Faculty of Science and Engineering

Profile report: Computational Protein (Re)design (Computationele eiwit(her)engineering)

- Discipline: Chemistry
- Level: Assistant or Associate Professor
- Fte: Full time (1.0)

1. Scientific discipline

The professor in Computational Protein (Re)Design integrates advances in computer sciences with clever experimental concepts to redesign biological macromolecules towards new or altered functionalities. The envisioned research group uses computer sciences (computational design, multiscale modeling, machine learning) and combines this with existing expertise in biochemistry (enzymology, protein engineering, drug design) to further our understanding of the molecular processes of life and to expand the potential of enzymes and other biomolecules for biotechnological or biomedical purposes.

2. Vacancy

This position is offered at the Faculty of Science and Engineering (FSE) of the University of Groningen and will be embedded in the Groningen Biomolecular Sciences and Biotechnology Institute (GBB). The GBB institute has 12 vibrant research groups, targeting challenging biological questions in the focal areas 'Molecular Mechanisms of Biological Processes' and 'Physiology and Systems Biology'. The position has been approved by the Faculty board, is part of the Dutch Sector Plans in Chemistry, and falls within the framework of 'Career Paths in Science 4' ('Bèta's in Banen 4').

3. Selection committee

- Prof. Bert Poolman (Professor in biochemistry), chair
- Prof. Marco Fraaije (Professor in molecular enzymology)
- Prof. Siewert Jan Marrink (Professor in molecular dynamics)
- Prof. Shirin Faraji (Adjunct Professor in theoretical and computational chemistry)
- Prof. Marleen Kamperman (Professor in polymer chemistry)
- Prof. Dirk-Jan Scheffers (Director of Education, GBB)
- Prof. Nigel Scrutton (Professor in Biological Chemistry, University of Manchester)
- Mrs. Gwen Tjallinks (Student member)

Additional (external) advisors:

- Prof. Dirk Slotboom (Scientific Director, GBB)
- Prof. Frances Arnold, California Institute of Technology
- Prof. Derek Woolfson, University of Bristol
- Prof. Don Hilvert, ETH
- Prof. David Baker, University of Washington
- Prof. Dick Janssen, University of Groningen
- Prof. Lucia Gardossi (Università degli Studi di Trieste
- Prof. Rebecca C. Wade, University of Heidelberg
- Mrs. Linda Bosveld-Verburg (Human Resources, FSE)
- Dr. Engel G. Vrieling (Managing Director of GBB), secretary

4. Research area

The advances in biophysical design algorithms, artificial intelligence (AI) and multiscale modeling will transform computer simulations into a powerful tool for i) generating new insights into the functioning of individual biomolecules, and ii) guiding (re)design and engineering of enzymes, drugs, and other biomolecules for industrial and medical applications. Computational biochemistry combined with clever experimental strategies (*e.g.* directed evolution) has the potential to strongly reduce expensive and time-consuming (*in vitro* screening) or undesirable (toxicology) laboratory research required for finding biomolecules with new functions or improved performance. The increasing power to simulate macromolecules (better algorithms, hardware) and multi-scaling (CG-MD, QM-MM) will soon allow the screening of large protein libraries. New computational protocols can also provide accurate predictions for tuning enzyme properties through targeted mutagenesis. Such computational predictions together with sophisticated experimental screening approaches can greatly accelerate the redesign of enzymes towards desired functionalities. Such a pipeline of protein redesign can also benefit from AI technologies. Machine-learning tools will allow new features to be learned from both computational and experimental data. The field of protein (re)design builds on the synergy between computational science and the study of dynamic structures and their interactions with small molecules. Protein redesign, drug development, as well as biocatalysis will greatly benefit from these developments by shortening timelines of laboratory evaluation and improving predictability of experiments. Furthermore, cheaper DNA synthesis and rapid small-scale (robotic) evaluation feasible with novel screening technologies narrows the gap between the modest output of traditional laboratory experiments and the large amount of data needed for machine learning.

5. Embedding: institute (and base unit)

The position will be embedded in the institute GBB as an independent research unit Computational Protein Redesign, that is, when the position is filled at the level of associate or full professor. An assistant professor will until his/her tenure be embedded in a biochemistry or structural biology group. Depending on the research focus, the newly appointed staff member will be able to connect to studies in biotechnology and molecular enzymology (Profs. M.W. Fraaije, D.B. Janssen), structural biology (Profs. S.J. Marrink, D.J. Slotboom, and Drs. C. Paulino and A. Guskov), chemical biology (Profs. G. Maglia, B. Poolman), systems biology (Prof. M. Heinemann, Dr. A. Millias) and/or synthetic biology (Profs. A.J.M. Driessen, R.A.L. Bovenberg, O.P. Kuipers, and Dr. S. Billerbeck). Furthermore, the work connects to research in the area drug development (Profs. G.J. Poelarends, A.S.S. Dömling, M.R. Groves) at the Groningen Research Institute for Pharmacy (GRIP), bio-organic chemistry (Profs. J.G. Roelfes, A.J. Minnaard, B.L. Feringa, M. Witte) at the Stratingh Institute for Chemistry, and artificial intelligence (Profs. N.A. Taatgen, L.C. Verbrugge) at the Bernoulli Institute for Mathematics, Computer Science and Artificial Intelligence. The envisioned research also directly contributes to activities in the FSE themes Molecular Life & Health, and Data Sciences and Systems Complexity, and the research of the Groningen Cognitive Systems and Materials Center.

6. Local and (inter)national position

Current state in Groningen:

Computational chemistry in Groningen is organized in the Berendsen Centre for Multiscale Modeling, with expertise ranging from quantum mechanics, all-atom and coarse-grain molecular dynamics all the way to continuum methods, spanning a wide range of time and length scales. The current position adds to the activities in structural biology, which is an acknowledged gravitation point of the national Sector Plans in Chemistry. Computational

chemistry at GBB concentrates on biocatalysis to redesign enzymes for novel and improved processes in industrial biotechnology and targeted biosynthesis of chemical building blocks, integrating computational tools *(e.g.* molecular dynamics, docking) to enhance success rates for the advanced engineering of biocatalysts.

Current state in the Netherlands:
The importance of biophysical studies and molecular modeling for biological understanding, drug design, metabolic engineering and applied biocatalysis is widely recognized in the Netherlands. For many years, CMBI/IMLS at the Radboud University Nijmegen (Prof. G. Vriend) has been at the forefront of the development and use of tools that support biomolecular structure analysis and protein engineering. Interactions at protein-ligand and protein-protein/DNA interfaces are explored at Utrecht University by a range of computational tools (Prof. A. Bonvin). Computational chemistry with implications for (bio)catalysis is further pursued at the Van 't Hoff Institute for Molecular Sciences (University of Amsterdam), with research on multiscale modeling and simulations (Profs. P. Bolhuis, E.J. Meijer). Tool development for quantum mechanical analysis of reactions in (bio)organic-chemistry is investigated at the Free University of Amsterdam (Prof. F.M. Bickelhaupt). Also, the Dutch life sciences industry has a strong interest in computation-supported protein redesign (e.g. DSM), as well as in AI and machine learning (e.g. Bio-Prodict). Research in protein design in Groningen can occupy a strong position in this field when exploiting its unique strength in biophysical force field development and molecular simulations with its strong expertise in molecular enzyme engineering for biocatalysis. This research field hardly overlaps with that of other Dutch centers, yet will become increasingly influential, also by serving the biotechnology community.

Current state international:
The most prominent groups in enzyme engineering are in the US. The work has demonstrated the enormous potential of directed evolution (Prof. F. Arnold, Caltech) with influence on European laboratories (Prof. M. Reetz, Muhlheim/Marburg; Prof. U. Bornscheuer, Greifswald; Prof. N. Turner, Manchester). Computational protein design has been pioneered by Prof. D. Baker (University of Washington), Prof K. Hauk (UCLA), and Prof. S. Mayo (Caltech), with important breakthroughs in the development of non-natural reactions. The combination between directed evolution and enzyme design has proven successful (Prof. D. Hilvert, ETH; Prof. D. Tawfik, Weizman Institute). In Europe, computation-supported research on enzyme catalysis and drug design is pursued, for example, by groups in Barcelona (Prof. V. Guallar), Bristol (Prof. A. Mulholland), Brno (Prof. J. Damborsky), Heidelberg (Prof. R. Wade) and Girona (Prof. S. Osuna). Most of this research is aimed at detailed understanding of individual proteins, or at tool development. A promising emerging trend is the integration of molecular dynamics and protein design in engineering pipelines. Both biophysical force fields and databases are used, occasionally integrated and made available through webservers. In view of this situation, the activities in Groningen may well be aimed at multiscale approaches for tool- and pipeline development, producing open source or web-based applications that are distributed to the scientific community, with their applicability proven by solid experimental data.

7. Expected contribution to research
The research tasks entail fundamental research resulting in publications of high impact, appearing in internationally renowned scientific journals. The research activities are expected to contribute to the strengthening of the international position of the GBB as research institute in biomolecular sciences. Furthermore, the research will form a bridge to

research in (bio)catalysis at GRIP and the Stratingh Institute for Chemistry and to computational work (e.g. machine learning) at the Bernoulli Institute for Mathematics, Computer Science and Artificial Intelligence. Obtaining substantial external funding is crucial. Supervision of PhD students also is an important part of the research activities.

8. Expected contribution to teaching

The successful candidate contributes to the relevant teaching programs of the bachelor, master and PhD programs of the Faculty of Science and Engineering, appropriate to the career stage. The requirements for the University Teaching Qualification will have to be fulfilled. Teaching is affiliated to Chemistry, Life Sciences, Physics (track Physics of Life) and Biomedical Sciences.

9. Expected contribution to the organization

An active input is expected in order to provide a valuable contribution to the management and organizational tasks of the institute GBB and the Faculty of Science and Engineering, appropriate to career stage. At the level of the faculty, the staff member may participate in working groups and committees in the fields of teaching, research and management. At the more senior level, the candidate is also expected to participate in relevant national and international science forums.