journals (more than 130 as principal author) [2]	FIC (cumulated IF of ISI papers as author) > 180
80 communications in intl. Conferences [2]	Citations: more than 1400
11 books with ISBN (6 in Romania, 5 in USA), (Table 4a-b)	Hirsch-index 20, i-10 index 48, (Googleschoolar)
5 teaching books (UPBuc.) [2]	
6 book-chapters with ISBN (Engl.) [2]	

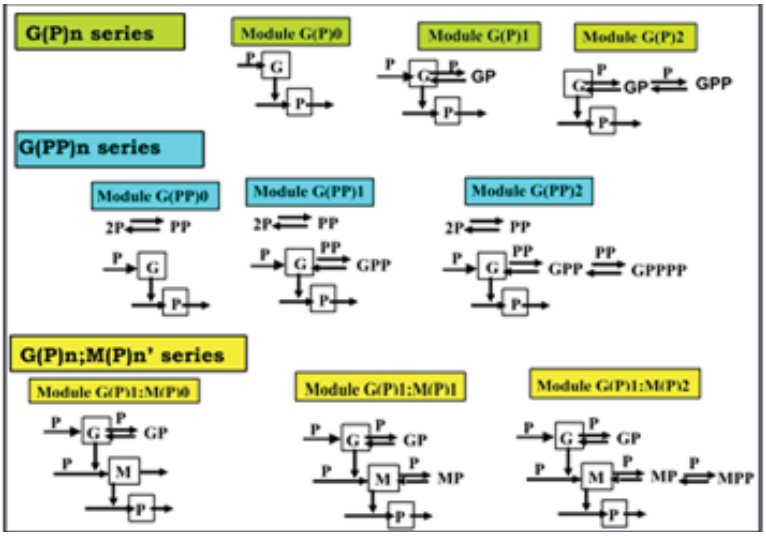

Figure 10b: The library of gene expression regulatory modules (GERM) used by Maria (2003-2014) [13] to model genetic regulatory circuita (GRC) in various cells (generic G= gene, DNA; P= protein; M= mRNA).

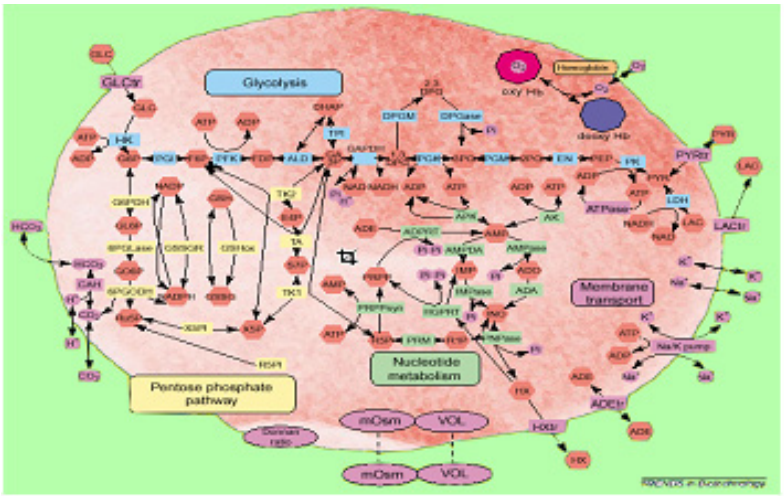

Figure 10c: The central carbon metabolism (CCM) in the holistic Variable-Volume-Whole-Cell (VVWC) modelling approach of Maria [13,17,18] textbooks.

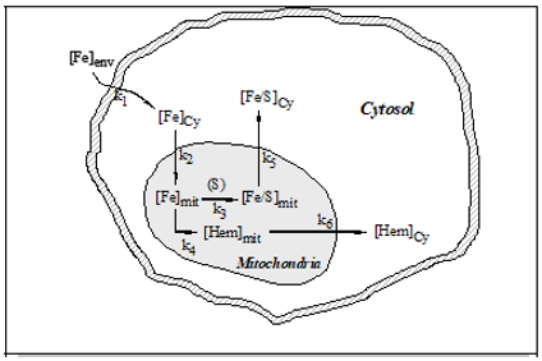

Figure 10d: The VVWC structured reduced model of Hudder, Maria, et al., 2002 used to simulate the heme synthesis in mitochondria [18].

Dr. Maria reported significant contributions in a wide range of inter-disciplinary topics, such as: safety analysis and optimization of chemical, multi-enzymatic, and biological reactors; modelling the drug release kinetics in biological fluids; design of optimized drug release systems., bioinformatics, etc. In short, these publications include many original contributions in the following areas:

a) (Bio)Chemical reaction engineering,

b) CAPE (computer application in process engineering)

c) Computational biochemistry, Bioinformatics,

d) chemical, biochemical, and biological reactors optimization

e) modelling the kinetics of chemical, biochemical (enzymatic) processes, including metabolic processes (genetic regulatory circuits, central carbon metabolism)

f) chemical, biochemical, and biological reactors (design, optimization, control)

g) (Bio)Process Systems Engineering

The complete list of their publications and more information are on his personal website [2]. Among their research areas, are to be underlined the following directions:

1. Chemical and Biochemical reaction engineering [bio(chemical) process kinetic modelling, model-based (bio)chemical reactors analysis, and optimization], Process Systems Engineering. This subject also includes contributions in the Statistical estimation theory and applications in (bio)chemical reaction engineering, and bioengineering, (bio)chemical reactor optimization, proposal of a large number (more than 40) kinetic models, and rules to derive lumped kinetic models.
2. Bioinformatics, Systems Biology [modelling the dynamics of metabolic processes, in-silico design of genetic modified micro-organisms (GMO)], (Bio)Process Systems Engineering
3. Bioengineering (optimization of complex biological, and enzymatic reactors).

More specifically, some contributions are grouped as below.

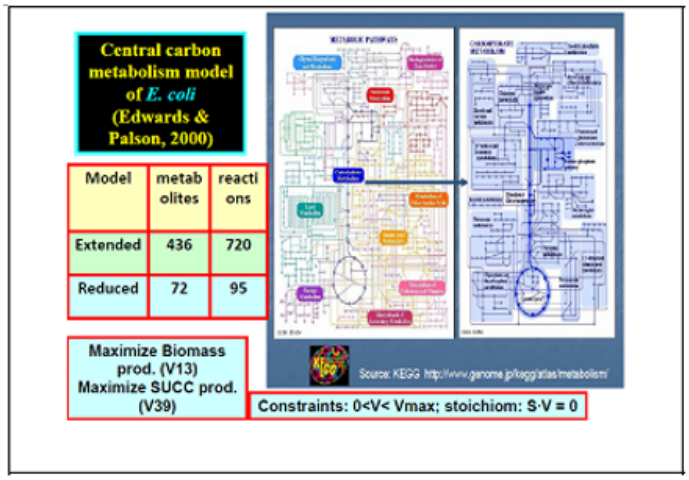

Figure 11a: Succinate production maximization in GMO *E. coli*. Carbohydrate metabolism in E. coli (KEGG). The reduced model of includes 72 metabolites, and 95 reactions [18].

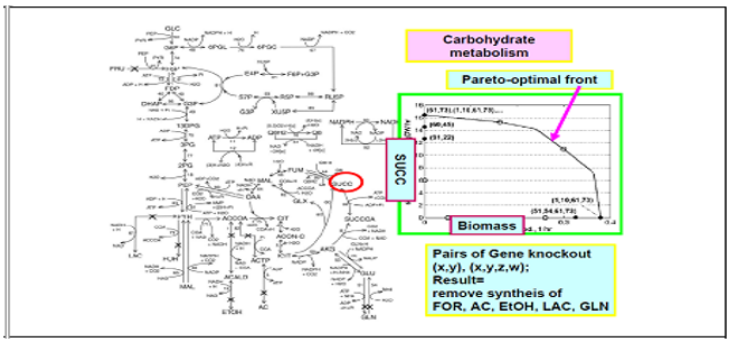

Figure 11b: In-silico design of a GMO E. coli cell to concomitantly maximize the production of biomass and succinate (the Pareto-optimal front method, below-right), by Maria et al., [18]. In the parentheses are the deleted gene numbers from the genome (see the corresponding reaction in the left scheme). The used structured reduced model is those of Edwards and Palsson [2000]. See the computing details of Maria [18].

7-1. Development of novel and complex kinetic models

Prof. Maria developed a very large number (more than 40) of novel and complex kinetic models for various processes: chemical catalytic, enzymatic, cell metabolic, or drug release. These models have been validated at lab, pilot or industrial scale. Among them are to be mentioned the followings [2]:

KM1. Kinetic model for the catalytic selective conversion of methanol to olefins (MTO).
KM2. Kinetic model for the catalytic selective conversion of methanol to gasoline (MTG).
KM3. Kinetic model for the catalytic selective conversion of methanol to A6-A8 hydrocarbons (BTX).
KM4. Kinetic model for the catalytic selective conversion of ethanol to olefins
KM5. Kinetic model for Benzene Alkylation in Vapour-Phase with Ethene (EB)
KM6. Kinetic model for olefins alkylation in vapour-phase with methanol (OA)
KM7. Kinetic model for the catalytic Fischer-Tropsch synthesis
KM8. Kinetic model for methylcyclohexane catalytic dehydrogenation to toluene (MCH),
KM9. Kinetic models on dispersion and bioaccumulation of persistent organic pollutants in the aquatic environment and sediments
KM10. Proposal of modular kinetic models for gene expression regulation (GERM), and genetic regulatory circuits (GRC) in bacteria of interest [13,18]
KM11. Proposal of VVWC kinetic models to simulate and design cell genetic switches (GS)[13,19]
KM12. Proposal and validation of a modular VVWC dynamic cell model to simulate the induced mer-operon expression in Gram negative bacteria. The model can be used for In-silico design of cloned E. coli with a maximized capacity of mercury uptake from wastewaters (Fig.12B);
KM13. Proposal of a structured reduced dynamic model to simulate the glycolysis in Escherichia coli cells under stationary or oscillating dynamic conditions (Fig.12A)[14]. The model can be further used as the core of a modular dynamic model to simulate CCM and regulation of a certain metabolite systhesis, with application to in silico reprogramming of the cell metabolism and design of GMO of various applications. The model was used to In-silico design of a genetic modified E. coli with a modified glycolytic oscillator; the same model can be used to modulate lot of metabolic pathways interfering to glycolysis [17,18].
KM14. Proposal of mechanistic (compartmented) kinetic models for the programmed drug release in biological fluids [2].
KM15. Development of kinetic models to simulate the chemically controlled drug release in human plasma (Fig.16).
KM16. Kinetic modelling and optimization of some complex enzymatic processes from saccharides industry. Examples includes the two steps of the Cetus process for fructose production from D-glucose, that is: I) enzymatic oxidation of D-glucose to keto-D-glucose in the presence of pyranose oxidase and catalase and, then ii) the enzymatic reduction of keto-D-glucose to fructose in the presence of aldose reductase and NADPH as proton donor (Fig.13B). Then, iii) the fructose can be then converted, for instance to mannitol by enzymatic hydrogenation, with the in-situ continuous enzymatic regeneration of the NADH cofactor by the expense of formate enzymatic decomposition (Fig.14); iv) A novel kinetic model for enzymes deactivation in complex multi-enzymatic systems [2,3].
KM17. A novel kinetic model for enzymes deactivation in complex multi-enzymatic systems (cexemplification for the enzymatic oxidation of D-glucose to keto-D-glucose in the presence of pyranose oxidase and catalase) (Fig.13B);
KM18. Proposal of a reduced VVWC modular model to simulate the iron metabolism in mitochondria (Fig.10D);
KM19. Proposal of a kinetic model for enzymatic reduction of fructose to mannitol (Fig.13B,14) [18];
KM20. In-silico analysis of interference of the oscillating glycolysis with the oscillating tryptophan synthesis in the E. coli cells (Fig.12C). The complex structured model was used to In-silico modulate the bioreactor operating conditions with a modified E. coli to maximize the production of tryptophan [18].
KM21. Proposal of a time-dependence for the enzyme deactivation constant (kd) in the [E]=[Eo]*exp(-kd*t) 1-st order deactivation expression, in complex multi-enzymatic reaction cases.
ETC. Details in their ebooks [13,17,18]

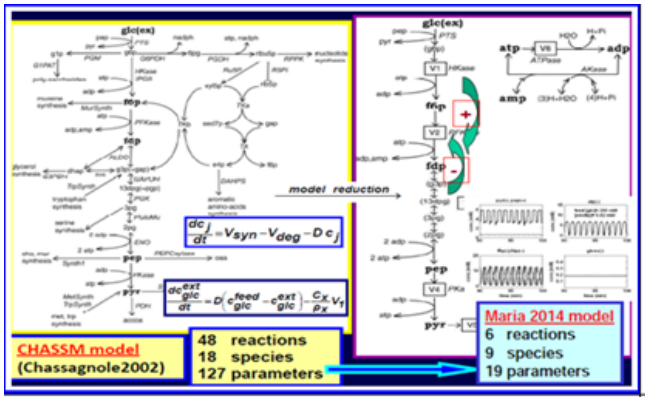

Figure 12a: Case study: In-silico modulate the glycolytic oscillator in a of a GMO E. coli using the reduced model of Maria [14,18] with applications in the biosynthesis industry.

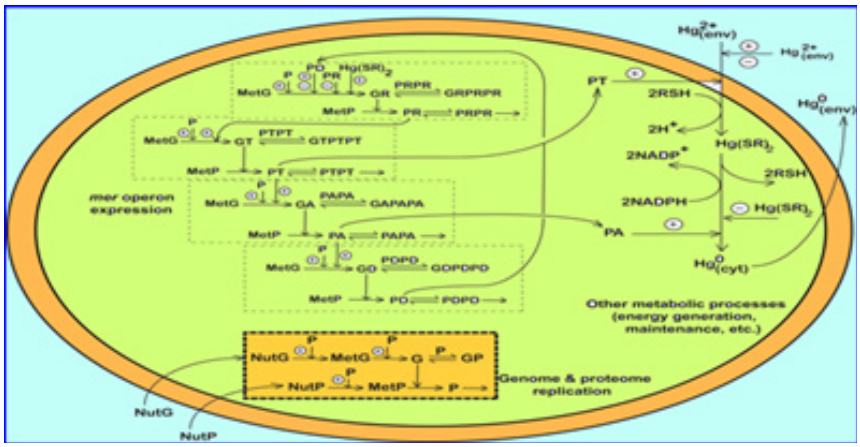

Figure 12b: The structured modular VVWC dynamic model proposed by Maria, 2009-2014 to simulate the regulation of the mercury (mer)-operon expression involved in the mercury ions uptake by E. coli cells. Model also accounts for G/P lumped proteome/genome replication [18].

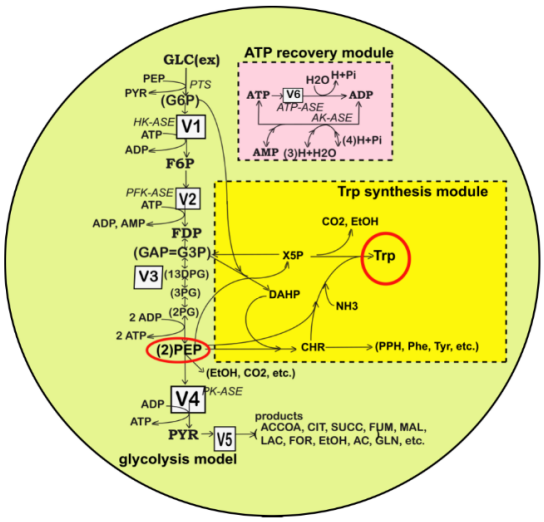

Figure 12c: Simplified reaction schemes of glycolysis connected to tryptofan synthesis in E. coli to base the kinetic model of Maria [19], with including ATP, ADP, AMP synthesis. Species in parenthesis are not explicitly included in the dynamic mode. Italic letters denote the enzymes. Squares denote enzymatic reactions. Species abbreviations in [2-5]. The central carbon metabolism (CCM) model was formulated in the holistic Variable-Volume-Whole-Cell (VVWC) modelling approach of Maria [13,14,17,18].

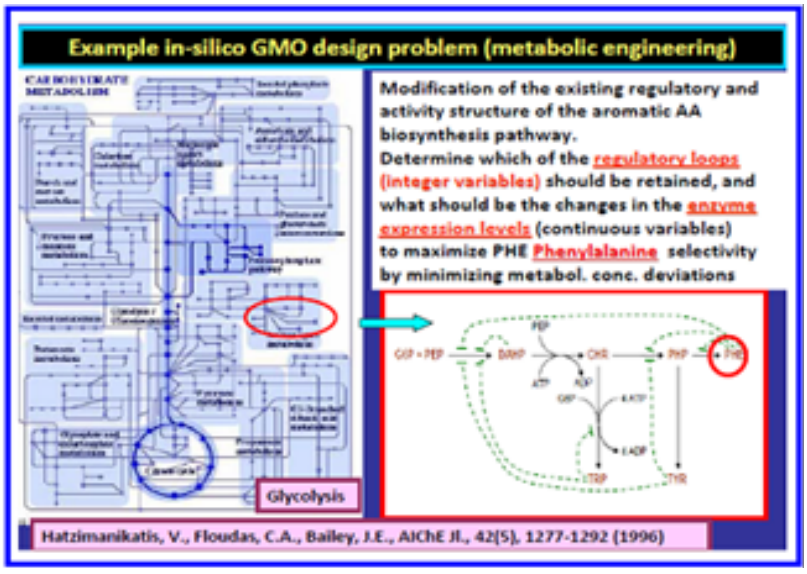

Figure 12d: In-silico re-configure the metabolic pathway for Phenyl-alanine synthesis in E. coli [18] to maximize its production by using a deterministic model and a biochemical engineering approach.

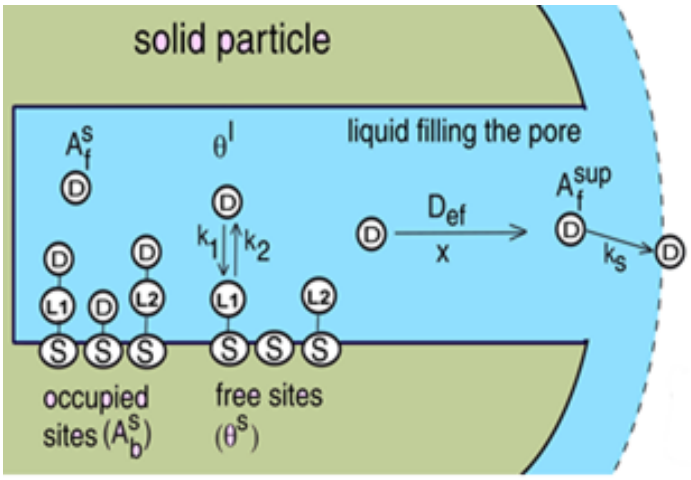

Figure 13a: Modelling the controlled drug release kinetics (chemically and diffusionally controlled) [2].

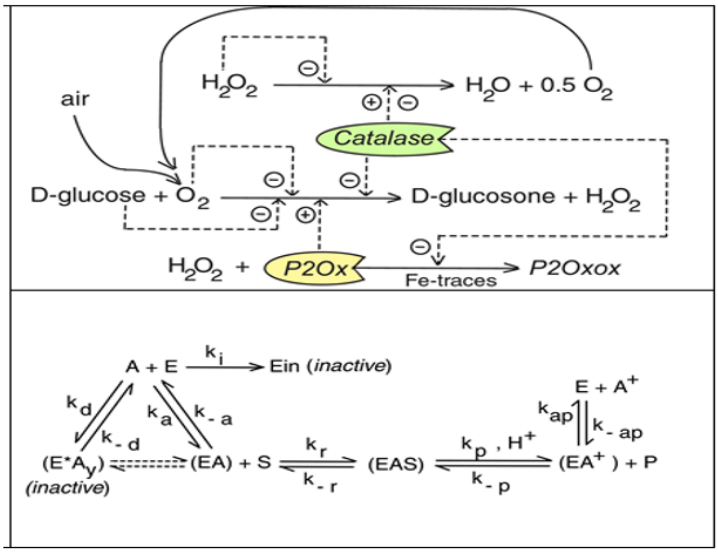

Figure 13b: Modelling enzymatic kinetics: D-glucose oxidation to keto-glucose by P2Ox (up), and then keto-glucose reduction to fructose using ALR and NADPH (down)[2].

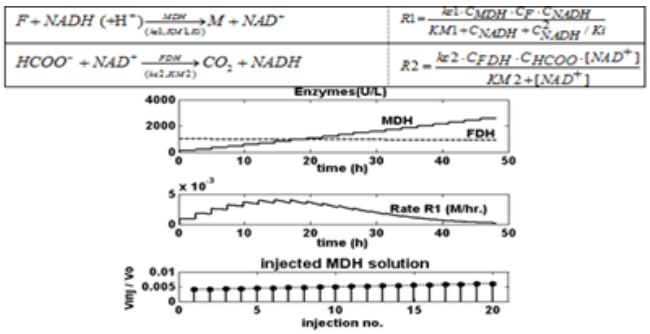

Figure 14: Simulation of the enzymatic reduction of fructose to mannitol in the presence of NADH with intermittent addition of MDH enzyme (Crişan & Maria, 2017)[2].

7-2. Modelling dynamics of metabolic processes in the living cells

Prof. Maria paid special attention over the last 20 years to modelling dynamics of metabolic processes in the living cells, by introducing novel modelling concepts and rules translated from (bio)chemical engineering principles and nonlinear systems theory. Lot of applications have been developed on In-silico design of genetic modified micro-organisms GMO (Systems Biology and Bioinformatics), reviewed in their last 3-books published in USA (2017-2018) [13,17,18] of chap.6.

7-3. Contributions in the risk assessment and multi-objective optimization of chemical reactors

The developed optimization computational methodology (process/reactor model-based predictive control MPC) is seeking multi-objective goalS, by also including, beside economic objectives, also safety requirements (in a probabilistic/stochastic form) (Fig.15A-B,22) [2]. In this area, dr. Maria reported a significant number of contributions, by elaborating novel numerical algorithms to estimate the critical operating conditions and safety operation limits for batch, semibatch, or tubular continuous reactors of high thermal sensitivity, i.e. where exothermal hazardous reactions are conducted, including potentially hazardous side-reactions. The proposed algorithms to evaluate the critical operating conditions based on the process math models, performe complex analyses to determine conditions leading to operating parameter divergence from the nominal operating conditions of the chemical reactor (in the parametric space) in the proximity of the safety operating boundaries. The novel algorithms to evaluate the chemical reactor critical operating conditions in the presence of operating parameter uncertainty are briefly described below. A review of the chemical process quantitative risk analysis is presented in his teaching book no.2 (Table 4a), which is the first in Romania dealing in a systematic way with quantitative (math models- based) evaluation of the technological risk of chemical reactors and processes. In short, these contributions are listed in Table 5.

Table 5: Main Contributions of Prof. Maria in Model-Based Risk Analysis of Chemical Reactor of High Thermal Sensitivity [2], See also his Short CV and Publication List [3].

An algorithm to evaluate the quasi-stable QFS operating conditions ("quick onset, fair conversion and smooth temperature profile") of an industrial chemical reactor using the generalized sensitivity criterion of Morbidelli-Varma, corresponding to a super-critical or severe operation characterized by a high economic efficiency and quasi-stability of the thermal regime due to the very rapid chemical reactions. Exemplifications are made for some industrial reactors (catalytic synthesis of aniline in vapour phase, or aceto-acetylation of pyrrole in homogeneous liquid catalysis). The novel criterion determines the incipient risky operating conditions of the chemical reactors (Figure: 22).
A novel algorithm to evaluate risky operating conditions of chemical reactors. (Divergence from the stable trajectory in the parametric space) by modification of the Zaldivar et al. (2003) rule, based on the analysis of the eigenvalues of the math model Jacobian, and detection of incipient critical conditions from the change of the sign of the maximum of the real parts from negative to positive.
A novel algorithm to evaluate risky operating conditions of chemical reactors (divergence from the stable trajectory in the parametric space) by modification of the Strozzi-Zaldivar (1994) rule, based on the analysis of Lyapunov exponents derived from the eigenvalues of the reactor model information matrix (that is the product of the Jacobian matrix and its transpose). The modification detects the proximity of the critical operating conditions in the parametric space from the « breaking points » of the slope of the positive maximum curve of the Lyapunov exponents function of operating parameters.
A modification of the divergence criterion of Hedges & Rabitz (1985) to detect the loss of thermal stability of chemical reactors based on the analysis of the Lyapunov numbers derived from the eigenvalues of the Green matrix. The modification associates the incipient risky operating conditions of the chemical reactors to the "breaking points" of the curve slope of the positive maximum of Lyapunov numbers function of operating parameters.
Proposal of a probabilistic index for evaluation of the runaway probability of a chemical reactor in the presence of multiple sources of uncertainty. The stochastic index includes both the uncertainty resulted from the random fluctuations (statistically distributed) of the operating and control parameters, but also the uncertainty in estimate the runaway boundaries (the se-called "critical surface"). This novel probabilistic criterion allows determining an optimal operating policy of a chemical reactor, more robust, of higher economic quality, and under an assumed tolerable risk. This index also allows evaluation of the proximity risk associated to severe operation of chemical reactors in the vicinity of runaway boundaries.
Proposal of a computing methodology for robust multi-objectiv optimization of industrial chemical reactors of high thermal sensitivity, by using a mixed deterministic-stochastic criterion. The considered optimization objectives are of economic nature (productivity, yield), but also safety ones related to the process runaway probability in the presence of operating parameter uncertainty and fluctuations.
Studies on the occurrence of the accident Domino effect after a chemical accident in chemical plants located in a close proximity. Exemplification is made for the aniline synthesis plant, and the butane oxidation plant [2], and short CV and publications of [3].

7-4. An industrial outstanding realization of high impact

On 1980-1985, while working with ICECHIM-IECB, dr. G. Maria elaborate kinetic models for the MTO/MTG catalytic processes, and was a key engineer in-charge with the design of an industrial pilot-plant at Petrochemical works Refinery Ploiesti (Romania) for the methanol conversion to olefins (MTO), or gasoline (MTG)(1985). This industrial pilot (see chap. 2) was also used to test several catalytic processes, such as: I) the selective alkylation of olefins with methanol; ii) catalytic alkylation of benzene or ethylbenzene with olefins (EB); iii) methanol conversion to BTX (aromatic hydroc.); iv) ethanol conversion to olefins (EtOH). For such an achievement, dr. G. Maria received the "Nicolae Teclu" Prize of the Romanian Academy on 1985. At that time this plant was the first in the world to test MTO/MTG processes. A detailed and documented description (with references) of this industrial achievement is done in his Ebook [15].

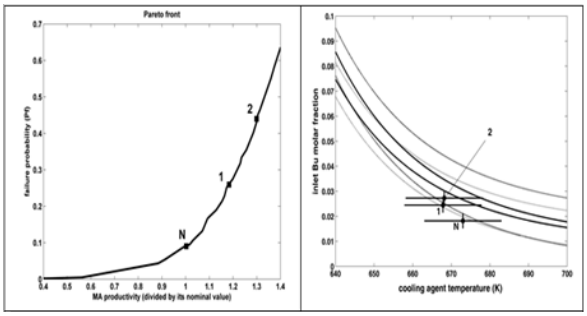

Figure 15a: Risky chemical reactor sensitivity analysis, and optimization, by using the Pareto-front rule, with including an original probabilistic safety index [2], see also his short cv and publication list of [3]. Optimal Pareto solutions for the industrial fixed-bed catalytic reactor used for oxidation of butane to maleic anhydride in vapour phase (left), and the selected operating policies in the [inlet butane fr. vs cooling agent temperature,Ta] plane, by placing the

tried setpoints in the runaway boundaries (solid lines) and their 68% confidence bands (dash lines)[2,3].

7-5. Contributions to the basic numerical calculus and statistical algorithms

Prof. Maria was very productive in developing novel numerical methods for solving nonlinear optimization/estimation problems (finding the global extremum of a multi-modal objective function in the presence of multiple constraints, that is solving NLP, MINLP problems) to be of use for identification of (bio)chemical kinetic models. For instance, he proposed of a new statistical test to detect the redundant part of a mathematical model [29]. Proposal of an expert system and numerical algorithms for the identification of (bio) chemical kinetics, by using kinetic model reduction and transfer-of-information from kinetic databanks [25-28]. Proposal of a procedure for solving nonlinear algebraic models of (bio) chemical processes [2]. The most important are below summarized. See also above textbooks in Romanian no.1, 3, and 5 of Table 4a, and [19-22]. The most important novel numerical algorithms are shortly described in Table 6.

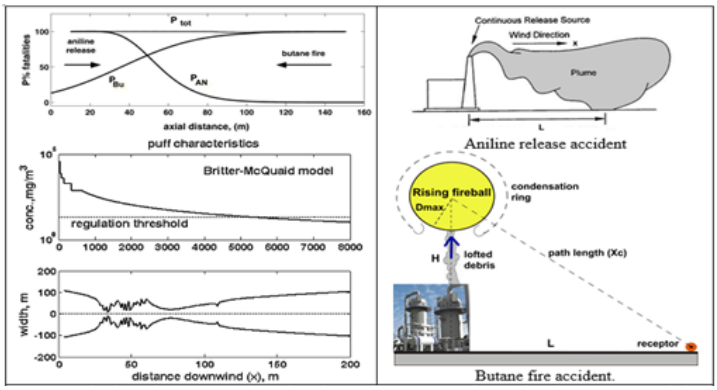

Figure 15b: Risky chemical reactor sensitivity, risk analysis, and optimization. Influence of production capacity and plant proximity on the severity of accident consequences and domino-effect occurrence, for two neighbour risky reactors: I) catalytic hydrogenation of nitrobenzene (NB) to aniline (AN) in vapour phase, and ii) n-butane (Bu) catalytic oxidation with air to maleic anhydride (MA) in vapour phase.

Table 6: The Most Important Numerical Algorithms Developed and Published by Prof. Maria [2], See also his Short CV and Publication List [3].

MMA, MMAMI – a very effective numerical optimization structured procedure for iterative adaptive random search of a function global extremum, in the case of a nonlinear multi-modal objective function (convex or non-convex, in the presence of multiple constraints), that is the nonlinear programming (NLP) problem.(Maria,1986-2003)[30,31]. MMA can solve NLP by using an iterative adaptive random search with successive automated expansion/contractions of the search domain. Later, Dr. Maria extended the MMA procedure applicability, by proposing the MMAMI numerical algorithm able to successfully solve MINLP optimization problems [31] (i.e. NLP with mixed integer and continuous variables). Dr. Maria chose to donate the right to use these routines to several universities: TU Saarlandes (1999); TU Erlangen/Karlsruhe (Germany) (2000), and Tianjin Inst. Ind. Biotechnology (China) (2010).
CPEMR – a combination of numerical algorithms to concomitantly estimate and reduce a (bio)chemical kinetic model. The procedure is based on classic statistical tests but also on an original statistical test [2,25-29].
KINEXP – an expert system for identification of a (bio)chemical kinetic model from kinetic curves available from kinetic experiments. KINEXP uses a transfer of information rule from kinetic data-banks (an "artificial intelligence" like original algorithm) [2,25-29].
MIP – a shortcut direct numerical algorithm [28] for (bio)chemical process kinetic model estimation by using a transfer of information algorithm from kinetic data-banks [2,25-29].
RSA – an original statistical test to determine the redundant part of kinetic (math) model [2,25-29].
GHSM- a novel numerical procedure for solving nonlinear mathematical models by using a generalized half-search method (Maria & Smigelschi,1986) [2].
DSC-MIP- Proposal of a combined experimental method (DSC calorimetry) with a numerical method (MIP) to identify the global chemical kinetic models (Maria& Heinzle,1998-1999) [2].
Proposal of a numerical procedure to detect complex reaction invariants. Such a procedure will allow gradual reduction of the kinetic model by using lumping techniques [2,34] (CABEQ-2006). The method allows determining the relationships between the rate constants of an apparent reduced model (identified from experimental kinetic data) and those of the intrinsic extended kinetic model. Exemplification have been made in the case of a complex kinetic model (64 reversible reactions and 16 species) used to simulate the chemically controlled drug release from a multi-valent dendrimeric support. The kinetic model was finally reduced to only 4 reversible reactions including 5 lumped conformational isomers, with rate constants identifiable from experimental data [33,34].

7-6. A combined experimental method (DSC calorimetry) with a numerical method (original shortcut MIP)

The procedure is able to identify the global chemical kinetic models in the early safety assessment of chemical processes. The combined experimental method (DSC calorimetry) and the numerical method (the shortcut estimator MIP of Maria & Rippin, 1997) was applied to identify the global chemical kinetic models in the early safety assessment of a chemical process.

7-7. Proposal of a numerical procedure to detect the complex reaction invariants for the gradual reduction of kinetic models by using lumping techniques

The method allows determining the relationships between the rate constants of an apparent reduced model (identified from experimental kinetic data) and those of the intrinsic extended kinetic model. Exemplification and tests have been made in the case of a complex kinetic model (64 reversible reactions and 16 species) used to simulate the chemical controlled drug release from a multi-valent dendrimeric support

based on melamine. The kinetic model was finally reduced to only 4 reversible reactions including 5 lumped conformational isomers, with rate constants perfectly identificabile from experimental data [33]. Then, the method detect the linear relationships between the rate constants of the extended and reduced kinetic models [34].

7-8. Contributions in bioinformatics, systems biology, and computational biology

Dr. Maria proposed novel concepts of modular modelling of living cells (belonging to the central carbon metabolism, genetic regulatory circuits (like genetic switches, operon expression), individual gene expression regulation), based on application of chemical engineering modelling principles, lumping techniques, and nonlinear systems theory with applications in Systems Biology and Synthetic Biology for the in-silico design of GMO-s.). Among these are to be mentioned the followings:

7-8a. Significant contributions in bioinformatics

Among them, proposal of a large number of dynamic models (on a deterministic basis) to simulate various metabolic processes in living cells, related to the central carbon metabolism (CCM), and others, such as (Table 8): i) individual gene expression regulatory modules (GERM); ii) genetic regulatory circuits (GRC) of a modular construction used to design novel GMO of industrial interest [13,17,18] (Fig.12A-D); iii) glycolysis, and glycolytic oscillations (Fig.12A)[14]; iv) interference of two oscillatory processes, that is glycolysis and tryptophan synthesis in E. coli (Fig.12C); iv) mercury-operon expression, induction, and amplification in cloned E. coli or of Pseudomonas sp (Fig.12B); v) the in-silico „gene knockout" techniques to obtain GMO (E. coli) displaying a high biomass and target succinate production rate [18]. In short, the excellent recent contributions of dr. Maria in Bioinformatics concern a novel modelling framework in developing cellular metabolic processes simulators, that is the so-called "variable-volume-whole-cell" VVWC approach. While the past and current cell dynamic models ensure some holistic cell properties (such as homeostasis, self-regulation of syntheses, and of gene expression, perturbation treatment, etc.), by imposing lot of constraints (such as "the total enzyme activity" and "total enzyme concentration", etc.), but ignoring the cell volume increase, dr. Maria promoted inclusion of thermodynamic isotonicity relationships/ constraints, and, proves step-by-step in a mathematical way; in the VVWC, such constraints ensure cellular intrinsic properties in a natural way (and not derived from artificial hypotheses). Such concepts, and rules translated from (bio)chemical engineering principles and nonlinear systems theory are explained, proved, and exemplified over their large number of papers in this respect (reviewed in [13,17,18] textbooks).

7-8b. The so-called "variable-volume-whole-cell" VVWC modelling framework

As a major contributions in the theoretical / math modelling of the metabolism in the living cells (single cell analysis), a novel modelling concept / framework was promoted by dr. Maria to derive dynamic models of cell metabolic reactions, in a holistic approach. This so-called "variable-volume-whole-cell" VVWC approach ensures cell processes homeostasis, and the individual / holistic GRC regulatory properties, by including in a natural way constraints related to the cell system isotonicity, and the variable-volume in relationship to the species reaction rates [13]. Such an isotonicity constraint is required to ensure the cell membrane integrity, but also to preserve the homeostatic properties of the cell system, not by imposing "the total enzyme activity" or the "total enzyme concentration" constraints suggested in the literature. This novel modelling framework is leading to accurately simulate lot of cell metabolic effects, such as: relationships between the external conditions, species net synthesis reactions, osmotic pressure, cell content (ballast) influence on smoothing the continuous perturbations in external nutrient concentrations, etc. [13,17,18]. While the past and current cell dynamic models ensure some holistic cell properties (such as homeostasis, self-regulation of syntheses, and of gene expression, perturbation treatment, etc.), by imposing lot of constraints (such as "the total enzyme activity" and "total enzyme concentration", etc.), dr. Maria promoted inclusion in the VVWC models thermodynamic isotonicity relationships/ constraints, He proved step-by-step, in a mathematical way, how such constraints ensure cellular intrinsic properties in a natural way (that is not derived from artificial hypotheses). Such concepts, and rules translated from (bio)chemical engineering principles and nonlinear systems theory are explained, proved, and exemplified over their large number of papers in this respect (reviewed in [13,17,18]).

7-8c. Characterize some cell holistic properties under the novel VVWC kinetic modelling framework

By using several case studies, Prof. Maria proved in a math-way that VVWC modelling framework is superior to the classic (default) CVWC ("constant-volume-whole-cell") modelling concept. Thus, VVWC offers more realistic predictions [13,17,18] of the local and global properties of GRC controlling the metabolic syntheses (e.g. efficient treatment of stationary or dynamic environmental perturbations, species connectivity, cell homeostasis stability and multiplicity, responsivity to perturbations, etc.). Also, VVWC holistic formulation inherently points-out and well reproduce various cell properties (Table 7).

Table 7: Cell Regulatory Properties Inherently Reproduced by the VVWC Holistic Formulation.

1. Secondary perturbations transmitted via the cell volume.
2. System isotonicity constraint reveals that every inner primary perturbation in a key-species level (following a perturbation from the environment) is followed by a secondary one transmitted to the whole-cell via cell volume.
3. Allows comparing the regulatory efficiency of various types of GERM-s.
4. Allows a more realistic evaluation of GERM performance indices.
5. Allows studying the recovering/transient intervals between steady-states (homeostasis) after stationary perturbations.
6. Allows studying conditions when the system homeostasis intrinsic stability is lost.
7. Allows studying the self-regulatory properties after a dynamic/stationary perturbation, etc.
8. Allows studying the plasmid-level effects in cloned cells.

7-8d. Contributions to modelling the dynamics of regulatory cell systems, referring to individual GERM-s, and GRC controlling the metabolic syntheses

More specifically, contributions to simulate cell regulatory systems are referring to the following issues [13,17,18]:

a) The VVWC math-modelling approach, explicitly linking the volume growth, external conditions, osmotic pressure, cell content ballast, and net reaction rates for all cell-components is more suitable for predicting local and holistic properties of the metabolic network, leading to more realistic predictions of some cell properties (e.g. evaluation of the regulatory efficiency indices of individual GERM-s, or GRC; cell content inertial/smoothing effect in treating perturbations). The considered regulatory efficiency indices are the following: stationary regulation, dynamic regulation, regulatory robustness, species interconnectivity, quasi-steady-state (QSS, homeostasis) stability, QSS stability strength,

b) Promotion of the holistic and modular approach in dynamic modelling GRC-s;

c) Elaboration of various models for GERM-s; in-silico study of GERM chain properties by placing them in a growing cell, and by mimicking the cell behavior under in-silico simulated environmental conditions (stationary or perturbed); Eventually, GERM kinetic models have been organized in a library (Fig.10A-B) easy to be used to build-up modular genetic regulatory circuits GRC. [13](see Table 8 for some applications);

Table 8: Some Case Studies of In-Silico Design of GMO Approached by Dr. Maria [13,18].

a) In-silico design of a genetic switch in E. *coli* with the role of a biosensor [13,17,18].
b) In-silico design of a genetic modified E. *coli* with a maximized capacity of succinate (SUCC) production (Figure: 11A-B).
c) Simulations using a modular structured VVWC dynamic cell model to reproduce the induced mercury(mer)-operon expression in Gram negative bacteria (Pseudomonas *putida*, E. *coli*) for mercury ion uptake and reduction [17,18] (Figure: 12B,18).
d) In-silico design of a cloned E. coli with a maximized capacity of mercury uptake from waste-waters, and optimization of the corresponding industrial bioreactor [17,18] (Figure: 12B,18).
e) In-silico design of a genetic modified E. coli with a modified glycolytic oscillator (Fig.12A) with applications in the biosynthesis industry [14,18].
f) In-silico modulate the bioreactor operating conditions and design a modified E. coli to maximize the production of tryptophan [18] (Figure: 12C).
g) In-silico modulate the iron metabolism heme synthesis in mitochondria using a GMO eukaryotic cell using a VVWC structured reduced model of Hudder, Maria, et al. (2002) [EBOOK3] [18], with applications in medicine [18] (Figure: 10D).
h) In-silico re-configure the metabolic pathway for Phenyl-alanine synthesis in E. *coli* [18] to maximize its production. That implies to modify the structure and activity of the involved enzymes, and modification of the existing regulatory loops. Searching variables of the formulated mixed-integer nonlinear programming (MINLP) optimization problem are the followings: the regulatory loops (that is integer variables, taking "0" value when the loop has to be deleted, or the value "1" when it has to be retained); the enzyme expression levels (that is continuous variables), and all these in the presence of the stoichiometric and thermodynamic constraints. To solve this complex optimization problem, two contrary objectives are formulated: maximization of the Phenyl-alanine selectivity, with minimization of cell metabolites' concentration deviations from their homeostatic levels (to avoid an unbalanced cell growth). The elegant solution of the problem is the so-called Pareto-optimal front, which is the locus of the best trade-off between the two adverse objectives. By choosing two problem solution alternatives from this Pareto-curve, it is to observe the large differences between the two pathways into the cell, fully achievable by genetic engineering [18] (Figure: 12D).

d) Development of a methodology for GERM assembling to simulate a defined operon expression via its associated GRC, the methodology is useful for in-silico design of GMO with desired motifs for industrial or medical applications [13,17,18];

e) Applications of the modular and VVWC holistic modelling approach for in-silico design of GRC-s, such as those mentioned in Table 8;

f) Study of the criteria associated to gene knockout strategies for in-silico design of optimal metabolic fluxes allowing the cell growth with maximizing chemical production targets (case study for succinate and biomass production maximization in E. coli cells; case studies for production of amino-acids) [18].

7-9. Applications of using modular GRC kinetic models for in-silico design of GMO of industrial use.

Applications refer to building-up dynamic models for simulating essential cell processes related to CCM by using the novel VVWC modelling framework [13,17,18]. Examples concern genetic regulatory circuits (GRC) for protein synthesis, glycolysis, synthesis of amino-acids, expression of some operons (Table 8). Eventually, the developed GERM models have been organized in the form of a library of GERM module types, extremely useful to individually study the GERM-s regulatory properties, and for the in-silico design of GRC to get genetically modified micro-organisms (GMO) with desirable characteristics, with potential applications in industrial biosyntheses (e.g. production of vaccines), medicine (gene therapy), construction of new devices based on cell-cell communicators, biosensors, etc. (Fig.10A-C). VVWC cell models allow to characterize the dynamics of various metabolic cell processes, including GRC-s [13,17,18]. Applications include improving bioprocesses of industrial interest. Several exemplifications are extensively described in [18], as mentioned in Table 8. GERM models can be in-silico studied concerning their regulatory efficiency and properties, by using quantitative measures introduced by dr. Maria. GERM can be then used to build-up complex GRC-s by using building blocks rules of Systems Biology (ex. for E. coli, P. putida). Rate constants are estimated from the homeostatic cell data and from mimicking the GRC response to dynamic or stationary perturbations. GERM models can be used for the in-silico design and test GMO of desired characteristics (Figure 10A-C; Figure 12 B-D);

7-10. Development of kinetic models to simulate the drug release in biological fluids

7-10a . **Proposal of novel kinetic models to simulate the controlled drug release** from (non-)functionalized porous supports in biological fluids with chemical and/or diffusional control. Examples include the release of various test drugs (irinotecan, amikacin, anti-TBC, cephalosporines, cefotaxime, cefuroxime, cefalotine, etc.) from (Al-)MCM-41 (non-)functionalized silica supports in intestinal fluids (Figure 13A), or controlled released of drugs from multi-valent dendrimeric supports based on melamine in human plasma (Figure 16).

7-10b . **in-silico design of optimized drug-linker-support systems** .The developed deterministic math models for drug release include enough parameters, related to the support characteristics (composition, morphology, BET area, porosity, pore volume, tortuosity, pore size and distribution), together with the drug parameters (structure, initial load on the support, diffusivity), reticulation agent properties (structure, hidrophobicity, support coverage), and the biological receptor fluid properties to allow the in-silico design of optimized drug-linker-support systems, including multi-linker systems (Figure 13A).

7-10c. Development of kinetic models to simulate the chemically controlled drug release in human plasma

The case study refers to the release of a drug linked by disulphide bonds on a tetra-valent dendrimeric support based on melamine. The reduced (apparent) reaction scheme includes 4 reversible reactions for successive release of the ligand (drug) and 5 groups of conformational isomeric intermediates, perfectly identifiable from experimental data of [33]. This reduced kinetic model was linked, via linear relationships to the extended (intrinsic) kinetic model of the process (64 reactions and 16 species, Maria [34]) by using invariance relationships. The computing methodology to estimate the intrinsic kinetic model rate constants from the apparent model rate constants is described by [34], being of high generality (Figure 16).

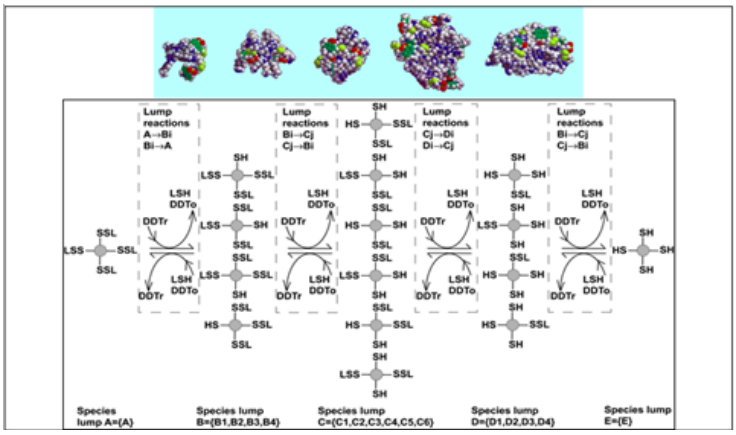

Figure 16: (up) Multi-valent dendrimeric structures. (down) Scheme of the successive drug release from a tetra-valent dendrimeric support (the intrinsic model, [33,34]).

7-11. Modelling, and optimization of chemical, enzymatic reactors, and bioreactor operation in various constructive and operating alternatives

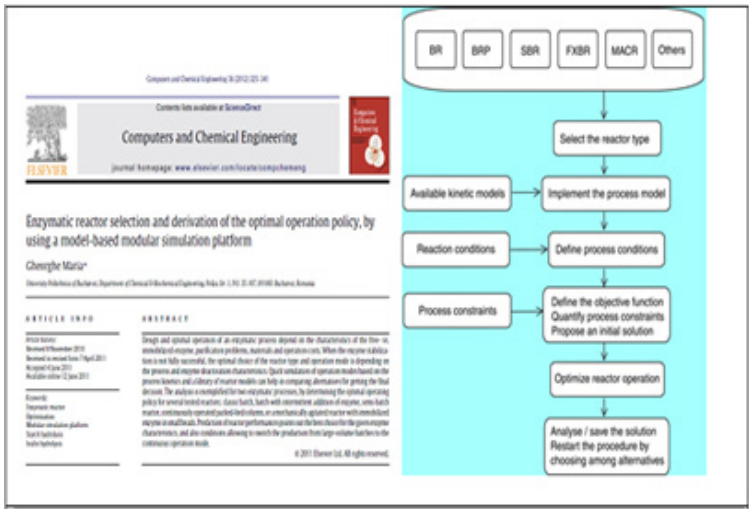

Figure 17: Scheme of the modular simulation platform of Maria (2012) used to determine the optimal operating policies of enzymatic reactors for a given enzymatic process [2,3].

On [2012], dr. Maria proposed a systematic computing methodology based on a modular simulation platform (Figure 17) [2,3] for the most suitable reactor selection by comparing the performances of the main types of enzymatic reactors for a given enzymatic process of known kinetics and, eventually, for optimizing its operation. This procedure can help in determining the level of enzyme stability that makes an operating alternative to be economically preferred. The simulation-optimization platform included the following enzymatic reactor models:

o batch reactor with initial addition of enzyme (BR);
o batch operation with intermittent addition of enzyme following a certain addition policy (BRP);
o semi-batch reactor with a continuous constant or variable feed flow rate of the enzyme and/or substrate solution (SBR);
o mechanically agitated continuous reactor (MACR) with immobilized enzyme on a suspended suitable porous support;
o fixed-bed continuous reactor (FXBR) with immobilized enzyme on porous support packed in columns.

To support such a large computational effort for kinetic model identification and reactor optimization in the presence of multiple constraints, Dr. Maria developed and published original numerical methods (MMA, MMAMI, CPEMR, KINEXP, MIP, RSA, see chap.7E, and Table 6). The used methods also included advanced multi-objective optimization rules, such as derivation of the Pareto-optimal fronts technique, that concomitantly considers contrary optimization objectives. Exemplification has been made for the case studies of Table 9.

Table 9: Some Case Studies Approached by Dr. Maria for Optimization of Enzymatic Reactors and Bioreactors.

Optimization of the MACR multi-enzymatic reactor for D-glucose oxidation to keto-glucose in the presence of pyranose oxidase and catalase by means of the Pareto-optimal front numerical technique (Maria & Crisan, 2015,2017) [2,18] (Figure: 19).
Optimization of the MACR multi-enzymatic reactor for fructose reduction to mannitol in the presence of MDH (mannitol dehydrogenase) and NADH (Nicotinamide adenine dinucleotide), with intermittent addition of MDH enzyme. The process co-factor NADH is continuously regenerated in-situ by the expense of formate decomposition in the presence of FDH (Formate dehydrogenase) (Maria & Crisan, 2017) [2,18] (Figure: 14).
Optimization of an SBR multi-enzymatic reactor for inuline hydrolysis (Maria, 2012) [2,3].
Optimization of an SBR multi-enzymatic reactor for starch hydrolysis (Maria, 2012) [2,3] (Figure: 20).
Optimization of the tri-phase MACR bioreactor for mercury ions removal from wastewaters by using bacterial cultures immobilized on porous alginate supports (Scoban & Maria, 2016,2017) [2,3] (Figure: 18).
Optimization of the tri-phase MACR bioreactor for mercury ions removal from wastewaters by using a fluidized-bed bioreactor and bacterial immobilised cultures of Pseudomonas putida cells (Maria, Luţă, 2013) [2,3,18] (Figure: 12B).
Optimization of the SBR bioreactor used for the tryptophan production by using a culture of E. coli (Maria et al. 2018) [2,18] (Figure: 12C).
In-silico analysis of optimal operating conditions of a batch or of a semi-batch bioreactor for monoclonal antibodies (mAbs) production using a hybridoma cell culture. The study is aiming at determining bioreactor optimal operating conditions leading to maximization of mAbs production in batch or fed-batch operating mode [2,18]. (Figure: 12D,21).

8. Service to Chemical & Biochemical Reaction Engineering

Prof. Maria has been active in professional organizations and supportive of the chemical and biochemical reaction engineering, and process system engineering community. Thus, Dr Maria has undergone an intense activity in the CAPE (Computer Application in Chemical Engineering), that is a dedicated section of the EFCE (European Federation of Chemical Engineering) being the Romanian representative on 2005 (Davos meeting), and 2011 (at 1st European Congress of applied Biotechnology, 25 – 29 Sept. 2011, Berlin). Prof. Maria was one of co-chairmans of the ESCAPE-17 conf. of CAPE in Bucharest (2007) (Fig.23). He published lot of papers in Computers & Chemical Engineering (CACE) (more than 15). CACE is a top journal including the most representative contributions of CAPE. He participated with consistent contributions to various ESCAPE Conf, as followings: 1992, Toulouse (France); 1995, Bled (Slovenia) (plenary lecture); 1996, Rhodes (Greece); 1999, Budapest (Hungary); 2000, Florence (Italy); 2007, Bucharest (Romania). Prof. Maria presented more than 31 invited Lectures to various Universities in EU, CAN, USA, China (among them: Princeton Univ. 1994, Texas A&M University 2002, EPFL Lausanne 1992-1997, Queen's Univ. Kingston 1994 Canada, BASF Ludwigshafen 1996).

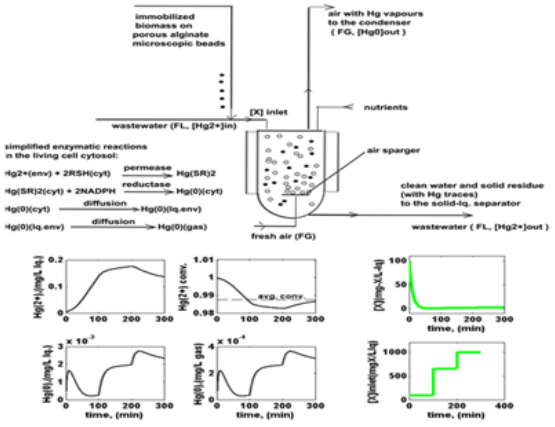

Figure 18: Optimization of a mechanically agitated bioreactor used for the removal of mercury ions from wastewaters by using immobilized E. coli on alginate beads (Scoban and Maria, 2016). Cloned cells with mer-plasmids have also been design in this respect (Maria & Luta, 2013; Maria,2010) [2,3,18].

He is a reviewer for many (bio)chemical engineering journals (25). He also has an intense editorial activity, being member in the scientific/ editorial board of the followings scientific journals.

I) Chem. & Biochemical Eng. Q. (Zagreb)
ii) Revista de Chimie (Bucharest)
iii) The Scientific Bulletin of University POLITEHNICA of Bucharest
iv) Bulletin of Romanian Chemical Engineering Society
v) ECOTERRA Journal of Environmental Research and Protection (edited by Romanian Society of Environmental Sciences and Engineering, Cluj-Napoca Romania).

He was also an expert for various research programs of EU (FP6-Bioengineering, and NEST safety engineering sections, 2003-2006), or of national level (Biotech, 2006).

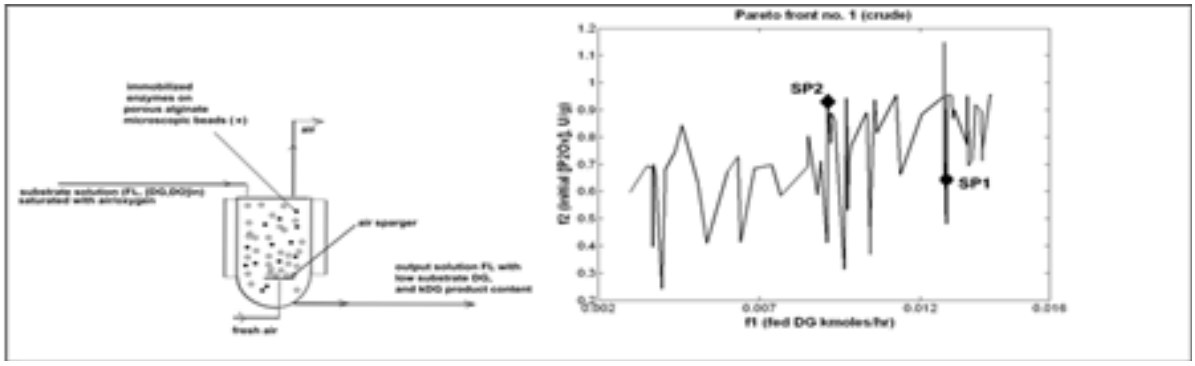

Figure 19: Optimization of a multi-enzymatic mechanically agitated reactor used for oxidation of D-glucose, by means of the Pareto-optimal front numerical technique (Maria & Crisan, 2017) [2,3,18].

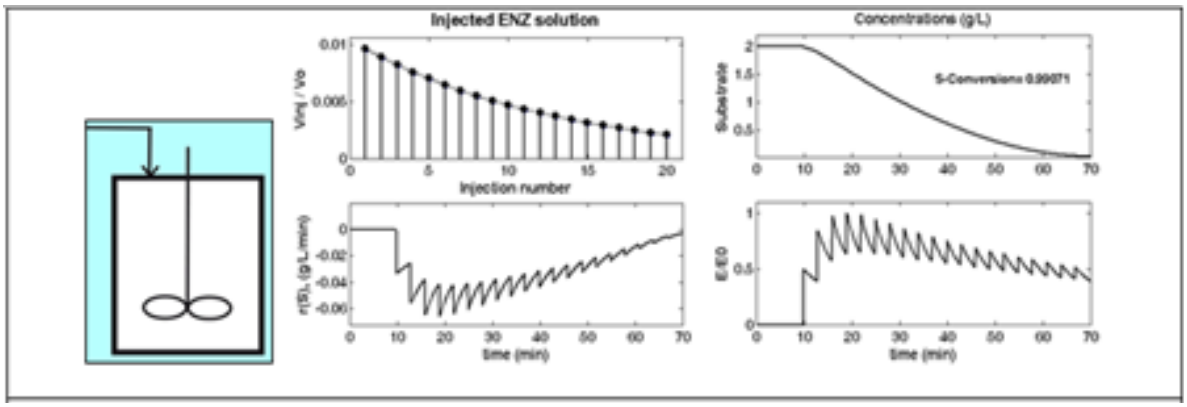

Figure 20: Optimization of the semi-continuous reactor used for starch hydrolysis in diluted solutions (Maria, 2012) [2,3].

Prof. Maria co-chaired or was member of the organizing Committees of 16 international conferences Among them: 5th Int. Conference on Computational Bioengineering (ICCB-5), 11-13 September, 2013, Leuven, Belgium; ROMPHYSCHEM-15, 15-th International Conference of Physical Chemistry, 11-13 September, 2013, Bucharest; 13th Edition of Academic Days, June 13-14, 2013, Timişoara (Romania); ELSEDIMA 10th , 11th, and 12th International Conference (Environmental Legislation, Safety Engineering and Disaster Management), 18-19 September 2014; 26-28 May 2016; 17-19 May 2018, Cluj-Napoca (RO), etc.

He presented a large number of plenary and key lectures (more than 15) to various national and international conferences. Among them: 5th European Symp. Computer Aided Process Engineering, June 11-14, 1995, Bled (Slovenia); 20th Croatian Meeting of Chemists & Chemical Engineers, Feb. 2007, Zagreb (HR); 12 th National Conference of Academic Days, Timisoara (RO), 26-27 May 2011; 15th ROMPHYSCHEM, International Conference of Physical Chemistry, 11-13 September, 2013, Bucharest; International Conference on Chemistry and Chemical Engineering RICCCE-18, Sinaia, 4-8 Sept. 2013; National symposium "Environment & Progress", University Babes-Bolyai Cluj-Napoca, 25 October, 2013; 10th ELSEDIMA International Conference on "Environmental Legislation, Safety Engineering and Disaster Management", 18-19 September 2014, Cluj-Napoca (Romania); Symposium SICHEM-2016 (8 Sept. 2016; Rom. Soc. Chem. Eng.), and SICHEM-2018 at University Politehnica of Bucharest, 6-7 Sept.2018, etc.

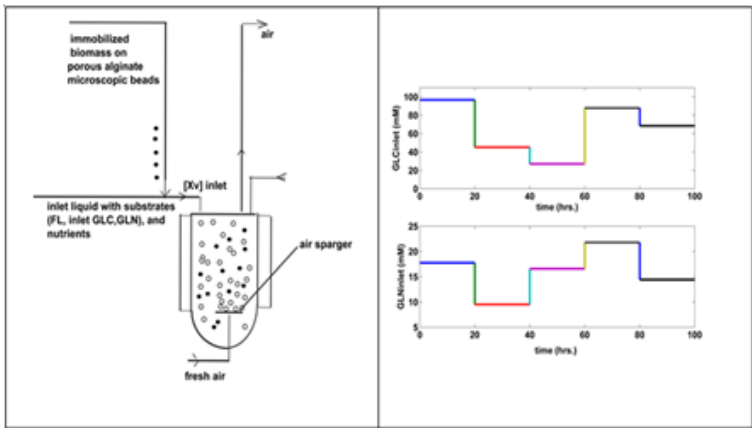

Figure 21: In-silico derivation of optimal control policies for a semi-batch bioreactor for monoclonal antibodies production using a hybridoma cell culture (Maria et al., 2018) [2,3,18].

Table 10: Some International Cooperative Projects Promoted by Dr. Maria [2-3].

2010 (July-August). Visiting Professor within project KIP KSCX2-YW-G-030 on "Simulation and applications of integrated cellular networks", at Tianjin Institute of Industrial Biotechnology, Chinese Academy of Sciences, Tianjin (China) (Prof. Jibin Sun).
2009 (July-August). Visiting Professor with DAAD Research Grant no. A/09/02572/2009, on: "Dynamic modelling of some genetic regulatory circuits to simulate the bacterial resistance in a polluted environment by using the whole-cell modelling approach", at Technische Universität Hamburg (TUHH), Institute of Bioprocess & Biosystems Engineering (Germany) (Prof. An-Ping Zeng).
2006 (July). Guest Research Scientist at Technische Universität Braunschweig (Germany), and German Research Centre for Biotechnology, within project DFG-578 on "Development of Biotechnological Processes by Integrating Genetic and Engineering Methods" (Prof. Wolf Deckwer).
2002 – 2003 (March). Research Scientist at Texas A&M University (College Station, Texas, USA), Department of Chemistry and Cellular Biology, within projects National Institute of Health NIH PAL-GM63958 / 2002-2003: „Kinetic simulations of minimal living systems", and NIH EES-GM64650 / 2002-2003: "Molecular recognition in dendrimers based on melamine - Kinetics of programmable drug release in human plasma", (Prof. E. Simanek).
2000 (June-Aug). Guest Professor at TU Erlangen-Nürnberg (Germany), Dept. Chemical Engineering, within project: "Kinetics Identification and Process Simulation for the Drinking Water Denitrification via a Three-Phase Catalytic Membrane Reactor" (Prof. G. Emig, Prof. Roland Dittmeyer).
2000 (Feb-March, Nov-Dec). Guest Professor at University of Porto (Portugal), Departamento de Engenharia Quimica (Automatics & Robotics in Bio-Chemistry), director of NATO Grant no. 974850-99/1999-2001 "Identification of Optimal Operating Conditions and Risk Limits for Biological Wastewater Treatment Plants" (partners Prof. Sebastiao Feyo de Azevedo, Prof. Romualdo Salcedo).
1999 (July-Aug). Visiting Professor with DAAD Research Grant no. 324-ro-99/1999 at Universität des Saarlandes Saarbrucken (Germany), Dept. Biochemical Engineering, on: "Testing Novel Short-Cut Methods for Kinetic Characterization of Biochemical Processes" (Prof. Elmar Heinzle).
1997 (Aug-Oct). Research stage at Swiss Federal Institute of Technology ETH Zürich (Switzerland), Depatment of Chemical Engineering, within project SNSF (Swiss National Science Foundation) no. 7IP - 050113 /1997-1998: "Ecological and Risk Analysis in Chemistry" (Prof. Konrad Hungerbühler).
1992-1997. Asistant Professor (Oberassistent Klass 18) with Swiss Federal Institute of Technology - ETH Zürich (Switzerland), Chemical Engineering Department, (Universitat Strasse 6, CH-8092), Systems Engineering Group of late Prof. David W.T. Rippin (1992-1995), and Non-conventional Source of Energy Group of Prof. Alexander Wokaun (1996).

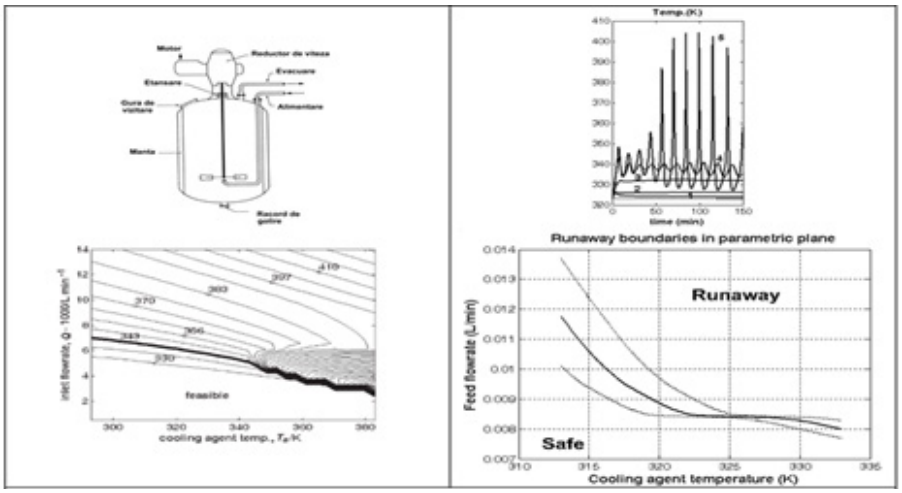

Figure 22: [LEFT] Detection of the QFS operating region for the semi-continuous reactor used for acetoacetylation of pyrrole (Maria et al., 2010)[2]; [RIGHT] Prediction of critical operating conditions for a catalytic semi-continuous batch reactor (Maria and Dan, 2011,2012) [2,3].

He was very supportive for the chemical and biochemical engineering community, with supervising /coordinating more than 50 BSc licence projects, more than 18 MSc-dissertations, and 10 finalized PhD-s in chemical and biochemical engineering at UPBuc. (1980-2019). With an impressive scientific production of over 230 papers in ISI journals and intl. Conferences, 11 books (RO,USA), 5 teaching books (UPBuc., RO) (Table 4a-b)[2-4], with one design industrial plant (chap.2), and several pilot plants design and put in operation in Romania (at PWB,1985, chap. 2), or Switzerland (at Paul Scherer Inst., NEFF project,1992-1996, chap. 3), or with optimized SBR reactors under safety requirement (CIBA-Novartis, Basel, 1994-1996; Maria & Dan, 2010-2012)[2], Prof. Maria has had a significant impact on the science and the practice of Chemical and Biocemical Reaction Engineering in Romania and world-wide. He also very supportive for the chemical and biochemical engineering teaching, with introducing novel courses in this curricula at UPBuc (Table 2), with elaboration and publication of dedicated teaching books (Table 4a-b). In recognition to his service to academic community, he received several honours and awards, as mentioned in Table 11.

His involvement and publications in a large area of research topics are coming from his vivid and very creative spirit, and tireless search in the vast domain of modelling, design, and optimization of (bio)chemical processes. Thus, many of their publications are coming from his participation over the past 25 years to more than 15 international Projects, making short research stages at various universities in EU, USA, CAN, China (see Table 10).

Being a strong personality, marked by dedication, and initiative, Prof. Maria was actively involved in educational and research activities in Romania, being part to PhD analysis committees, and participating to chemical eng. conferences organized by various Romanian universities (Iasi, Timisoara, Cluj). Thus, he carried out a meritorious activity for the benefit of the academic community:

a. He presented more than 10 invited plenary lectures in intl. Conferences;

b. He was a member of the International Conferences' Scientific Committees (more than 15);

c. He was a member of Profesoral Councils of the Faculty of Applied Chemistry of UPBuc. (2012-2014);

d. He was an Assistant Professor with ETH Zurich (Technische Chemie Dept. 1992-1997);

e. He was a fellow of National Institute of Health (NIH) USA at Texas A&M University, Dept. of Chemistry and Cell Biology (College Station USA) (2002-2003);

f. He was a member of the national Romanian Council for Attestation of University Titles, Diplomas and Certificates CNATCDU (2010-2012);

g. He is a Member of: Romanian Society of Chemical Engineering, Romanian Society of Chemistry, Romanian Society of Bioengineering and Biotechnology, DAAD Alumni Fellow Association (Germany), National Society of Science and Environmental Eng. (Romania);

h. He is a member of EFCE (European Federation of Chemical Eng.)- national representative 1995,2011.

9. Academic Accomplishments

With supervising /coordinating more than 50 BSc licence projects, more than 18 MSc-dissertations, and 10 finalized PhD theses (Figure26) in chemical and biochemical engineering at UPBuc. (1980-2019), and by publishing over 150 ISI papers[2], 9 books (Table 4a-b), and 80 communications in intl. Conferences, [2] with design and put into operation of one industrial plant (chap.2), and several pilot plants in Romania and Switzerland (Paul Scherer Inst., chap.3), Prof. Maria has had a significant impact on the science and the practice of Chemical and Biocemical Reaction Engineering in Romania and abroad. He also introduced novel courses in the chemical & biochemical engineering curricula at UPBuc. (Table 2). In recognition to his service to academic community, he received several honours and awards (Table 11).

Table 11: Some honours and awards received by prof. Maria.

• 'N. Teclu' Prize of the Romanian Academy for kinetic studies on selective conversion of methanol to olefins, and for the design and scaleup of the industrial plant at Petrochemical Works Brazi (1985)(Fig.2);
• Diploma of excellence in research of the Romanian Federation of Biomedical Engineering, 2006[2];
• included in "Who's Who in the World in Science & Technology" (1996 - in present);
• the gold medal obtained at the Chemistry Olympics for highschools on 1974 (11 participant countries, among which Russia, Germany, Austria, Sweden, Czech Republic, etc.)[23a-b]
• EU Scientific Expert for EC-FP6 Programme - NEST Group (Safety engineering, and Bioengineering), 2003-2005.
• Swiss National Science Foundation Scientific Expert (Switzerland), 2005-2006.
• Scientific Expert for the Bioengineering Romanian Research Program of the Ministry of Science & Education, and of the Republic of Croatia, 2006.
• top-cited paper (>100) of the Chemical and Biochemical Engineering Quarterly (Croatia), for the paper:
Maria, G., A Review of Algorithms and Trends in Kinetic Model Identification for Chemical and Biochemical Systems, CABEQ 18(3), 195-222 (2004). IF = 1.4. ISSN= 0352-9568.
• 12 awards for the best published papers from the Romanian Res. Agency UEFISCDI (2010-2017).
• member in the Chemistry/Chemical Eng. Committee of national CNATCDU (2011-2012).
• appointed as a correspondent member [35,36](Fig.27) of the Romanian Academy (2019).

Figure 23: Chairing ESCAPE-17 international conference.

Figure 24: Together with my wife on 2005.

Figure 25: [first on the right] To the public defence of one of their PhD students on Jan. 2019 (after his severe stroke suffered on 2014).

The total devotion to the school of Prof. Maria, even at the cost of his health (a severe AVC on 2014, Fig.25), his strong sense of responsibility, self-exigency, team spirit and involvement, brought to Prof. Maria respect and recognition from the colleagues from the Department of Chemical and Biochemical Engineering of U.P.Buc., being appreciated as a balancing factor, but also as a dynamic element in the perpetual renewal of the Department and its adaptation to the requirements of a modern European education and performance.

In any type of activity with students, Prof. Maria managed to mobilize them to participate in research topics of great novelty at national and European level, transmitting to them the passion for science, seriousness and education of the "well done job", the joy to participate through continuous self-improvement and getting results published in top international engineering journals. For us, it was a privilege to collaborate with Prof. Maria, to several publications. Thus, we had the occasion to discover that behind the outstanding scientist there is an encyclopedic personality. Thanks to him we got involved with the fascinating area of modelling the kinetics of very complex metabolic processes in living cells, but also optimization of risky chemical reactors, which are some of their major and worldwide recognized research areas.

Figure 26: Some PhD-s in chemical and biochemical engineering supervised and trained by prof. G. Maria (2008-2020). From left to right: 2011, Dragos Nicolae STEFAN (VEOLIA WATER Techn. Bucharest); 2013, Anca DAN (VTU Engineering s.a. Bucharest); 2013, Manuela Diana BUBOI (married Ene)(Biotehnos s.a. Otopeni); 2014, Ionela LUTA (married TULIGA) (Siemens s.a. Bucharest); 2017, Hasan Hadi Salman KHWAYYIR (Najaf Technical College, Iraq); 2018, Constantin MUSCALU (Siemens s.a. Bucharest); 2019, CRISAN Mara (Siemens s.a. Bucharest) ; 2020, Marina MIHALACHI (married MUSCALU)(Petrodesign Bucharest).

In particular for me (Mara Crisan), it was a privilege to work with Prof. Maria, even for a short period of time, being one of his PhD students. As a scientist he teaches you how to quest for challenges and focus on novelties. Thanks to him I got involved with the fascinating area of modelling the kinetics of very complex multi-enzymatic systems, one of his recognized research areas. For his upcoming 65th birthday on October 2020, their colleagues and co-workers, their many friends, former students and all those who had and have the honor to work with him send their wishes for many happy and fruitful years, and a quick recovery of his health. Finally, we want to wish to Prof. Maria good health, fruitful years of scientific activity, by keeping alive the same intense scientific spirit for the benefit of the new generations of chemical engineers.

ACADEMIA ROMÂNĂ

DIPLOMA

În sesiunea din 30 mai 2019, Adunarea Generală a membrilor
Academiei Române a ales, prin vot secret, pe domnul

GHEORGHE MARIA

Membru corespondent al Academiei Române

PREȘEDINTE
ACAD. IOAN-AUREL POP

SECRETAR GENERAL
ACAD. IOAN DUMITRACHE

BUCUREȘTI, 2019

Figure 27: The Diploma conferred to Prof. Gheorghe Maria to certify him as a correspondent member of the Romanian Academy [36]

Acknowledgements

Dr. Maria full of creative effervescence realizations, involved large sacrifices in his personal life, and have been done with costs of his health (Fig.25). Nothing would have been possible without the full support of his family. This is why Dr. Maria is deeply grateful to his family and, specifically to his wife (Fig.24), for the continuous support over his rich career.

More information and complete list of publications on his personal website:

https://sites.google.com/site/gheorghemariasite/

Supplementary information also on [1]:

http://sicr.ro/wp-content/uploads/2017/01/BRChES_2_2016.pdf

Abbrevations

BTX benzene, toluene, xylene

EB ethylbenzene

CAPE computer application in process engineering

CCM central carbon metabolism

EtOH ethanol conversion to olefins

FBR fluidized-bed reactor

GERM gene expression regulatory module(s)

GMO genetically modified micro-organisms

PSE Process system engineering

GRC genetic regulatory circuits

GS genetic switches

IECB Chemical and Biochemical Institute Bucharest (part of ICECHIM)

MEdC Minister of Education and Research of Romania

MTH methanol to hydrocarbons

MTG methanol to gasoline

NLP nonlinear programming

MINLP mixed-integer nonlinear programming

MPC model-based predictive control

MTO methanol to olefins

NIH National Inst. Of Health of USA

OA C4 olefins alkylation with methanol

PWB Petrochemical Works Brazi (Ploiesti, Romania).

TAMU Texas A&M Univ. (College Station, USA)

UPB, UPBuc. University Politehnica of Bucharest

VVWC the holistic Variable-Volume-Whole-Cell modelling approach of Maria [EBOOK1-3] textbooks 13,18,19]

NIH National Institute of Health of USA

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