WATer ELectrostatics in Starch crystalline structures

Summary :

Starch, a polysaccharide, is the most important carbohydrate source for human nutrition, present in the form of granules, semi-crystalline structures containing ordered crystalline regions. Starch crystallinity varies between different nutritional plants and has a different water content according to the type. Hydrostatic pressure can modify the molecular structure of starch crystallites, but its influence is not yet understood. Our project aims at a quantitative understanding of the role of the water content on starch crystalline structures. Our key hypothesis is that the influence of water on the molecular structure of starch crystallites can be understood by a quantitative mapping of internal water interfaces with the help of electrostatic potential. Obtaining a clear view on the molecular and atomic level of how the present water molecules modify the structure of starch relates to understanding how environmental moisture influences the starch crystal type, of which our study might give a first indication.
To this end, we propose a multiscale computational approach, ranging from atomistic to structural length scales. A central quantity here is the electrostatic potential, which will be used to identify interactions and estimate their strength.

State of the Art :

Starch, a polysaccharide, is the most important carbohydrate source for human nutrition, as it is produced by most green plants for energy storage. It consists of two types of molecules, the linear and helical amylose and the branched amylopectin. Depending on the plant, starch contains 20 to 25% amylose and 75 to 80% amylopectin by weight. In plant cells, starch is present in the form of granules, semi-crystalline structures containing ordered crystalline regions, formed by the starch polymers, and resulting in double-helical and lamellar structures. Starch crystallinity varies between different nutritional plants, of which three are considered canonical: maize (A-type), potato (B-type), and pea (C-type). This nomenclature reflects the water content in the crystallites: A-type crystals contain only 8 inter-helical water molecules per crystal unit, while B-type crystals have a more open packing with 36 water molecules per crystal unit[1,2] . C-type starch consists of both A- and B-type polymorphs[3]. The water content of the crystallites is influenced by the environmental conditions. Earlier studies make it clear[4,5,6] that environmental hydrostatic pressure modifies the starch structure[7], but it is not understood ***how***. On the other hand, the role water plays in the structure of cellular fibrils and crystallites is well-acknowledged in the literature, e.g. for cellulose[8] and amyloid fibrils[9]. For nanocellulose, the significance of water in cellulose structures is reviewed[8]. But for starch granules, very little is known about how native granules transition between A-, B-, and C-type starch structures in response to hydration changes, particularly under climate-relevant stresses. Our study might give a first indication hereof, making this academic study towards the ***impact of water evaporation on crystalline structures very timely in the context of the current climate change***.
Further, to tackle our research questions, we use a multidisciplinary approach at the frontline of the state of the art, hereby providing **I**. ***macromolecular electrostatics*** at the starch assembly level[10] and **II**. insight at the ***atomistic level***, using ***electrostatic potential*** calculations.

Methodology :

This project is designed around multiscale modeling, ranging from atomistic to structural length scales.
We combine ***3 levels of modelling***, going from a broad vision to a detailed description at the atomistic level. This multi-level system approach has recently been successfully used before in our team[11,12], and consists of:
1. ***Continuum models*** for the electrostatic potential based on the Poisson-Boltzmann model and its variants, which have matured over the last years to include the role of water in recent years[10] (*cfr*. amyloid fibril aggregates as example[9]). These models will be used to quantify the free energies of starch assemblies, hence allowing for an understanding of the formation of the different entities' structures.
2. ***Molecular dynamics simulations*** will reveal how structures are held together. They give an overview of details of the structural and dynamical aspects of the starch assemblies.
3. ***Quantum mechanical calculations*** will give information on the atomistic level. Hereby, the details of the interactions will be revealed. We will perform all-electron single molecule calculations giving more precise data for the interactions, but on smaller systems.

A central quantity at all three modelling levels will be the electrostatic potential. It will be calculated at the classical physics level and at the quantum mechanical level, hereby providing the student an ***overall training in different methodologies*** of molecular modelling.
At the classical physics level, a detailed comparison of continuum approaches with MD simulations, giving criteria for their applicability, was performed in our team[13]. These models will be used to quantify the free energies of starch assemblies, hence allowing for an understanding of the formation of the different entities' structures.
At the quantum mechanical level, the electrostatic potential will be calculated at the molecular surface to visualize and quantify the non-covalent water-glucan interactions. In using electrostatic potentials to analyze noncovalent interactions, $V(\mathbf{r})$ is now generally computed on a molecular surface[14]. Our new contribution here is that we consider the full 3D nature of the electrostatic potential, not only at outer iso-density surfaces, as suggested in the 1990's[14], but at contours much closer to the nuclei, a methodology established in work by recent our team[15–17].

Host institute and team :

The research topics in the host institute UGSF evolve around the study of glycoconjugates, including their structural biology and modelling, their biosynthesis and degradation, and their function and pathologies due to deregulation. The institute adopts a multi-disciplinary and multi-scale approach to this, combining experimental and computational approaches at all levels. The present project fits the scope of these research activities perfectly.
The host team, "Biomolecular Interactions and Dynamics" (BIND) led by Dr. Marc Lensink, plays a key role in the modelling research axis within the institute. The team members have complementary expertise in different theoretical techniques, by which computational modelling is feasible from the atomistic to the structural length scale.
Apart from having a long-standing expertise in the computational modeling of (bio)molecular interactions, they also have an internationally recognized expertise in structural bioinformatics methods, including modelling-based approaches the study of protein function and network approaches to study protein-protein interaction networks and pathways.

Over many years, the team has developed methodologies for the evaluation of interactions in (large) molecular systems using the electrostatic potential as key quality, both at the classical physics and the quantum mechanical level.

Objectives :

Our project aims at a quantitative understanding up to the molecular and atomic level of the role of water in starch crystallite structures. Our **key hypothesis** is that the influence of water on the structure of starch crystallites can be understood by a quantitative mapping of internal water interfaces with the help of electrostatic potential[10,18]. Our goal is to elucidate the fundamentals of the interactions making the water-interfaces in the different crystal types found in stored starch, up to the molecular and atomic level. Indirectly, this can give some understanding how environmental moisture modifies the starch crystal structure [6,7]. This relates to ***identifying how altering climate conditions impact starch storage***.

Required skills :

This interdisciplinary theoretical project combines quantum mechanics, molecular dynamics and continuum theory, requiring knowledge in all three different theoretical techniques. We expect the candidate to have a strong background in at least one of these theoretical disciplines. The student will receive training in the other ones within our team as all necessary expertise is present, and thus the student should be motivated to learn new theoretical methods. In return, the student will develop a broad spectrum of different theoretical skills, resulting in a qualification for integrated modelling assignments.
A degree in theoretical chemistry or statistical physics is not strictly mandatory, but is recommendable.

Gantt Chart :

In our work we will analyze the water-interactions in different types of starch crystals at different levels. We start with the macromolecular electrostatic level in continuum models[5]. MD simulations of starch entities will be performed, in the presence and absence of water, as a second level. In a third level, we analyze the atomistic details of the interactions by means of the electrostatic potential at the quantum mechanical level[10,18].
We start with existing crystal structures, but throughout our work also the structures coming out of the MD runs can again serve as input for further analysis. This allows to generate an overview of the water-glycan structures for which interactions can be studied in detail. As such, by following this work-flow a complete overview of the interaction patterns in each crystal type will be obtained.
Throughout the course of the project, but mostly in the last two years, we will frequently present and discuss our results within our research team and with our collaborating (experimental) partners to obtain feedback prior to publication and thesis writing.

The following Gantt chart is indicative for the development of the project:

Milestone	**Year 1**	**Year 2**	**Year 3**
1. Definition of models of existing crystal structures that can be used at the different levels of the multiscale modelling	V		
2. MD simulations to generate further structures; modelling in presence and absence of water	V	V	

3. Analyzation of the impact of the presence of water molecules on the assembly and molecular structure level	V	V	
4. Poisson-Boltzmann macro-molecular electrostatics; free energies of assembly formation		V	
5. Analysis at the atomistic level; quantum mechanical electrostatic potential calculations to obtain an overview of the water-starch interactions		V	V
6. Presenting and discussions of the results within our research team and with our collaborating (experimental) partners		V	V
7. Publication of the results; thesis writing		V	V

Collaborations :

This project makes a connection between **four research teams** (including BIND) with complementary expertise on local, national and international level. All teams function in established collaborations. Our team ***BIND***, located in ***UGSF, Univ***. Lille can benefit from the experimental work of ***Integrative Biology of Storage Polysaccharides*** group ***in UGSF, Univ. Lille*** and from ***THz spectroscopy*** group in INL, Lyon. A collaboration with the ***Institute for Materials Research (imo-imomec), Quantum & Artificial inTelligence design Of Materials (QuATOMs), U. Hasselt, Belgium*** will give additional theoretical expertise in periodic DFT calculations.
These groups will bring in additional expertise and validation of the theoretical results. On the other hand, our theoretical study will also guide the experimental work. **Frequent meetings** and **occasional visits** with the other teams will be planned.

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