Faculty of Science and Engineering

Profile report: Computer-Aided Drug Design

- Discipline: Photopharmacology, Smart Drugs, Medical Imaging, Theranostics
- Level: Assistant Professor
- Focus: Research
- Fte: Full time (1.0 fte)

1. Scientific discipline

Computer-Aided Drug Design (CADD) is the scientific discipline that develops a broad range of theoretical and computational approaches towards the identification and development of potential lead molecules in the drug design process with a considerable gain in time and cost, complementing or substituting laborious screening strategies. CADD can be applied throughout the drug discovery process, from molecular design, to interactions of drug candidates with targets of interest. CADD as a research field encompasses several computational approaches, such as structure- and ligand-based drug design, de novo and fragment-based drug design, molecular dynamics, and Quantum Mechanics/Molecular Mechanics (QM/MM) approaches.

2. Vacancy

This position was created in the context of the sector plan Pharmaceutical Sciences and will be embedded in the Groningen Research Institute of Pharmacy (GRIP), joining the recently formed group of *Medicinal Chemistry, Photopharmacology and Imaging* (MCPI). The position falls within the framework of the newly instated career development program, Career Paths in Science and Engineering. As the focus domain of the position is research, the criteria of the career path with a focus on research apply. Please see the link for more information.

3. Selection committee (BAC)

Prof. G.J. Poelarends, Scientific director GRIP, chair of the selection committee
Prof. K. Poelstra, Director education cluster pharmacy
Prof. W.C. Szymanski, chair of Medicinal Chemistry, Photopharmacology & Imaging
Prof. S.J. Marrink, Molecular Dynamics
Prof. A. Salvati, Nanomedicine
Prof. A.K.H. Hirsch, Drug Design and Optimization (HIPS, Germany)
Student member: Ms Desanka Stoppels

Advisors: F.J. Salverda (HR advisor), Dr. R. van Calck (scientific coordinator GRIP)

4. Research area

Computer-Aided Drug Design (CADD) plays an increasingly important role in the process of drug discovery. In itself, the drug discovery process is costly in time and resources, which is further compounded by high failure rates in subsequent clinical

trials. The process starts with target discovery and validation, and proceeds to the stages of hit identification, and hit-to-lead optimization. Particularly in those early stages, CADD plays a pivotal role, significantly reducing development time and costs.

CADD is not a singular design strategy, but in fact encompasses several computational approaches. **Structure-based drug design** utilizes existing structures of protein targets (derived e.g. from X-ray crystallography, cryo-EM or NMR spectroscopy) to predict the binding affinity of ligands by simulating interactions between them *in silico*. If structures are not available, computational structure prediction (with an increasingly important role of AI models, e.g. AlphaFold) is performed, followed by binding site detection. **Ligand-based drug design** focuses on known ligands, and uses similarity searches, scaffold hopping, QSAR and pharmacophore models to optimize existing molecules. For designing new drug molecule classes, **De novo and fragment-based drug design** can be used. With continually increasing computational power, it has become possible to expand static *in silico* docking by incorporating **molecular dynamics** to provide dynamic structural insights into biomolecules, and to provide precise energetic information of receptor-ligand complexes. Finally, to explore the interaction between ligands and proteins and the ADME processes, the high-level **quantum mechanics** calculations can be applied.

5. Embedding: institute (and base unit)

GRIP is positioned within the Faculty of Science and Engineering (FSE) and physically located within the University Medical Centre Groningen (UMCG) of the Faculty of Medical Sciences (FMS) - hence, in ideal proximity to benefit from collaborations between the two faculties. Together with Medical Sciences, GRIP participates in a joint UMCG-FSE Research Institute. Pharmaceutical research within GRIP is multidisciplinary. It bridges the clinical and biomedical sciences on the one hand, and chemistry, mathematics (statistics) and physics on the other. The interaction between the pharmaceutical sciences with these fundamental and clinical sciences offers excellent opportunities for cutting-edge research.

With this vacancy, it is GRIP's ambition to strengthen the MCPI research group, which focuses on the design of molecules that selectively and strongly bind to their targets for therapeutic and imaging purposes. A particular area of molecular design within MCPI is photopharmacology, in which drugs are designed with the intention to control their activity with light. This relatively new discipline urgently needs computational support on its fundamental (photochemistry) and pharmacological (drug design) aspects. Within MCPI, this new CADD expertise will be complemented by the existing organic synthesis and bioactivity assay expertise, forming a perfect combination of computational formation of hypothesis and its experimental validation. Additionally, the research group MCPI and the assistant professor in Computer-Aided Drug Design will be further supported by the appointment of a PhD-graduated technician working on Computational Target and Drug Discovery (Sector Plan Pharmaceutical Sciences).

The research of the CADD professor will also perfectly align with existing pharmaceutical and/or medicinal chemistry research in GRIP (for instance in the groups Chemical and Pharmaceutical Biology, and Molecular Pharmacology). This topic also builds on GRIP's existing external collaborations. This type of research also holds tremendous potential for translation to the clinic, and radiology/medical imaging applications, and many collaborations can be foreseen with researchers at the UMCG.

Due to the fundamental chemistry approach central to this field and the highly relevant prospect of including Machine Learning and AI techniques, further collaborations are foreseen with researchers from the Stratingh Institute of Chemistry, Zernike Institute for Advanced Materials (ZIAM), the Groningen Biomolecular Sciences and Biotechnology Institute (GBB, particularly their Molecular Dynamics and Computational Chemistry groups), and the Bernoulli Institute. Furthermore, key biomedical connections are enabled through the UMCG, especially in the fields of Systems Genetics, and Bioinformatics, which also facilitates access to advanced assays and models (organoids, human post-mortem models, and the small animal facility including the imaging GronSAI facility).

6. Local and (inter)national position

Setting up a dedicated CADD is of key importance not only for GRIP, but for the whole medicinal chemistry community in The Netherlands, where this expertise is largely under-represented. The key expertise is present at the University of Leiden (Prof. Gerard van Westen) and Technical University of Eindhoven (dr. Francesca Grisoni). Otherwise, CADD is used in leading Dutch medicinal chemistry groups mostly as a support for the main actions (see the groups of Prof. Iwan de Esch, Dr. Barbara Zarzycka and Prof. Rob Leurs at VU).

In Europe, the important Photopharmacology centres are located in Germany, UK and Switzerland, any many CADD applications are explored in commercial institutions (pharma companies in Europe such as AstraZeneca, Bayer AG, Ely Lilly, Hoffmann-LaRoche and Novartis).

With this position, GRIP aims to capitalize on the close collaboration with UMCG and other institutes at FSE to create a unique position in which photopharmacology can be inspired by and synergizes with clinical disciplines, including medical imaging, radiotherapy, medical oncology, and clinical microbiology.

7. Expected contributions to research

Depending on their career stage, the candidate is expected to (further) develop an excellent and internationally leading, independent research line on *Computer-Aided Drug Design*. This can vary from molecular design, to investigating the interactions of

drug candidates with targets of interest. Within the research group MCPI, this could entail computational approaches to predicting the structures of molecules that bind selected targets, and various projects on general drug discovery, photopharmacology, and molecular imaging.

Importantly, the assistant professor is expected to take an active approach in not only using existing computational methods in CADD, but also developing new approaches, methods, and algorithms. In this respect, the application of emerging AI technologies and/or the focus on the hybrid MM/QM methods, taking advantage of increasing computational power, will be seen as an important asset. In the context of the QM calculations, additional synergies will emerge within MCPI through (TD-)DFT expertise on the design of photochemical tools of photopharmacology and imaging.

Local collaborations with relevant groups in the Faculty of Medical Sciences and the FSE, and with colleagues on both a national and international level is also expected. An important aspect of the function will involve the acquisition of substantial external funding and the supervision of PhD candidates.

8. Expected contributions to teaching

Depending on their expertise, the staff member is expected to contribute to a number of courses in the Bachelor and Master degree programmes of Pharmacy, for example *Medicinal Chemistry and Biophysics*, *Proteins for Biopharmaceuticals & Drug Discovery*, and *Receptor Pharmacology*. Furthermore, based on their background, the candidate can be envisioned developing and teaching courses on *Computer-Aided Drug Design*, *Artificial Intelligence and Machine Learning, and Computational Chemistry* in the research master Medical Pharmaceutical Sciences.

9. Expected contributions to the organization

The candidate is expected to have an active interest and to provide a positive contribution to the management and organizational tasks of the institute. At the level of the FSE, the candidate will contribute to the organization of the faculty, for example by participating in working groups and committees, in the fields of teaching, research and management. The candidate will participate in relevant national and international organizations.