European experience of running Infrastructure Systems Biology: perspectives for Russia

Systems Biological modelling as a client-oriented service

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L C S B

Luxembourg Centre for Systems Biomedicine, Luxembourg

UNIVERSITY OF AMSTERDAM

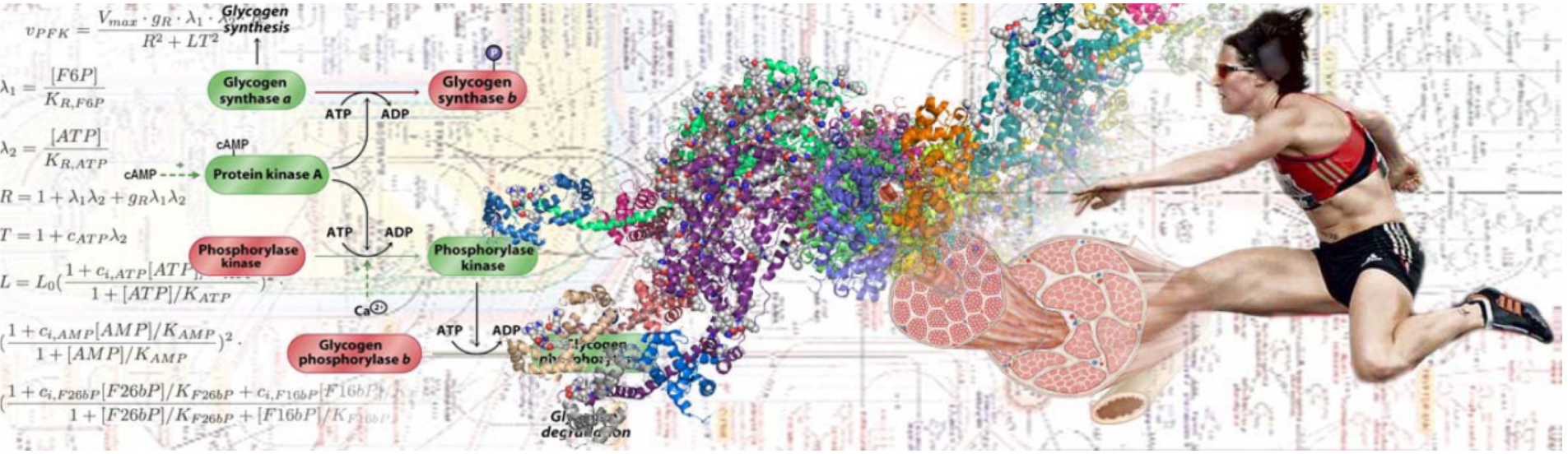
VU University Amsterdam

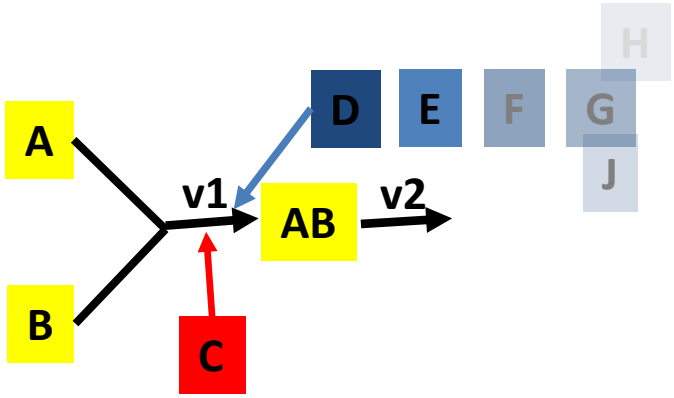
University Amsterdam

VU University

November 13, 2018

Systems Biology – reconstruction of biological emergence *in silico*





High state-dependency of component properties E.g. interactions between proteins A and B depends on

- **Other components (C,D,E,F…)**
- **Hysteresis**
- **Flow of mass and energy through the system**
- **Initial and boundary conditions, etc.**

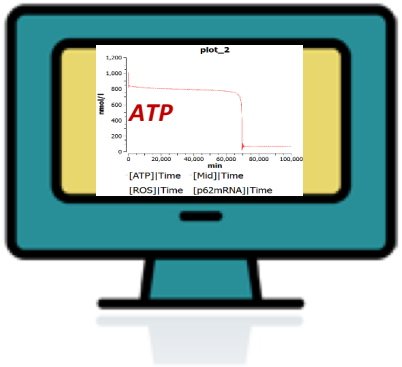
Solution through the systems biological approach:

Protein A + Protein B = Complex AB

v1= kf*[A]*[B]*[C] – kb*[AB]

v2=…..

d[AB]/dt=v1-v2….



ISBE

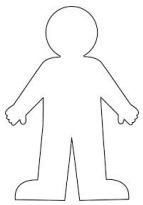
The Infrastructure Systems Biology Europe (ISBE) provides stewardship and help with biological and medical data, their acquisition, their analysis and their understanding. It consists of 5 interconnected infrastructure pillars:

1) The Make Me My Model (M4) pillar consists of a software infrastructure that helps customers to make their various types of data (genome sequence, transcriptome, proteome, metabolome, physiological, kinetic, etc.) predictive and understood via modeling (www.isbe.nl).

2) The Do Me an Experiment pillar is a distributed hardware-plus-service infrastructure that performs systems-biology quality assays as a service (M5; Make Me My Mass Spectra Measurements, enzyme kinetics, metabolomics, and epigenetics will be soon available. For the time being, there is a Systems Metabolomics service at ISBE.IT (www.sysbio.it/isbe): a complete metabolomic platform to perform ad hoc experiments, coupled with constraint-based modeling approach.

3) The Live Model Repository (LMR) of ISBE is a software infrastructure of interconnectable, systems-biology-quality kinetic models through JWS Online (https://jjj.bio.vu.nl/) and COSYS (sysbio.it/cosys/), where users can perform construction, modification, and simulation of kinetic models, and storage of curated ones (JWS), or define mathematical models of biological systems and perform constraint-based (e.g., Flux Balance Analysis) and mechanism-based dynamic simulations (either deterministic or stochastic), drastically accelerated by GPUs (COSYS).

4) The Data and Model Stewardship of ISBE called FAIRDOM (http://fair-dom.org). The FAIRDOM Project was started under the auspices of the ERA-NET programme ERASysAPP and ISBE, jointly funded by CH, DE, NL and UK. FAIRDOM assists researchers to be in control of collecting, managing, storing, and publishing data, models, and operating procedures. FAIRDOM takes responsibility for the Stewardship of research assets services of ISBE.



5) Help Me to Model (HMTM) provides training to customers wishing to make models themselves, in online or workshop tutorials (www.isb.nl).

Nodes

ISBE-light: Active nodes in:
Italy (Naples, Milano)
the Netherlands (Amsterdam, Leiden, Wageningen, Eindhoven, Maastricht),
Slovenia (Ljubljana);

ISBE synergizes with other ESFRIs through Corbel

www.isbe.nl;
www.sysbio.it;
www. nh.cas.cz/isbelight

The Netherlands arm of the Infrastructure Systems Biology Europe (ISBE):

The Netherlands' arm of ISBE-Light Infrastructure for Systems Biology Europe

ISBE.NL

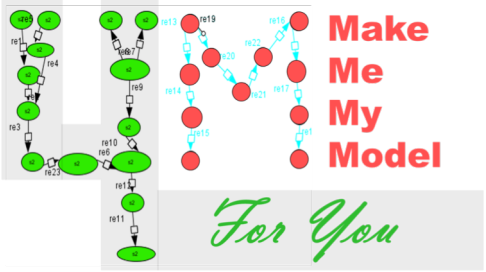
Alexey Kolodkin, Matteo Barberis, Ablikim Abdukerim, Zahid Hassan, Thierry Mondeel, Samrina Rehman and Hans V. Westerhoff

executive director

founding director

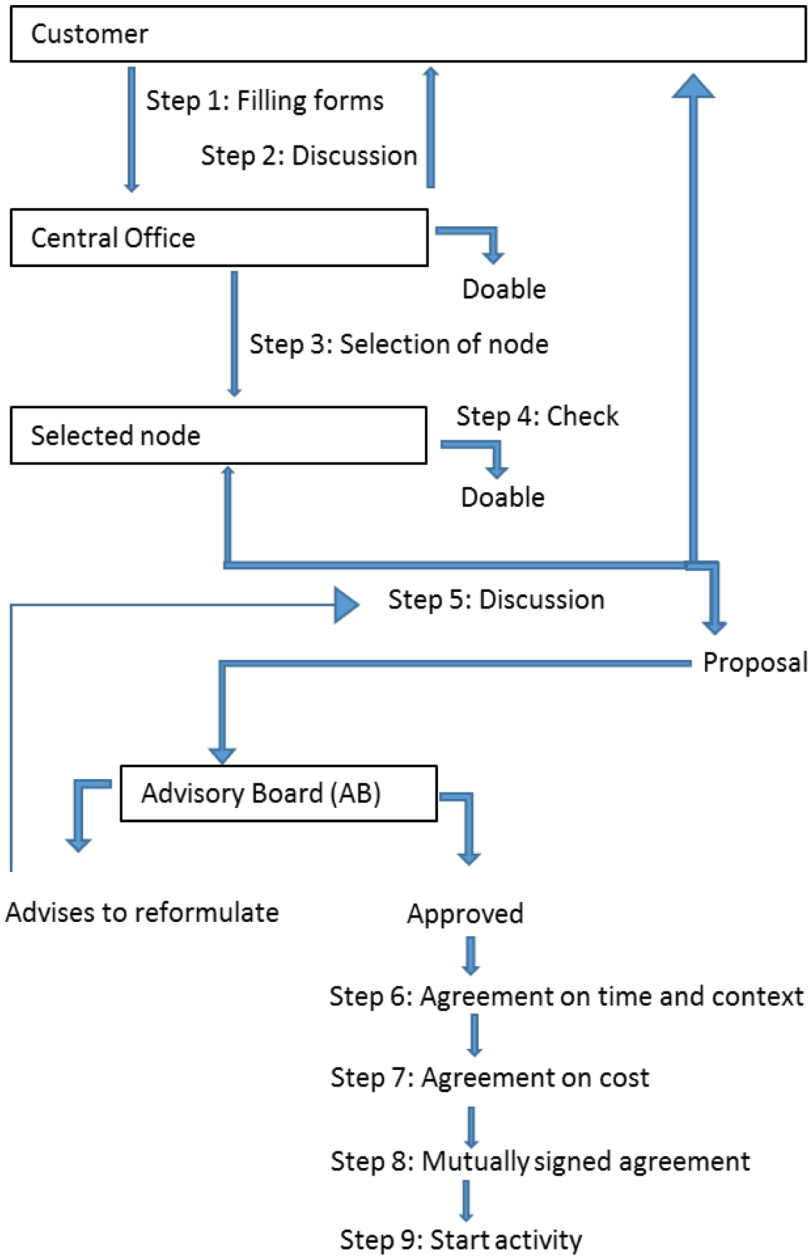
Stefania Astrologo, Ewelina Weglarz-Tomczak , YanFei Zhang, Jacky Snoep

- Executive director Dr Alexey Kolodkin (UvA, VU, LCSB, Corbel)
- Postdoctoral fellow Dr Ewelina Weglarz-Tomczak (UvA)
- Part-time help from Westerhoff group members (VUA, UvA, UoM)
- Pending integration with Wageningen (Vitor Martins dos Santos et al)



M4 mission:

to service the Life Sciences community by facilitating the implementation of systems biology



Proposed ISBE M4 access management

ISBE.NL services

The services provided at present

ISBE.NL M4 services (currently running and planned to be completed within the next 12 months and in negotiation phase):

Completed services

1. University of Duisburg-Essen, Germany: Cool design of hot metabolism: GAPN
2. Sanquin, Amsterdam: Modelling of acute and chronic inflammation

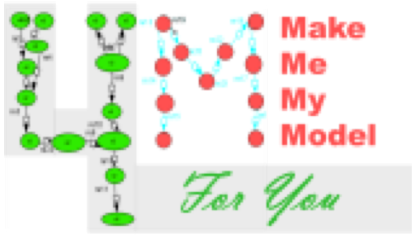
Active services

3. LCSB, Luxembourg: ROS management in Parkinson's disease and cancer
4. Milano-Bicocca, Italy: Modelling ROS management and mitochondrial dysfunction
5. Sheffield, UK: Mitochondrial perfect adaptation
6. Lisbon, Portugal: CFTR maturation
7. URV Tarragona, Spain: Safety assessment of endocrine disrupting chemicals
8. Institute of Experimental and Clinical Medicine, Novosibirsk, Russia: Modulation of ROS management by TC13 for Parkinson's disease therapy
9. Universidade Católica Portugues, Portugal: Molecular Insight into Autism Spectrum Disorder (ASD)
10. Jožef Stefan Institute, Slovenia: Protease signaling network in neurodegeneration

Prospective services

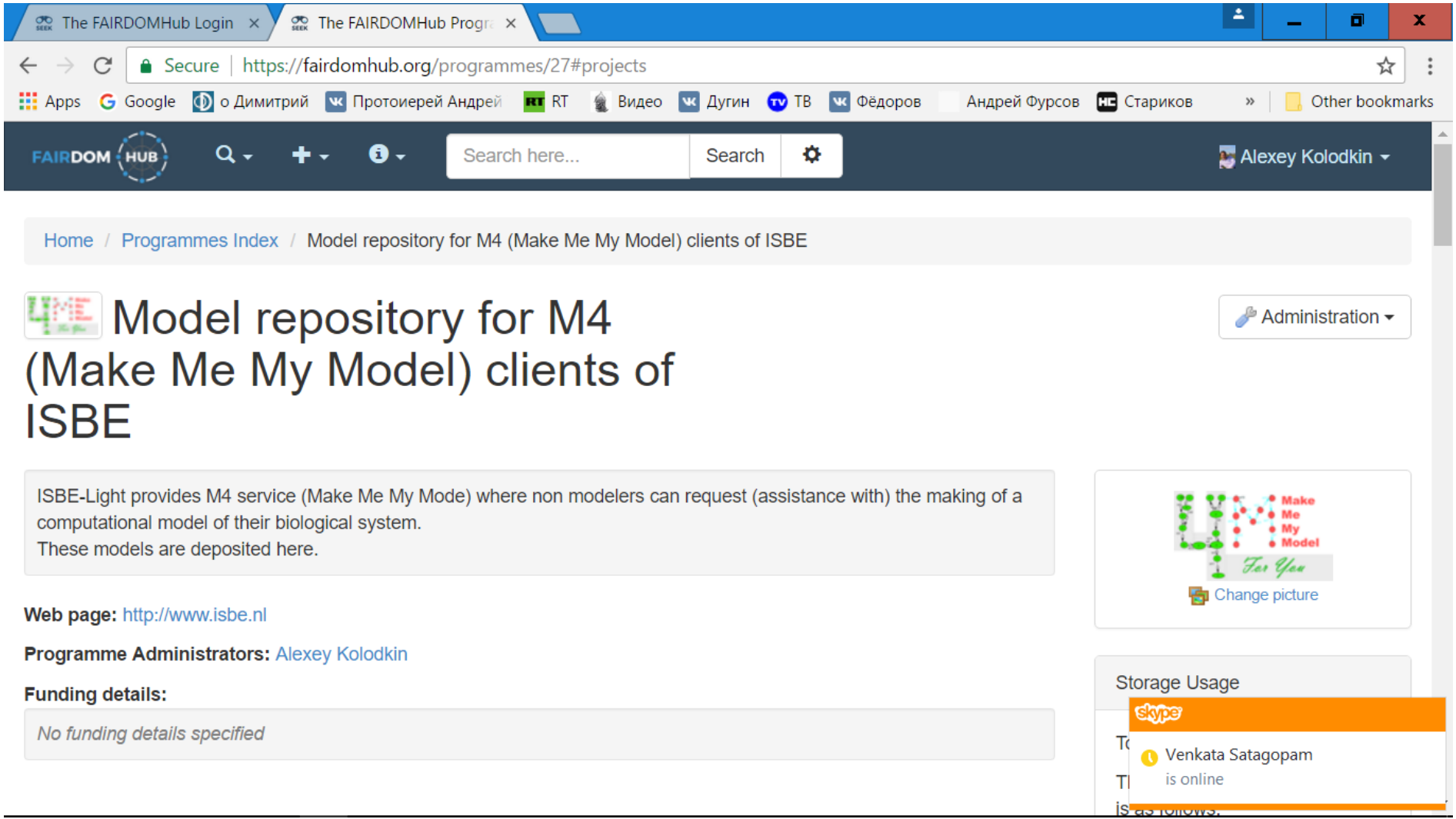
11. Munich, Germany: Charged peptide to charged membrane binding model
12. Helmholtz Center Munich, Germany: Modelling substrate diffusion and metabolism in biofilms
13. Institute of Cytology and Genetics of RAS, Novosibirsk Russia: Merged ODE and agent-based model for multilevel integration of signalling pathways
14. Manchester, UK: Modelling fibromatosis (Dupuytren's disease), Chronic Myeloid Leukaemia (CML), and urothelial cancer
15. University of Duisburg- Essen, Germany: The Yin-Yang of Metabolism; Endometatoxicity (YYME)

ISBE.NL M4 services



			WP 1	WP 2	deliverabl	WP3	milestone	deliverable	WP4	milestone	deliverable	WP5	milestone	deliverable
			setting model idea	building network	Diagram in SBGN	building mathematical model in	first simulations	working toy model COPASI	model fitting & improving	working final model	model presented to customer	model analysis	model predictions	report for customers
Completed														
1	Essen-GAPN													
2	Sanquin-Infallmation													
Active														
3	Luxembour	LCSB-ROS												
4	CORBEL	Milan-ATP												
5		Sheffield-Perf Adapt												
6		Columbia- Hemoglobin												
7	CORBEL	Lisbon -CFTR												
8	CORBEL	Tarragona												
9		Novosibirsk												
10	CORBEL	Portugal-Autism												
11	CORBEL	Slovenia-Neurodegen												
Prospective														
12		Munich-membarane												
13		Helmholtz-Biofilms												
14		Novosib-signalling												
15		Manchester-Leukaemia												
16		Essen-Endotoxicity												

Findable, Accessible, Interoperable, Reusable (FAIR) Model management for ISBE services in FAIRDOM



5 CORBEL supported services

VIP: Margarida D. Amaral - Cystic Fibrosis Transmembrane Regulator maturation

Anna Maria Colangelo - Modelling ROS management and mitochondrial dysfunction in models of Parkinson disease
VID: 3441 - Molecular Cell Physiology, Vrije University Amsterdam Awaiting Conrmation | Fitting the dynamic model to experimental data
CORBEL Track 2VID: 3444 - Chemogenomics (ChEMBL) at EMBL/EBI Awaiting Confirmation | Profiling of chemotypes for potential off-target effects, measured ADMET properties, in-vivo efcacies
CORBEL Track 2VID: 3447 - Advanced Light Microscopy Facility at EMBL Awaiting Conrmation | Fluorescence resonance energy transfer (FRET) - EMBL HDAwaiting Conrmation | Electron microsocpy - EMBL HD

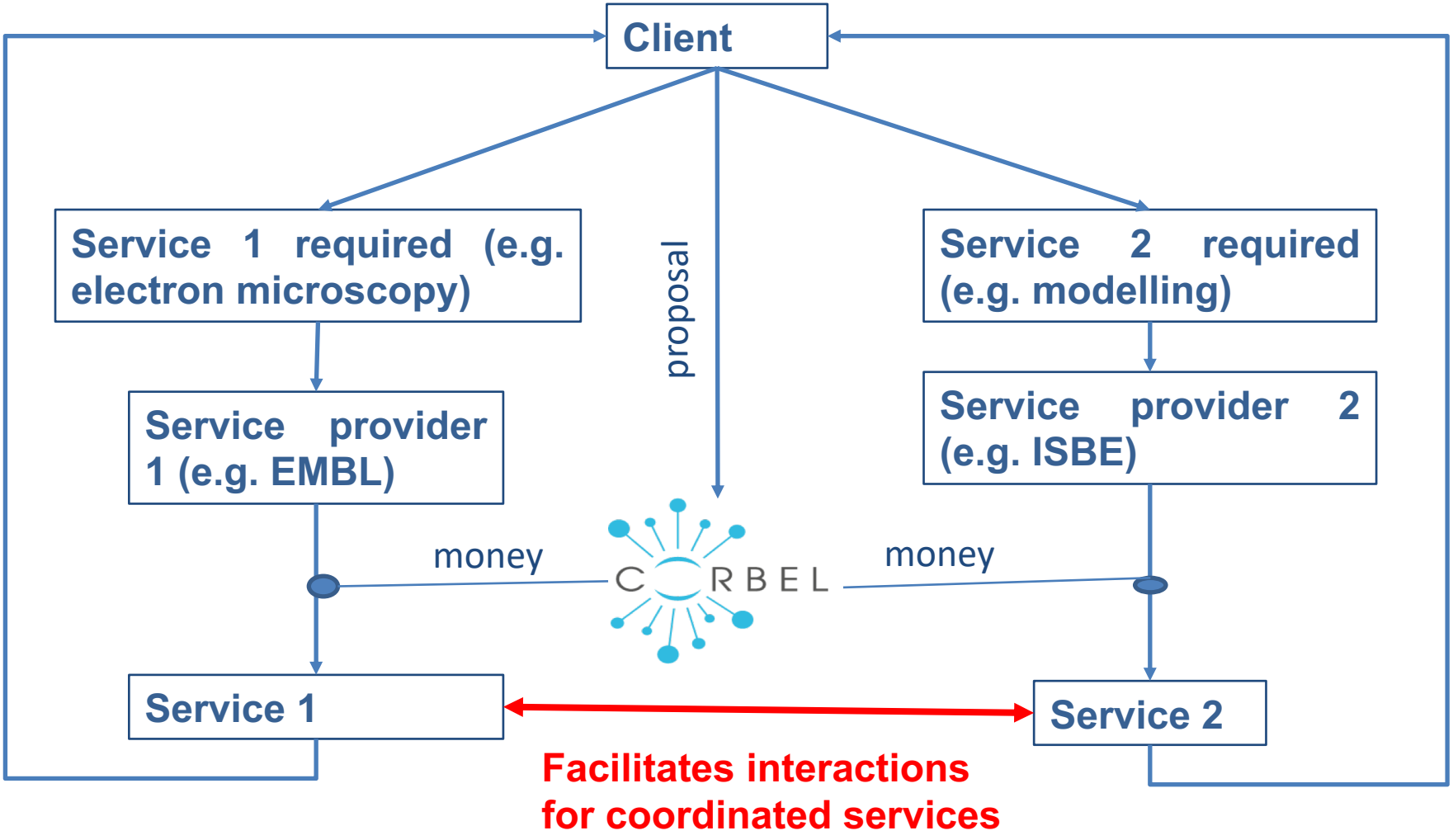
Vikas Kumar EDC-SysTox: Approaches towards Systems Toxicology model via coupled PBPK/PD-system biology benchmarking dosimetry for safety assessment of Endocrine Disrupting Chemical
VID: 3421 - Molecular Cell Physiology, Vrije University Amsterdam
CORBEL Track 2VID: 3422 - Chemogenomics (ChEMBL) at EMBL/EBI
CORBEL Track 2VID: 3423 - Screening and medicinal chemistry at Leibniz-Institute for Molecular Pharmacology (FMP)

Veronika Stoka Jožef Stefan Institute (Slovenia) - Protease signaling network in neurodegeneration

With Chemogenomics (ChEMBL) at EMBL/EBI; Advanced Light Microscopy Facility at EMBL; - Screening and medicinal chemistry at Leibniz-Institute for Molecular Pharmacology (FMP)

Maria Correia - Molecular Insight into Autism Spectrum Disorder (ASD)
1VID: 3248 - Biological Research Fondation Academy of Athens BRFAA Awaiting Conrmation | Genomics and transcriptomics services
CORBEL Track 1VID: 3530 - Molecular Cell Physiology, Vrije University Amsterda

Experience from CORBEL supported services: Integration of Systems Biological Infrastructures



ISBE at Novosibirsk (Institute of Cytology and Genetics)

Teaching (February 2017, October 2017)

"Systems Biology and Personalised Medicine" course

72 hours (lectures, seminars, tutorials individual work and exam)

Lectures: systems biology aims to reconstruct *in silico* the emergence of biological function in terms of interactions between biomolecules

Principles

Training in building mechanism based dynamic model (with ODE) → Approaches of model analysis → Application of modelling for personalized medicine

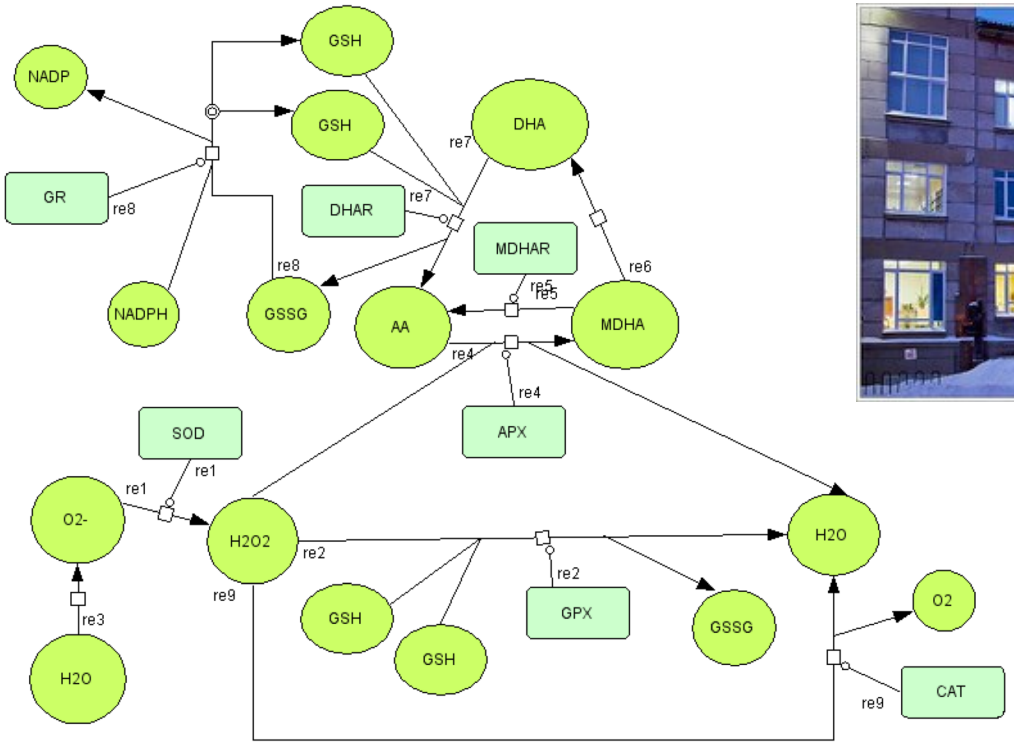
principles of modeling, building simple models on the back of envelope	using special softs (COPASI and Cell Designer) to build toy models, using already developed model	using already developed models, design principle studies, MCA

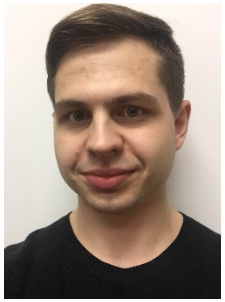
Practical individual work

From course to modelling research

ROS model for plants instantiation

Institute of Cytology and Genetics (Novosibirsk, Russia): Cold resistant wheat





Aleksandr Bobrovskih

Alexey Doroshkov

The Netherlands' arm of ISBE-Light Infrastructure for Systems Biology Europe

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CORBEL

Make Me My Model

The Netherlands' arm of ISBE-Light Infrastructure for Systems Biology Europe

ISBE.NL

CFTR maturation (Lisbon, Portugal)
With student from NSU/ICG

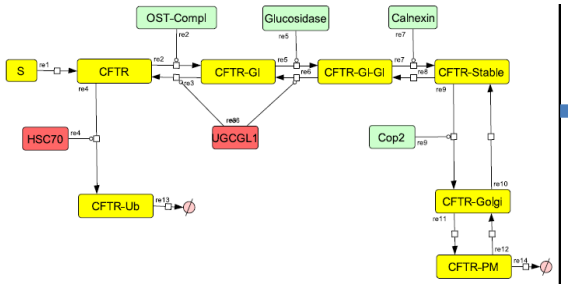
Make Me My Model For You

Cystic Fibrosis (CF)- lethal autosomic disease
CFTR - Cystic Fibrosis Transmembrane Regulator

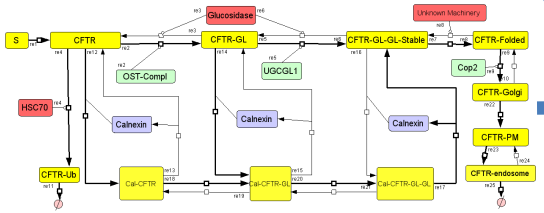
Dr. Hugo Botelho

Prof. Margarida D. Amaral

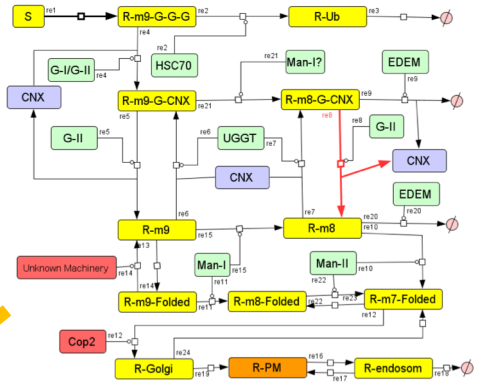
Daria Astapenko (NSU-ICG)



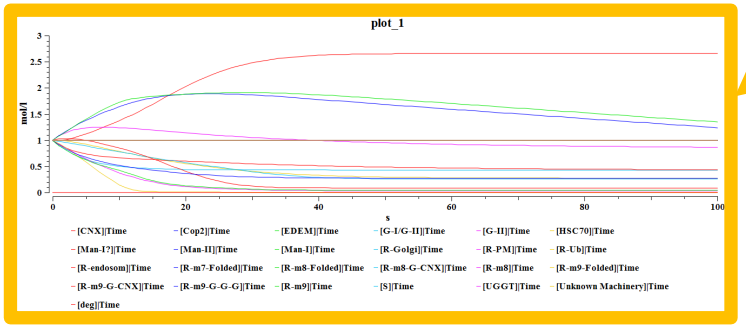
Version 1



Version 2



Version 3



Version 4

Supported by

CORBEL

ISBE at Novosibirsk (Institute of Cytology and Genetics)

Since February 2017

Nickolay A. Kolchanov Sergey A. Lashin

LETTER OF INTENT

with respect to the collaboration between the Federal Research Centre "the Federal Research Centre Institute of Cytology and Genetics of the Siberian Academy of Science", Russian Federation and the Centre of Systems Biology "Systems Biology Amsterdam", the Netherlands

The Federal Research Centre "the Federal Research Centre Institute of Cytology and Genetics of the Siberian Academy of Science" hereafter called **«ICG SB RAS»**, represented by its director Kolchanov Nickolay Alexandrovich and bound by the rules of aforementioned organization, on the one side, and **the Centre of Systems Biology "Systems Biology Amsterdam" (hereafter SysBA[1])** represented by its director Westerhoff, Hans Victor, on the other side, called together as «Parties» are herewith signing this agreement about the following:

1. Parties, i.e. the Division of Systems Biology «ICG SB RAS» (the head of the division is Kolchanov N.A.) on the one hand and «SysBA» on the other hand declare their willingness to collaborate with respect to the following

630090 Phone: (383) 363-49-80 Fax: (383) 333-12-78	University of Amsterdam Science Park, 904 (room C2.103) NL1098 XH Amsterdam (the Netherlands), EU

Director of ICG SB RAS
Kolchanov Nikolay A.

Director of SysBA
Westerhoff Hans V.

Responsible person from ICG SB RAS
Head of sector
Lashin Sergey A.

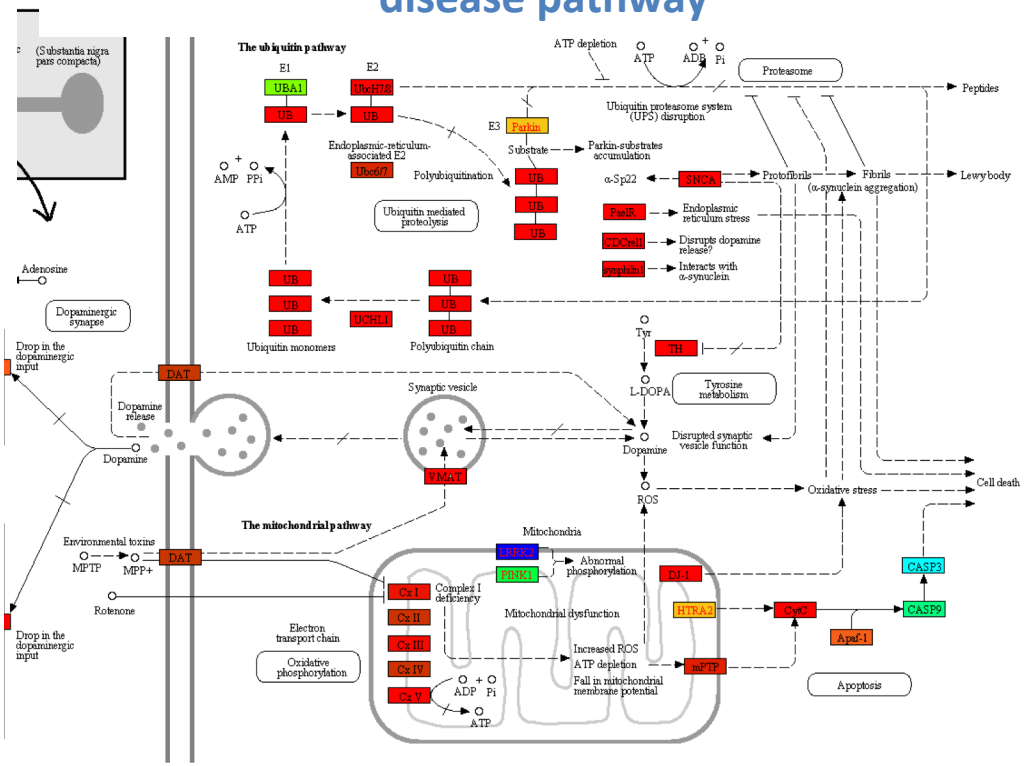
Responsible person from SysBA
Executive director of ISBE.NL
Kolodkin Alexey N.

August 2017

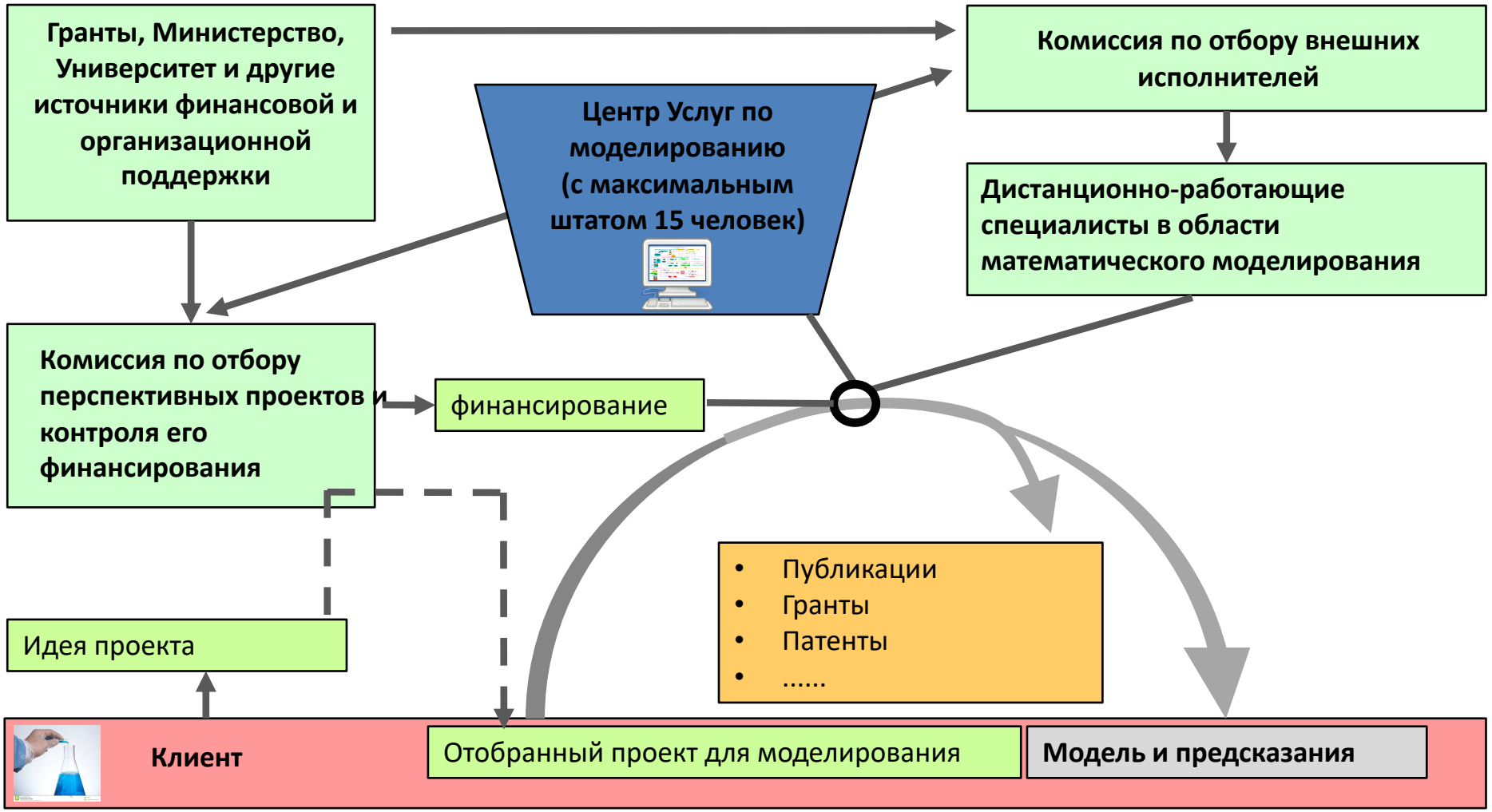
Vrije Universiteit Amsterdam
Faculty of Sciences
De Boelelaan 1083
1081 HV Amsterdam
The Netherlands

05012 1/20/14
(c) Kanehisa Laboratories

Several projects, e.g. DI analysis of Parkinson's disease pathway



Развитие потенциального Симстемно-Биологического центра: Компьютерное моделирование как сервисная услуга



Благодарю за внимание!