Curriculum Vitae

Personalia

Name: Tjaša Kumelj
Nationality: Slovene
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Education

2016-2021 **Philosophiae Doctor - Ph.D. in Biotechnology**
Ph.D. project was within Systems (Computational) Biology,
Genome-Scale Metabolic Modelling and Analysis of Complex Genetic/Metabolic Networks with application in Biotechnology, Bioengineering and BioMedicine[Footnote2]
University of Natural Science and Technology (NTNU), Dept. of Biotechnology and Food Science, Trondheim, Norway
AlmaasLab; https://almaaslab.nt.ntnu.no, supervisor Prof. Eivind Almaas.

2005 **Master of Science (Ms.Sc.) in Chemistry with specialization within Biochemistry and Molecular Biology**[Footnote3]**,**
University of Ljubljana, Slovenia, Faculty of Chemistry and Chemical Technology, Dept. of Biochemistry and Molecular Biology, in collaboration with Jožef Stefan Institute, Dept. of Biochemistry and Molecular Biology Ljubljana, Slovenia.

High school graduate in Mathematics and Natural Science, Bežigrad Gymnasium, Ljubljana, Slovenia.

Graduate in English language-study programme, Youth Language School, Ljubljana, Slovenia.

Work Experience

2022- **Researcher & Senior Engineer within Clinical Database Development and Development of Models in Precision Medicine**, Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Science, Norwegian University of Science and Technology (NTNU), Norway [Footnote1]

2016-2021 **Ph.D. research fellow in Biotechnology**
Ph.D. work was within Systems (Computational) Biology,
Genome-Scale Metabolic Modelling and Analysis of Complex Genetic/Metabolic Networks with application Biotechnology, Bioengineering and BioMedicine[Footnote2]**,**
University of Natural Science and Technology (NTNU), Dept. of Biotechnology and Food Science, Trondheim, Norway
AlmaasLab; https://almaaslab.nt.ntnu.no, supervisor Prof. Eivind Almaas.

2015-2016 **Translator (English, Norwegian, Slovene) for EURO translation agency.**

2005-2014 **Researcher within Theoretical/Computational Biomedicine using Atomistic Modelling and Computer Molecular Dynamics Simulations**, **supporting Medical Technology Research** [Footnote4]**,**
University of Natural Science and Technology (NTNU), Dept. of Chemistry and Dept. of Cancer Research and Molecular Medicine, Trondheim, Norway in collaboration with **California Institute of Technology (Caltech), USA** and **Autonomous University of Barcelona, Spain**.

2006-2010 **Lecturer and Laboratory Leader, Physical Chemistry Course (TKJ4205), University of Natural Science and Technology (NTNU),** Dept. of Chemistry, Trondheim, Norway.

2002-2005 **Researcher within experimental Biochemistry and Molecular Biology (Genomics, Proteomics, Enzymology, Kinetics), Microbiology, Chemistry, Analytical Chemistry, Biomedical Study of Resistance of Bacteria Against Antibiotics** [Footnote5]**,**
Pharmaceutical Company LEK Pharmaceuticals d.d., Ljubljana Slovenia (part of Swiss pharmaceutical company Novartis), Research and Development (R&D)-Drug Discovery Unit.

Researcher within experimental Biochemistry and Molecular Biology, Dept. of Biochemistry and Molecular Biology, Jožef Stefan Institute, Ljubljana, Slovenia.

IAESTE Exchange Student within Electrochemistry, NTNU, Faculty of Chemistry and Biology, Dept. of Material Technology and Electrochemistry, Trondheim, Norway.

Language Courses

2005- 2006 Norwegian language, Level-1 (beginners), Level-2 (intermediate) and Level-3 (advanced), NTNU (Dragvoll campus), Trondheim, Norway.
German language, Klagenfurt, Austria.
Graduate in English language-study programme, Youth Language School, Ljubljana, Slovenia.

Courses

Summer school om Artificial Intelligence in Medicine, Cambridge Centre for Artificial Intelligence in Medicine, University of Cambridge, UK
Genetic Epidemiology Course, University of Bristol, UK
R programming Course, University of Bristol, UK
Advanced course in metabolic engineering and systems biology, Norwegian University of Science and Technology (NTNU), Norway
Fifth international synthetic and systems biology summer school-SSBSS 2018
GWAS Study, UIO University of Oslo, Norway
Metabolic pathway analysis, Norwegian University of Science and Technology (NTNU), Norway
Sostrup Summer School in Quantum Chemistry and Molecular Properties in Aarhus, Denmark

Language skills

Slovene (native), English (fluent, written, spoken), Norwegian (very good, written, spoken), Croatian (very good, written, spoken), German (moderate, written, spoken)

Computer skills Programming in PYTHON and MATLAB, Proficient in WINDOWS, and LINUX operating system, Proficient in application of LaTeX, Windows Office Tools and Tools for Bioinformatics and Computational Science.

References

Given upon request.

Footnote 1

Projects:

1. Development of Clinical Database

2. Machine learning-NorHEAD project, NorHead, NTNU (Department of Neuromedicine and Movement Science): Lead on genomics & mechanistic interpretation of non-additive effects, e.g., systemic view on gene-gene interaction, protein-protein interaction, pathway interactions with possibility to infer metabolomic aspect as well (7T MRI). The study will try to give mechanistic interpretation of non-additive effects in headache disorders.

3. Analyses of genotype, genetic and genomic analyses in migraine patients

4. Applied Ethical Al on Nordic Patient Records, NorHead, NTNU (Department of Neuromedicine and Movement Science) & Nordic Applied Ethical Consortium: development of machine learning model to interpret the non-structured clinical notes and referrals, applying federated machine learning approach, in collaboration with Aalborg University, Denmark & Z-Inspection-Tempere University, Finland.

Conferences, regarding neuroresearch.

1. National Headache Conference, Trondheim, Norway, 2022
2. National Headache Conference, Trondheim, Norway, 2023
3. National Headache Conference, Trondheim, Norway, 2024
4. EHC2023 (European Headache Federation) conference in Barcelona, 2023
5. Regional Research conference Health-Central Norway (Regional Forsknings-konferance Helse Midt-Norge)
6. A conference about energy control and metabolism, Centre for Basic Metabolic Research, University (CBMR)of Copenhagen
7. Translational neurometabolism seminar, 2024, NTNU/St. Olavs University Hospital, Trondheim, Norway, 2024. K.G. Jebsens Centre for Alzheimer's Disease (JCA), the Norwegian Center for Headache Research (NorHead) and the Norwegian 7T MR Center
8. IHS (International Headache Society) 2024 iHEAD Science, Berlin, Germany, 2024
9. National Headache Conference, Trondheim, Norway, 2024

Courses:

1. Genetic Epidemiology Course, University of Bristol, UK
2. R programming Course, University of Bristol, UK
3. Genetic Epidemiology Course, NTNU (K.G. Jebsen center)
4. Summer School in Artificial Intelligence in Healthcare, the Cambridge Centre for Artificial Intelligence in Medicine, University of Cambridge, UK, September 9 -September 13, 2024
5. Genetic Epidemiology Course, Jebsen Center, Trondheim, Norway, 2025

Footnote 2

Ph.D. degree in Biotechnology.

Ph.D. research work was within Genome-Scale Metabolic Modelling, Metabolic Engineering and Analysis of Complex Networks with Application in Biotechnology, Bioengineering and Biomedicine at University of Natural Science and Technology (**NTNU**), Dept. of Biotechnology and Food Science, under the **supervision of Professor Eivind Almaas (AlmaasLab (https://almaaslab.nt.ntnu.no)).**

Summary of Ph.D. Dissertation:

Title of Ph.D. Dissertation:
'Genome-scale Metabolic Modelling and Consequences of Mass Constraints and Enzyme Availability'

Genome-scale metabolic reconstructions offer a system-level view of metabolic networks with genetic basis and suggest mechanistic determination of cell's physiological homeostatic states. Consequently, they offer the ability to compose strategies to manipulate cell's functional states. This is applicable in many research fields, from metabolic engineering in enhancing the production of existing or novel target metabolites to medical applications in determining susceptibility or immunity towards disease and drug targets.
The focus of this Ph.D. dissertation is the reconstruction, manual curation of genome scale metabolic models and their application in mechanistic determination of condition specific physiological, homeostatic states of the cell. A system level view and understanding the underlying mechanistic notion of cell's response to genetic and environmental perturbation, enabled optimization of the metabolic engineering strategies for enhanced heterologous production of polyketide antibiotics. This important research topic contributes to combating the global health crisis brought on by antibiotic resistance. For that purpose, first (***Article 1***) and third generation of genome-scale metabolic models of *S. coelicolor* (***Article 2***) were constructed, where the latter integrated time-resolved proteomics data into standard genome scale metabolic stoichiometric presentation with the purpose of giving mechanistic interpretation of both, proteomics, and transcriptomics data, sampled in batch fermentation. Mechanistic determination of metabolic switch between primary and secondary metabolism, proposed strain design metabolic strategies for heterologous expression host of *S. coelicolor*.
As cells have implicit optimality principle build into them when they evolve under selection pressure, distal causality needs to be accounted for in the reconstructions, by integration of biological objective into the stoichiometric framework. The condition-specific manner of the biomass objective was addressed by proposing approaches, based on linear optimization and linear interpolation (***Article 3***). Proposed strategies were evaluated by demonstrating various phenotypic traits, such as cell's optimal growth rate, respiratory state of the cell and gene essentiality.
Contextualized genome-scale metabolic reconstruction with integration of mass constraints and constraints on enzyme availability, enabled mechanistic determination of cell's metabolic response to perturbation on total protein availability (Ptotal) on various levels, such as wild type, single and double mutant (***Article 4***). Metabolic response was revealed by epistatic interactions when mass constraints and constraints on enzyme availability as dominant constraints were considered. This response tunes de-coupling/coupling of glycolysis to TCA cycle and oxidative phosphorylation (electron transport chain) as determined from cell's respiratory profile, where the onset of metabolic switch from oxidative fermentative to respiratory state is sensitive to Ptotal.

Broadly speaking, Ph.D. work was within an improved understanding of systems-level interplay and design principles of metabolic, gene-regulatory, and protein-interaction networks in cells, bringing extensive experience in both complex network analysis and high-performance computing. Complex network analyses have demonstrated great utility in a broad range of research fields, providing the ability to identify key interactions and components in a system. The recent introduction of the human disease network has allowed the discovery of new disease mechanisms and identification of candidate disease genes. The combination with molecular and biochemical networks and data, such as cellular metabolism, protein interactions, and gene-co-expression measurements, has the potential to signifi-cantly augment the investigative power of GWAS (Genome Wide Association Study). Developing new mathematical and computational methods leverages knowledge from molecular networks in the identification of e.g. genetic variation associated with disease.

Ph.D. degree resulted in three published articles and in additional one (4^{th}) in preparation as follows:

Article 1 (published):

Predicting Strain Engineering Strategies Using iKS1317: A Genome-Scale Metabolic Model of *Streptomyces coelicolor*; Tjaša Kumelj*, Snorre Sulheim*, Alexander Wentzel, Eivind Almaas
*equal authorship
Published in Biotechnology Journal 14(4), 2018.

Project conceived by Tjaša Kumelj, Snorre Sulheim and Eivind Almaas. Model curation, evaluation and validation done by Tjaša Kumelj, Snorre Sulheim and Eivind Almaas. Model application done by Tjaša Kumelj and Snorre Sulheim. Analysis and writing of the article done by Tjaša Kumelj, Snorre Sulheim and Eivind Almaas.

Article 2 (published and prize winner):
Enzyme-Constrained Models and Omics Analysis of *Streptomyces coelicolor* Reveal Metabolic Changes that Enhance Heterologous Production; Snorre Sulheim, Tjaša Kumelj, Dino van Dissel, Ali Salehzadeh-Yazdi, Chao Du, Gilles P. van Wezel, Kay Nieselt, Eivind Almaas, Alexander Wentzel, Eduard J. Kerkhoven
Published in iScience 23(9), 2020.
Received the Digital Life Norway Prize for transdisciplinary publication of the year 2020.

Project conceived by Tjaša Kumelj, Eduard J. Kerkhoven, Eivind Almaas, Alexander Wentzel, Snorre Sulheim, Ali Salehzadeh-Yazdi. Computational modelling done by Tjaša Kumelj, Eduard J. Kerkhoven, Snorre Sulheim, Ali Salehzadeh-Yazdi. Validation and formal analysis done by Tjaša Kumelj, Chao Du, Kay Nieselt, Dino van Dissel, Snorre Sulheim, Eduard J. Kerkhoven. Investigation done by Tjaša Kumelj, Alexander Wentzel, Snorre Sulheim, Eduard J. Kerkhoven. Data curation done by Tjaša Kumelj and Snorre Sulheim. Writing of original draft done by Tjaša Kumelj, Snorre Sulheim, Dino van Dissel, Chao du and Kay Nieselt. Writing-review & editing done by all authors. Visualisation done by Snorre Sulheim, Eduard Kerkhoven, Chao Du, and Dino van Dissel. Supervision done by Alexander Wentzel, Eivind Almaas, Eduard J. Kerkhoven and Gilles P. van Wezel. Project administration done by Alexander Wentzel. Funding acquisition done by Alexander Wentzel, Eduard J. Kerkhoven, Eivind Almaas, and Gilles P. van Wezel.

Article 3 (published):
Genome-Scale Metabolic Modelling when Changes in Environmental Conditions Effect Biomass Composition; Christian Schulz*, Tjaša Kumelj*, Emil Karlsen*, Eivind Almaas
*equal authorship
Published in PLOS Computational Biology 17(5), 2021.

Project conceived by Tjaša Kumelj, Christian Schulz, Emil Karlsen and Eivind Almaas. Code development done by Christian Schulz and Emil Karlsen. Method application done by Tjaša Kumelj. Writing done by Tjaša Kumelj, Christina Schulz, Emil Karlsen and Eivind Almaas.

Article 4 (in preparation):
Protein-Availability Constraint in Genome-Scale Metabolic Modelling Induces Pathway Competition with Broad Phenotypic Effects: Tjaša Kumelj, Pål Røynestad, Eivind Almaas
To be submitted

Project conceived by Tjaša Kumelj, Pål Røynestad and Eivind Almaas. Model curation done by Tjaša Kumelj. Phenotype Phase Plane Analysis done by Pål Røynestad. Wild type, Single and Double Knockout simulations done by Tjaša Kumelj and Pål Røynestad. Comparative analysis of experimental and double fitness done by Pål Røynestad. Simulations and analysis of epistatic interactions done by Tjaša Kumelj. Analysis and writing of the article done by Tjaša Kumelj, Pål Røynestad and Eivind Almaas.

Poster presentation and talks at conferences:

1. International conference on systems Biology (ICSB), Virginia Tech, Blacksburg, USA, August 2017 (talk): Extended GEM of *Streptomyces coelicolor* for production of secondary metabolites; Kumelj T, Sulheim S, Wentzel A, Almaas, E.
2. DLN workshop: Modelling living systems-from fundamental problems to applications, Bergen, Norway; September 2017 (talk): A genome-scale metabolic model for *Streptomyces coelicolor*; Kumelj T, Sulheim S, Wentzel, A, Almaas E.
3. DNL meeting on methodologies for digital life focus on metabolic systems, Bergen, Norway; September 2017 (talk): Metabolic engineering of genome-scale reconstruction of *S. coelicolor*; Kumelj T, Sulheim S, Wentzel A, Almaas E.
4. Annual NORBIS conference, Bergen, Norway, March 2018 (poster): Metabolic engineering as underlying strategy in enhanced production of antibiotics by *S. coelicolor*; Kumelj T, Sulheim S, Wentzel A, Almaas E.
5. NetSci conference, Paris, France, June 2018 (poster): Multilayer network approach to study metabolic switch in *S.coelicolor* to produce antibiotics; Kumelj T, Almaas E.
6. Annual DNL conference, Bergen, Norway, March 2018 (poster): Metabolic engineering as underlying strategy in enhanced production of antibiotics by *S. coelicolor*; Kumelj T, Sulheim S, Wentzel A, Almaas E.
7. SSBSS (International Synthetic and Systems Biology Summer School), Italy, July 2018 (poster): Metabolic engineering as underlying strategy in enhanced production of antibiotics by *S.coelicolor*; Kumelj T, Sulheim S, Wentzel A, Almaas E.
8. ICGSB and YCGSB, Conference and workshop of the international study group for Systems Biology, Tromsø, Norway, September 2018 (poster): Multilayer approach in metabolic engineering by *S. coelicolor*; Kumelj T, Almaas E.
9. Annual NORBIS conference, Voss, Norway, October 2018 (poster): Metabolic engineering as underlying strategy in enhanced production of antibiotics by *S. coelicolor*; Kumelj T, Sulheim S, Wentzel A, Almaas E.

Courses:

1. SSBSS 2018 (5th international Synthetic and Systems Biology Summer School), Italy.
2. Metabolic Pathway Analysis, Digital Life Norway (DLN)/NORBIS course, NTNU, Trondheim, Norway.
3. Large Genetic Studies in Biobanks: from registries screening to interpretation of GWAS and beyond, NORBIS course, Ulleval Hospital, Oslo, Norway.
4. Advanced course on Metabolic Engineering and Systems Biology, Chalmers University, Sweden.
5. Doing Science: Methods, Ethics and Dissemination (MN8000), NTNU, Trondheim, Norway.
6. Advanced course in metabolic engineering and systems biology, Norwegian University of Science and Technology (NTNU), Norway
7. Sostrup Summer School in Quantum Chemistry and Molecular Properties in Aarhus, Denmark

Footnote 3

Diploma project for Master of Science (Ms.Sc.) degree within experimental Biochemistry/Molecular Biology in Biomedical research (2001-2002), University of Ljubljana, Slovenia, Jozef Stefan Institute, dept. of Biochemistry/Molecular Biology, Slovenia:

Aim:

Study of the mechanism of autocatalytic activation of recombinant human procathepsin B in the presence of various glycosaminoglycans.

Methodology:

Isolation and purification (expression of recombinant human procathepsin B, isolation of inclusion bodies, dissolving and S-sulfonating, renaturating and concentrating) of recombinant procathepsin B, expressed from certain strain of *E. coli* BL21(DE3) plyS with transformed plasmid pRK.6.1., containing gene for procathepsin B. Further kinetic study of autocatalytic activation of recombinant

procathepsin B was done in the presence of various glycosaminoglycans, changing the size and density of the charge.

Results:
Defining the mechanism of autocatalytic activation of cysteine protease *in vivo* in the presence of glycosaminoglycans, which are recycling product of proteoglycans in acid environment of lysosome. Articles, written based on this research are collected at:
http://www.worldcat.org

Footnote 4

Project within Theoretical/Computational Biomedical research (May 2005-December 2014), NTNU, Trondheim, Norway:
The research work was done within Theoretical/Computational Chemistry applied in Medical Technology Research within Atomistic Molecular Modelling and Computer Molecular Dynamics (MD) Simulations to study the mechanism of DNA-repair, supporting Cancer Research.

Aim:
The aim was Theoretical/Computational research of Molecular Mechanisms and Manipulation of Enzyme Reaction in DNA-repair, supporting cancer research at Dept. of Chemistry and Dept. of Molecular Medicine and Cancer Research, NTNU, Trondheim, Norway in collaboration with California Institute of Technology (Caltech), USA and Autonomous University of Barcelona, Spain. The work involved Atomistic Molecular Modelling and Computer Molecular Dynamics (MD) Simulations, resulting in free-energy calculations of protein-ligand interactions within enzymatic reactions. Computer simulations were done in Linux environment, using web-based and in-house program codes in super-computer facilities.
Based on research project within theoretical/computational chemistry/bioinformatics at NTNU, three research topics were considered:
***Topic 1*:** Towards a reactive force field Fe(V): application to dioxygen activation in non-heme iron enzymes dependent on α-ketoglutarate (presented in Scientific Lecture in Bioinformatics Forum for Young Scientists (BFYS), Trondheim/Selbu, Norway.
***Topic 2*:** Free energy simulations of the oxidative dealkylation of DNA by the mononuclear non-heme Fe(II) α-ketoglutarate dependent hABH3 proteins using Reax reactive force field.
***Topic 3*:** Potential implications of oxidation of aminoacid *Leu177* on the enzymatic activity of mononuclear non-heme iron Fe(II) α-ketoglutarate dependent hABH3 protein to dealkylate DNA.

Methodology:
Regarding methodology used, I have been working with developing interaction equation (parameter optimization), Reax reactive force field (quantum-DFT calculations, using Gaussian algorithm) for modelling the dynamics of enzymatic reaction, involving dioxygen activation and oxidative demethylation of methylated DNA by iron non-heme α-ketoglutarate dependent, hABH3, enzyme (***Topic 1***).
Molecular dynamics, MD, simulation provided the change in free energy along the reaction, using thermodynamic integration (TI) method and as such, study the enzymatic mechanism (***Topic2***, unpublished, revised form).
Further, the potential influence on the enzymatic activity was analysed by the free energy simulation of the enzymatic reaction, where specific aminoacid in the enzyme that was important for the activity, was mutated (***Topic3***, unpublished, revised form).

Results:
Based on the research work I have written three papers (revised, unpublished form) on the following research topics
***Topic1*:** Towards a reactive force field Fe(IV): application to dioxygen activation in non-heme iron enzymes dependent on α-ketoglutarate (presented in Scientific Lecture in Bioinformatics Forum for Young Scientists (BFYS), Trondheim/Selbu, Norway)

***Topic2*:** Free energy simulations of the oxidative dealkylation of DNA by the mononuclear non-heme Fe(II) α-ketoglutarate dependent hABH3 proteins using Reax reactive force field
***Topic3*:** Potential implications of oxidation of aminoacid *Leu177* on the enzymatic activity of mononuclear non-heme iron Fe(II) α-ketoglutarate dependent hABH3 protein to dealkylate DNA.
With respect to this research work, I have passed the following exams: Computational Chemistry, Molecular Modelling, Protein Structures, Statistical Thermodynamics and Computer Simulations.

Courses

1. Sostrup summer school, Quantum Chemistry and Molecular Properties, Århus, Denmark.
2. Computational Chemistry and Molecular Modelling, NTNU, Trondheim, Norway.
3. Protein Structures, NTNU, Trondheim, Norway.
4. Statistical Thermodynamics and Computer Simulations, NTNU, Trondheim, Norway.

Footnote 5

Research work within Biochemistry/Molecular Biology (Genomics, Proteomics, Enzymology, Kinetics), Microbiology, Chemistry and Analytical Chemistry in Biomedical Research (2002-2005), Pharmaceuticals d.d., Ljubljana, Slovenia:

Aim:
Experimental biomedical research of β-lactamase inhibitors, playing a significant role in resistance of bacteria against antibiotics, done at internationally recognized pharmaceutical company LEK Pharmaceuticals d.d., Ljubljana, Slovenia (member of Sandoz, a generic part of Swiss company Novartis).

Methodology:
Isolation and purification of enzymes, β-lactamases from bacterial strains. Further, the kinetic studies of β-lactamase inhibitors were done to evaluate the kinetic parameters of those inhibitors. This evaluation determined the potential inhibitors for microbiological testing of bacterial strains with increased content of β-lactamases. Microbiological profile of β-lactamase inhibitors was done with the determination of MIC (minimal inhibitor concentration) with the use of microdilution method.

Results:
Determination of β-lactamase inhibitor that was added to antibiotic to extend its efficiency towards resistant bacteria.