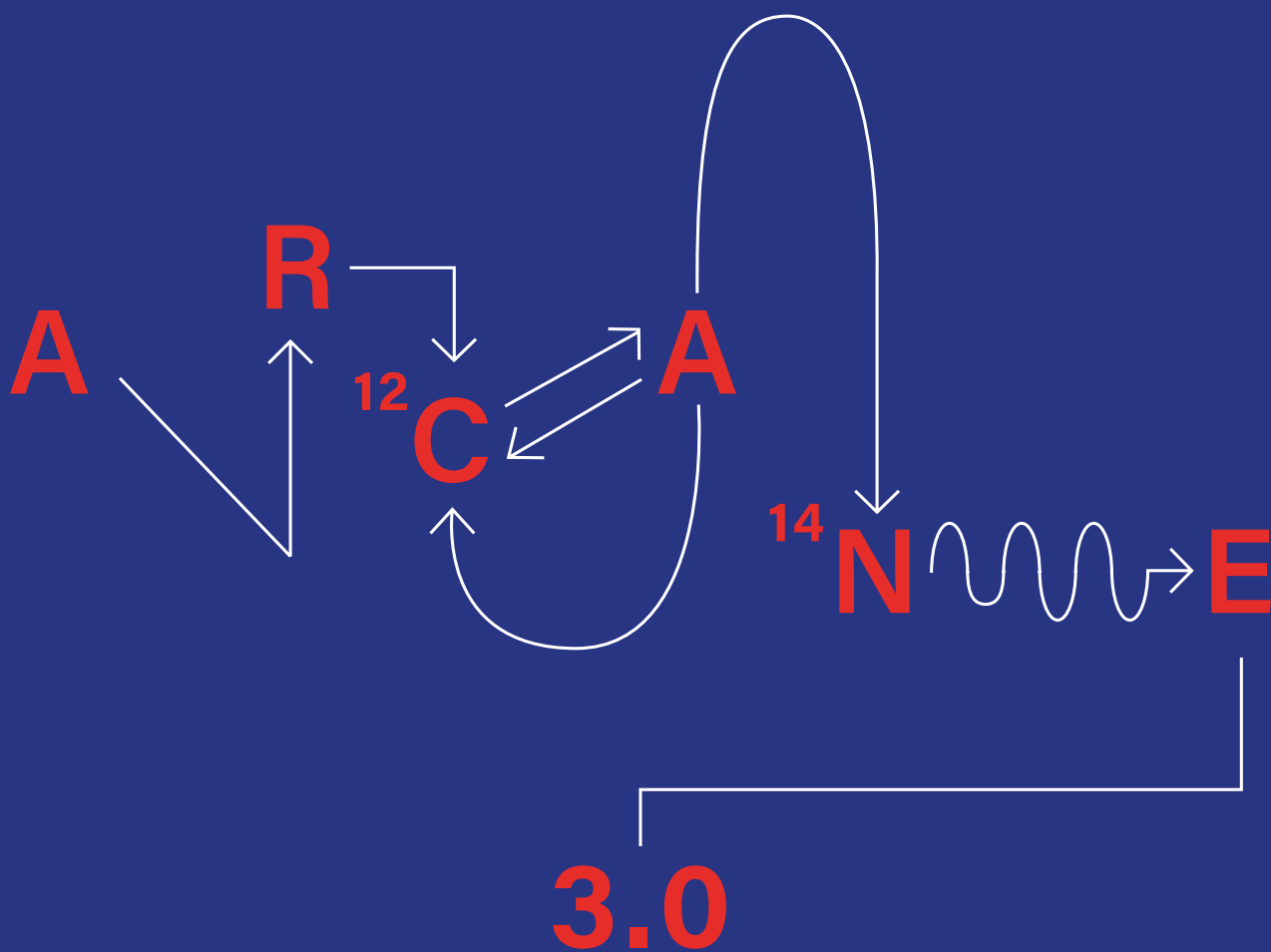


MOLECULAR CHEMISTRY

IN GRENOBLE



Arcane scientific project

To better represent all aspects of the molecular chemistry developed in Grenoble, Arcane 3.0 will be organized into five main interconnected thematic axes:

AXIS 1. BIOMOLECULAR, MEDICINAL CHEMISTRY & CHEMICAL BIOLOGY

AXIS 2. BIOANALYSIS, MOLECULAR RECOGNITION & TARGETING

AXIS 3. FUNCTIONAL MOLECULES & IMAGING AGENTS

AXIS 4. SYNTHESIS, MOLECULAR SELF-ASSEMBLY & FUNCTIONALIZATION

AXIS 5. MOLECULAR CATALYSIS, ELECTRO & PHOTO CHEMICAL PROCESSES

In addition to these, we have defined four transversal axes:

Advanced
Characterization

Quantum
Chemistry
& Simulation

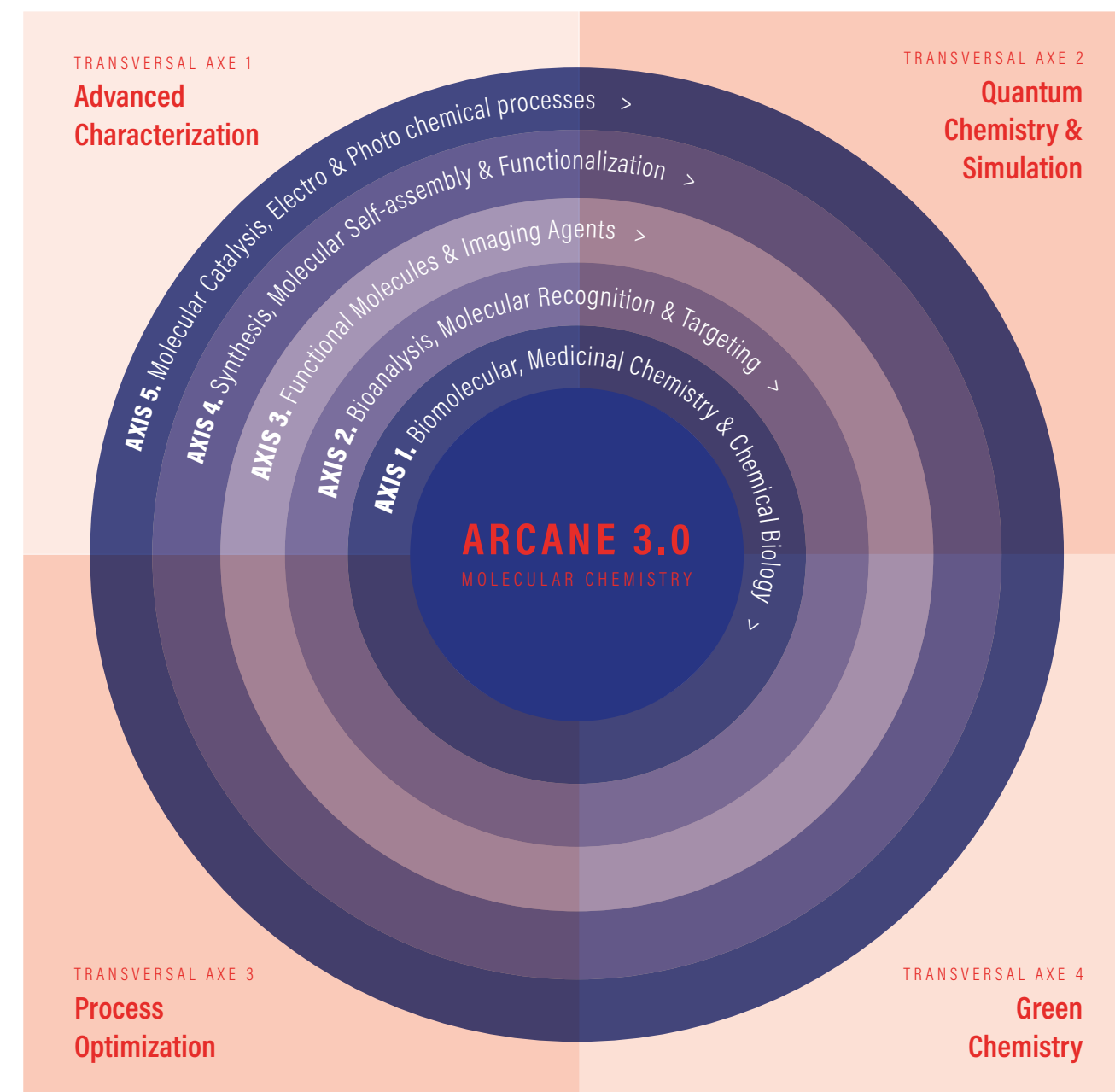
Process
Optimization

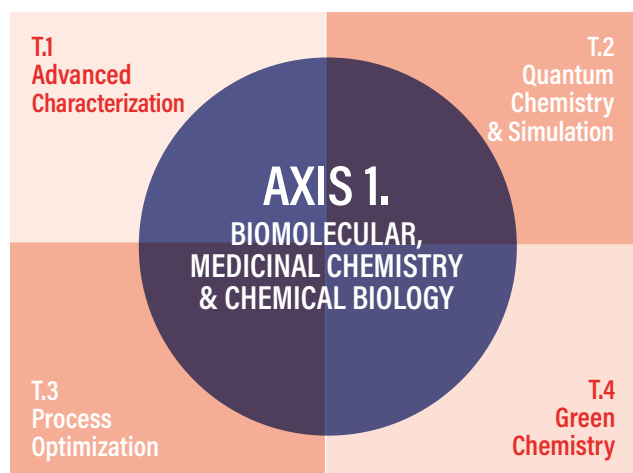
Green
Chemistry

THESE TRANSVERSAL AXES WILL SUPPORT AND ENHANCE
OUR RESEARCH ACROSS ALL PRIMARY AXES.

The chosen division of the project underscores the multifaceted role of molecular chemistry, showcasing its contributions to diverse applications. This structure also emphasizes the importance of collaboration: a molecule synthesized by one team or a methodology developed in a specific context can be applied across various projects by other teams. Consequently, certain aspects of the axes are interconnected, allowing themes to be explored in multiple contexts and enhancing the overall impact of our research efforts.

ARCANE 3.0 : MAIN AXES





Axis 1. Biomolecular Chemistry, Medicinal Chemistry & Chemical Biology

Chemists in Axis 1 of the Arcane community will pursue advancements in biomacromolecule, carbohydrate, oligonucleotide, and peptide chemistry. They aim to innovate new tools for chemical synthesis and therapeutic agents and to unravel complex biochemical processes. Focus areas include bioactive heterocycles, natural products, and their hemisynthetic derivatives to uncover novel bioactive compounds. By leveraging the power of biomolecular engineering and advanced biotechnological strategies, the consortium aims to revolutionize therapeutic agent development and diagnosis methods using chemical probes. Cutting-edge chemoselective ligation techniques and the exploration of metals in biological systems will drive the creation of groundbreaking biomaterials and the elucidation of intricate metabolic pathways.

Biomacromolecule chemistry. Biomacromolecules exhibit a vast diversity of chemical functions, resulting in unique chemical and structural properties. We plan to explore the chemistry of biological macromolecules (proteins, polynucleic acids, and polysaccharides), to understand and tune their properties through chemical modifications. We will investigate:

- DNA degradation and repair processes in the context of human health,
- structure-function relationship on proteins and glycoproteins (*e.g.*, lectins),
- degradation of polysaccharides and the enzymes responsible thereof, with the aim of discovering oligosaccharides with new reactivity,
- functionalized polysaccharides to develop chiral selectors, stimuli-responsive materials, and associated biomedical materials.

We will also explore the chemistry of the building blocks of these biological polymers, and associated biomolecules (carbohydrate, oligonucleotide, and peptide chemistry).

Carbohydrate chemistry. We plan to advance in various applications and methodologies. We will explore novel methods for the degradation of polysaccharides to generate new oligosaccharides, facilitating their synthesis enzymatically for the development of glycoconjugates. Such conjugates will serve as molecular probes with therapeutic applications, targeting lectins specific to cancer cells and other target cells. Additionally, our research will involve the synthesis of modified carbohydrates tailored for biosensors, chemical probes, and therapeutic agents. Methodological advancements will be a critical focus, aiming to enhance the specificity and efficacy of lectin targeting and develop biocompatible medical devices such as micro-needles. Furthermore, we plan to investigate polysaccharide-based redox gels for applications in (bio) electrocatalysis and (bio)electrochemistry, utilizing their unique properties for biomedical and environmental applications.

Oligonucleotide chemistry. We will focus on synthesizing modified nucleic acids for biosensors, therapy, catalysis, and molecular probes to study nucleic acid biology and nanotechnology. Our methodological developments aim to enhance synthesis and functionalization. For instance, we will explore DNA origami and metal nanoclusters for constructing nanostructures and developing biosensing platforms. We also develop bioconjugates by coupling oligonucleotides with antibodies for targeted therapies and diagnostics. We will also further develop DNA encoding technology for combinatorial library generation.

Peptide chemistry offers a wealth of opportunities to develop various strategies for health applications. We will synthesize:

- novel modified peptides including amphiphilic peptoids, cell-penetrating peptides with spatiotemporal control, and alpha-helix mimics, to detect and treat several diseases such as cancer, neuropathies, and even bacterial diseases with the development of innovative antibiotics,
- structured peptides and pseudo peptides employed as metal-binding site mimics to mimic or target natural processes,
- short peptides for use in electronic noses and biosensors.
- Besides, the prebiotic synthesis of peptides will be explored to elucidate the mechanisms underlying the origin of life.

Bio-active heterocycles. Heterocycles are motifs found in many natural biomolecules and synthetic molecules used for therapeutic purposes. Research efforts will focus on advancing efficient and, when necessary, enantioselective syntheses of azaheterocycles, iminosugars, alkaloids, or polyphenol derivatives while also aiming to discover new bioactive heterocycles. The main biological areas of study include fibrillation inhibitors, particularly for applications related to neurodegenerative diseases, and anti-infectives. In the case of antiparasitic compounds, the use of nitroaromatic prodrugs will be explored.

Natural products and hemisynthetic derivatives. The organic chemists of the consortium will conceive innovative synthetic pathways to produce, *via* total synthesis, *bio-active natural products* that cannot be easily extracted (or in insufficient quantity) or to have access to analogs of natural products to evaluate the impact of these modifications on their biological activity. The pharmacomodulation of compounds will thus yield crucial insights for structure-activity relationship studies, aiding in the optimization of the active structure through rational design strategies. Developing new methodologies for the chemical modification of extracts will enable the synthesis of hybrid molecules. These compounds will benefit from synthetic moieties with unnatural chemical functions linked to natural scaffolds. The high number of chiral centers and diversity of natural scaffolds will enlarge the chemical space explored, facilitating the identification of bioactive products.

Biomolecular engineering. Our research will focus on the design and synthesis of:

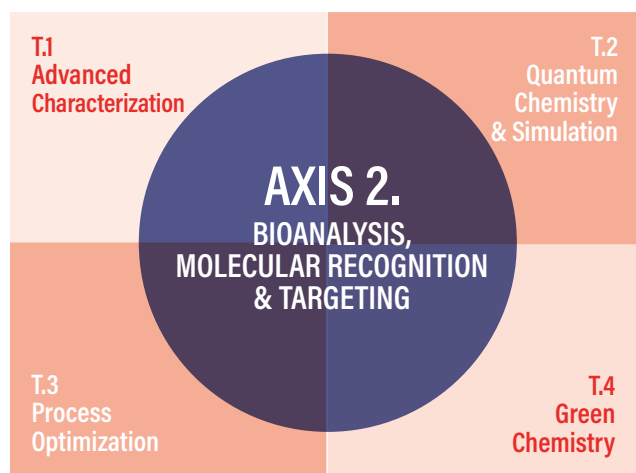
- biomolecular conjugates (in vitro) and modified metabolites (in living media) using click chemistry to enhance imaging, therapeutic applications, and molecular probe development,
- artificial metalloenzymes for selective catalytic processes,
- functional hybrid biopolymers (polysaccharides, peptides, proteins) as intelligent materials with catalytic capabilities,
- recombinant lectins for cancer marker applications, contributing to lectin arrays, glycomics, and synthetic biology for precision oncology diagnostic.

Biotechnological strategies. Innovative tools will be developed using biological systems at different levels, from biomolecules and biomolecular architectures to microorganisms. The molecular recognition properties of biomolecules (*e.g.*, lectins and specific glycoconjugates) will be utilized for diagnosis tools. Molecular architectures like self-assembled siRNA

delivery systems or decorated nanoparticles will be developed to improve cancer targeting and treatment. We will engineer enzymes to produce molecules of interest, *in vitro* but also in micro-organisms. Applications include the synthesis of organic compounds with artificial metalloenzymes catalyzing abiotic reactions and the production of specific glycoconjugates for therapeutics. Micro-organisms like methanogens will also be used for bio-methane production, in the context of energy applications.

Chemoselective ligation. Bioorthogonal chemical methodologies will be developed to selectively modify or conjugate biomolecules, including proteins, glycoconjugates, and nucleic acids. Regioselective reactions will be explored to obtain new glycoconjugates from biomass. Biorthogonal modification strategies will be applied to assemble biomolecular objects for diagnosis and therapy. Furthermore, these tools will also be used to investigate biological pathways in prokaryotic and eukaryotic cells, thereby enhancing our understanding of important biological processes in health and disease.

Metals in biology. We will develop and apply molecular tools to study the role(s) of metal ions in biological systems, and the consequences of metal imbalance in healthy conditions and diseases. Biomimetic complexes will be developed to understand the interactions of metals with biomolecules and to trigger the development of new strategies for chelation therapy. We will use various strategies, including biorthogonal labeling and metal-responsive probes, to investigate the molecular pathways of metal acquisition and trafficking by living organisms. Bioactive metal complexes will also be designed for therapeutic applications, *e.g.*, photo-activated chemotherapy, and photodynamic therapy.



Axis 2. Bioanalysis, Molecular Recognition & Targeting

Our future research in Axis 2 will address key challenges and pioneer innovative solutions across several critical areas. In sensors and transducers, we aim to design biosensors for medical diagnostics, environmental monitoring, and food safety, optimizing components for better selectivity, stability, and sensitivity. We will investigate biomolecular interactions to understand recognition mechanisms involving oligosaccharides, DNA, carbohydrates, phospholipids, antibodies, and enzymes. Cutting-edge detection techniques will be employed to develop miniaturized analytical devices like portable platforms and biochips, essential for enhancing applicability. We will develop advanced methodologies to quantify molecular biomarkers for diagnosing health conditions, and exploit multivalency to enhance ligand-receptor interactions for the design of robust biomaterials and biomedical tools. We will also improve therapeutic agent delivery using innovative chemistry and design treatments for enzyme-related, metal homeostasis, and musculoskeletal disorders. Our goal is to advance sustainable, bio-inspired chemistry for more effective and eco-friendly medical solutions.

Sensors & transducers: molecules & devices. Several strategies will be followed to design and develop innovative biosensors and biochips for medical diagnostics (*e.g.*, biomarkers of specific diseases, pathogen detection), environmental monitoring (detection of pollutants), and food safety (identification of contamination). The three main components of sensors will be investigated and optimized based on their intended use, which requires varying properties such as selectivity, affinity, stability, and sensitivity.

- For *(bio)-recognition* we will design different types of sensors: enzyme sensors, immunosensors (antibody-antigen interaction), aptasensors (aptamers interaction with a broad range of targets from small molecules to cells), DNA sensors (single-stranded DNA – complementary DNA sequence interaction), liquid crystal sensors (carbohydrate-lectin interaction).
- For *transducers* and to optimize the response, the interaction between the sensor and the target will be translated into a measurable signal. Our focus will be on multiple approaches: electrochemical methods involving surface electrode modifications and detection through (spectro) electrochemistry and impedance spectroscopy, optical transduction through the development of photoswitchable nanofibers and NIR-II emitting contrast agents, the use of advanced techniques such as surface plasmon resonance imaging, multispectral mid-infrared imaging, Raman and fluorescence spectroscopy.
- For *signal detection and amplification*, synergistic strategies will be developed based on molecular and biomolecular recognition accompanied by optical, spectroscopic, and electrochemical detection. Signal amplification will be studied based on enzymatic reactions, smart materials (plasmonic materials, photoswitchable, porous nanomaterials, and nano-biomaterials), and surface functionalization and nanostructuration.

Interactions between biomolecules, small molecules, and cells.

Our objective is to develop tools and strategies to facilitate the study of (bio)molecular interactions across various families of biomolecules. This involves creating biosensors and characterizing interactions with carbohydrates (including oligosaccharides and glycomimetics), nucleic acids (such as dsDNA, in-house selected aptamers, and G-quadruplexes), phospholipids, liposomes, extracellular vesicles, and their biological partners. We will explore the therapeutic potential of chaperone drugs for treating lysosomal diseases by stabilizing misfolded proteins. We will also study the interactions between volatile organic compounds and electronic noses for detection purposes.

Miniaturized analytical devices. It is crucial to develop reliable miniaturized analytical devices to broaden the range of potential applications and advance to higher TRL (Technology Readiness Level). Lab-on-chips gathering several steps on the same device (capture + detection for instance) are of great interest. We will target the conception of miniaturized microfluidic analytical platforms for cell analysis (*e.g.*, detection and quantification of secretome) or for the separation and analysis of extracellular vesicles, which are of growing interest in cancer diagnostics (*e.g.*, by using deterministic lateral displacement). Nanopore

sensing is also relevant for the separation and detection of single biomolecules and is particularly adapted to DNA and RNA sensing. We will enhance the performance of portable electronic noses based on SPRI sensing in the gas phase, which are also promising miniaturized tools for applications in cosmetics, food control, or health (*e.g.*, virus detection). Microneedle based sensors will also be conceived for the quantification of different biomarkers in interstitial fluids.

Molecular biomarkers. Molecular biomarkers are diverse and varied, and some have only recently come to light. Detecting and quantifying them is a major healthcare challenge, particularly for diagnosing diseases such as cancer (extracellular vesicles, microRNAs) or deciphering biological processes such as the immune response (cell secretions). The quantification of specific biomarkers will be targeted such as DNA damage by HPLC-MS detection in biological fluids and metabolites or small molecules in biological fluids and complex mixtures by NMR detection.

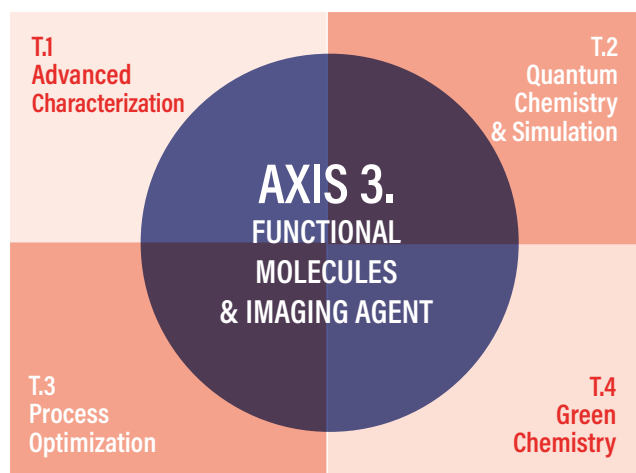
Multivalency. We will exploit supramolecular approaches to design novel templates to enhance ligand-receptor interactions by implementing multivalent cross-linking of polymer brushes. Our aim is to optimize the placement and density of ligands on surfaces, improving binding affinity and stability for optimized therapeutic and diagnosis efficacy. This includes investigating multivalent glycoconjugates and their impact on lectin recognition and function, and multivalent sugar arrays to mimic the glycocalyx on cell surfaces, creating dynamic platforms for studying cellular interactions and therapeutic targeting.

Vectorization, targeting & delivery. We will aim to improve the specificity, efficacy, and safety of therapeutic agents by enhancing their delivery to specific cells, and tissues.

- *In vivo* click chemistry will be used to target the tumor microenvironment and specific cancer receptors with high precision, improving the efficacy and specificity of treatments.
- The self-assembly of amphiphilic polysaccharides will offer innovative approaches for drug delivery systems, enhancing the stability and bioavailability of therapeutic agents.
- Cell-penetrating peptides will be explored to facilitate the intracellular delivery of these agents, overcoming one of the significant barriers in cancer therapy.

Therapeutic agents. We aim to design and synthesize a diverse array of therapeutic agents with the potential to address various health conditions, including:

- inhibitors of enzymes specifically involved in the production of sugars and glycoconjugates (cancer therapy),
- metal-chelators to manipulate copper homeostasis (cancer and Wilson's disease), and combat contamination by toxic metals,
- novel stimuli-responsive gold nanoclusters for cancer therapy,
- functional glycosaminoglycans to treat musculoskeletal disorders.



Axis 3. Functional Molecules & Imaging Agents

Biological research, medical diagnostics and therapeutics, and analytical science all require increasingly selective and precise tools and devices. These are essential for better understanding biological processes, detecting pollutants or biomarkers, and curing diseases. Environmental considerations are also driving the design of more efficient and eco-friendly industrial processes. Such advancements necessitate sophisticated chemical tools and intelligent molecules that offer superior performance and push the boundaries of current capabilities. Axis 3 aims to develop functional molecules for catalysis, analytical sciences, and intelligent imaging agents for biology and medicine. Molecular chemistry enables the fine-tuning of the properties and performance of the required tools and devices. By enhancing precision, efficiency, or selectivity/specificity, chemistry can improve technologies or lead to the creation of new ones.

Chemical probes, contrast agents, and radiopharmaceuticals for bio-imaging and treatment. Specific molecules or materials (hydrogels, nanoparticles, polysaccharides) will be designed for bio-imaging at various levels (in vitro for 2D or 3D cell cultures, *in vivo*, or at an intermediate level with organoids), utilizing MRI, fluorescence, or nuclear imaging, therapeutics, and targeted drug delivery. A special emphasis will be placed on the development of (i) new ligands for metal ions with luminescence or MRI properties or for radionuclides, (ii) targeting strategies, and (iii) probes with improved properties adapted to the biological environment (*e.g.*, NIR probes for optical imaging or phototherapy, bio-compatible materials). These tools will be employed in biological research, medical diagnostics and therapeutics, or theranostics by coupling both.

Stimuli-responsive molecules. The goal is to create molecules capable of altering their physical properties in response to interactions with other molecules or changes in the

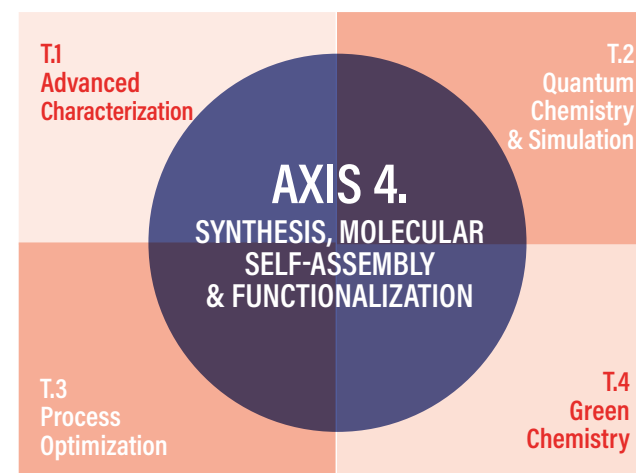
environment. This adaptive behavior has promising applications across various fields. Our focus will be specifically on:

- **Biotechnology development.** We will investigate several types of stimuli, including thermo-responsive liposomes, dynamic fluorescent nanostructures, in situ generated supramolecular hydrogels, glucose-responsive polymers, and metal-responsive protein labeling for applications in biomarker detection in biological fluids, and proteomics.
- **Bioimaging.** Novel bio-imaging probes able to specifically detect a chosen analyte of interest (metal ion, biomarker, pollutant, etc.) will be developed, with applications in fluorescence cell imaging or MRI.
- **Environmental applications.** We aim to develop sensors for detecting pollutants, leveraging the responsive behavior of these molecules.
- **Molecular machines.** We will design molecules capable of movement through light activation and chemically fueled smart materials.
- **Single-molecule magnets.** We will develop molecules whose magnetization can be controlled by an applied magnetic field, especially based on original molecular 2p-3d-4f assemblies and multiferroics. Such molecules hold significant potential in quantum computing and data processing.

Photosensitizers for two main applications:

- **Phototherapy.** In the context of *bio-applications*, we aim to develop molecules that produce reactive oxygen species under irradiation for *phototherapy applications*. This will require the development of chromophores with enhanced optical properties, operating in the NIR window. Another strategy involves photo-cross-linking agents that will form covalent bonds between molecules when exposed to ultraviolet (UV) or visible light. These agents can be used to «fish out» or isolate specific targets from complex mixtures.
- **Photocatalysis.** Our primary focus will be organometallic dyes based on 3d-metal ions and organic dyes (heptazine derivatives for example). These compounds will be developed for applications in solar fuel production devices and photovoltaics, aiming to enhance efficiency and performance in exploiting solar energy.

Polarizing agents. Innovative agents for Dynamic Nuclear Polarization (DNP) will be developed, as these radicals are essential as paramagnetic dopants for DNP experiments. The current challenge lies in designing effective molecules for experiments conducted at very high magnetic fields (greater than 18T), ultra-low temperatures (20-100K), or those based on photo-induced radical species.



Axis 4. Synthesis, Molecular Self-assembly & Functionalization

The development of strategies to synthesize, organize, and functionalize molecular frameworks is of paramount importance as it allows access to original architectures and enables us to control properties related to their 3D structures such as intermolecular interactions, redox, photochemical and/or catalytic properties, and biological activities.

Inorganic Synthesis and Coordination Chemistry. Projects related to the design of metal-based systems will require significant synthetic efforts to overcome challenges in the fields of biomimetics and bioinspiration, as well as the activation of small molecules in renewable energy and sensing. We will focus on developing a library of novel ligands that contain either thiolate, phosphine, and carbene functions, redox-active function, or enzyme insertion, polymerization, and surface anchoring abilities. These ligands will be used to synthesize 3d and 4f-based complexes that can serve as (photo)catalysts, photosensitizers, and chromophores.

Organic Synthesis. We will target the synthesis of complex organic molecules, natural products, or bioactive molecules, as well as labeled compounds, through asymmetric approaches requiring the development of innovative strategies in organic synthesis and novel synthetic stoichiometric and catalytic methods. Combining the natural products complexity with chemical modifications and the exploration of complex plant extracts, will furnish a unique diversity and chemical space exploration. The fundamental question of the origins of life will also be addressed through the synthesis of small peptides under prebiotic conditions. These efforts will strengthen the understanding and capability to produce complex organic compounds, with significant biological and chemical applications.

Radical-based Chemistry. We aim to exploit radical-based chemistry through the reactivity of redox-active ligand-based metal complexes and photoredox radical organic systems and to develop controlled radical polymerization processes.

Macromolecular chemistry. We will investigate various types of macromolecules obtained by chemical synthesis, supramolecular chemistry, or functionalization of natural polymers including polysaccharides, proteins, and peptides. The introduction of functional groups by grafting, copolymerization, or cross-linking will lead to functional molecular assemblies for catalysis, imaging, self-healing, and stimuli-responsive materials. The self-assembly of functionalized macromolecules can also lead to nanoparticles, thin films, or photonic crystals.

Surface functionalization. Three main applications will be targeted:

- **Catalysis and electrocatalysis of small molecules.** Our objective is the integration of molecular (bio)catalysts into functional materials and devices through nanomaterials functionalization with special focus on solar fuel production, artificial photosynthesis, water oxidation, H₂ production, CO₂ reduction, and, more broadly, the (photo) electrocatalytic activation of small molecules. To achieve this, we will functionalize (photo)electrodes based on the use of nanostructured materials, carbon-based nanomaterials, and (doped) graphene. Additionally, we will develop new strategies to immobilize catalysts, including metallo-enzymes, on electrode surfaces through electropolymerization or electrografting methods.
- **Environmental Applications.** Different types of materials will be functionalized to bring novel properties in the field of environment such as recyclability, water purification and bioremediation. To replace plastics in the food industry, we will functionalize the paper surface to produce hydrophobic paperboard.
- **Biosensors and Medical Devices.** Functionalizing surfaces with biomolecules is crucial for developing advanced biosensors and medical devices. We will develop innovative and durable methodologies employing 1D, 2D, and 3D functionalization techniques from fundamental aspects to industrial uses based on electrochemistry, impedance spectroscopy, IR, fluorescence, and Surface Plasmon Resonance (SPR) modeling.

Hybrid Systems Engineering. In addition to the modified electrodes discussed above, other hybrid systems will be designed.

- **Artificial metalloenzymes** based on the integration of synthetic photocatalytic systems in mesoporous protein crystals for artificial photosynthesis,
- **Hybrid composite materials** for water electrooxidation catalysis,
- **Polysaccharide-based nanohybrids** for delivering therapeutic agents with controlled release profiles, targeting specific tissues or cells, and minimizing side effects,
- **Polymer-protected gold nanoclusters** for advanced biomedical applications,
- **Hybrid materials combining polymers**, inorganic, metallic, or carbon nanomaterials, with molecular catalysts for homogenous and heterogenous catalysis.

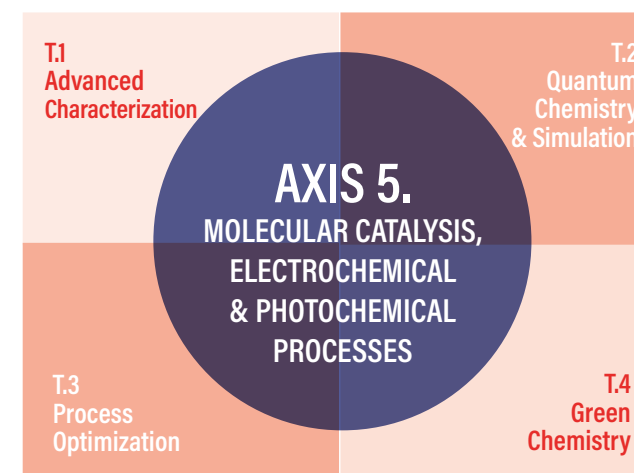
Surface Patterning. We aim to engineer biomimetic surfaces to enhance cell/surface and antigen/antibody interactions for selective recognition, using advanced techniques (Quartz Crystal Microbalance with Dissipation monitoring (QCM-D), Spectroscopic Ellipsometry (SE), Surface Plasmon Resonance (SPR)). Besides, we will develop nanopatterning methodologies through the self-assembly of proteins, with applications in the design of electronic noses and in the field of catalysis. We also aim to chemically modify the surface of polysaccharide nanoparticles to control their self-assembly behavior toward functional bio-based materials.

Nanochemistry. Several strategies will be developed to advance the synthesis and functionalization of nanomaterials for diverse applications.

- **Quantum Dots, (Metallo)Nanoparticles, and Metal-Organic Frameworks:** We aim to synthesize and functionalize these materials for (photo)catalytic processes for optimized sensor design and enhanced catalytic performance in various chemical reactions, including photocatalysis and electrocatalysis.
- **Atomically precise metal nanoclusters, and lipid nanoparticles.** Our goal is to synthesize and biofunctionalize these nanoclusters and nanoparticles to develop safe and efficient theranostic agents that will combine diagnostic and therapeutic functionalities, improve the effectiveness of treatments, and enable precise targeting of disease sites.
- **Cyclodextrin Derivatives.** We will focus on synthesizing cyclodextrin derivatives to develop nano- and micro-sys-

tem formulations for cosmetic applications and drug delivery. These systems will enhance the stability, bio-availability, and controlled release of active ingredients.

Flow chemistry. We will develop appropriate electrolytes for redox flow batteries and explore the potential of flow techniques for novel synthetic methods in organic chemistry, particularly those involving unstable intermediates.



Axis 5. Molecular Catalysis, Electro & Photo chemical processes

Molecular catalysis, electrochemistry, and photochemistry are interconnected areas at the heart of numerous industrial, medical, and environmental processes. They offer promising avenues for developing new, more efficient, and environmentally friendly technologies. Our multifaceted approach integrates these disciplines to address challenges such as reducing dependence on fossil resources, decreasing the carbon footprint of industrial processes, and designing innovative medical solutions. Among these disciplines, asymmetric synthesis is essential for producing chiral compounds employed in pharmacology, enabling the creation of more effective drugs with fewer side effects. Then, understanding catalytic processes at the origin of life can unravel the mysteries of life's emergence on Earth and inspire innovations in catalysis. Moreover, by harnessing solar energy, photoredox processes transform small molecules into useful compounds, while molecular electrochemistry explores fundamental mechanisms leading to more sustainable chemical processes. So, the electrification and solarization of chemical processes pave the way to artificial photosynthesis and clean fuel or chemical production. Finally, biofuel cells promise to contribute to more sustainable energy conversion technologies for *in vivo* applications.

Asymmetric Catalysis. The synthesis of chiral compounds is crucial in medicinal chemistry. To meet this demand, we will design new *organo-, metal- and bio-catalysts* for enantioselective reactions, by focusing on the following strategies:

- design of artificial metalloenzymes based on proteins or DNA G-quadruplexes, as homogeneous or heterogeneous catalysts,
- *in vivo* catalysis,
- bio-inspired organocatalysis,
- multi-catalytic approaches.

Catalysis at the origin of life. We will investigate the catalytic processes that may have played a crucial role in the origin of life, focusing on the prebiotic fixation of CO₂ catalyzed by metal ions. This research aims to gain a deeper understanding of how life emerged and evolved on Earth and to guide the development of novel catalytic systems inspired by these ancient pathways. Additionally, to explore the origins of life's homochirality, we will employ magnetochiral photochemistry to determine how magnetic fields can control the enantioselectivity of chemical transformations.

Photoredox processes. Taking advantage of the unlimited energy source provided by the sun, we aim to develop photocatalytic processes by focusing on the design of photoactive molecules including redox-active organic chromophores, photo-excited free radicals, and photo-organocatalysts that can serve

- as photosensitizers for the photo(electro)catalytic activation and transformation of small molecules,
- for the synthesis of building blocks for complex molecule synthesis and pharmaceuticals,
- for applications in cross-linking for the development of biosensors.

A detailed characterization of the photophysical properties of the new photoactive molecules will be carried out to understand the photo-induced reaction pathways and optimize their performance.

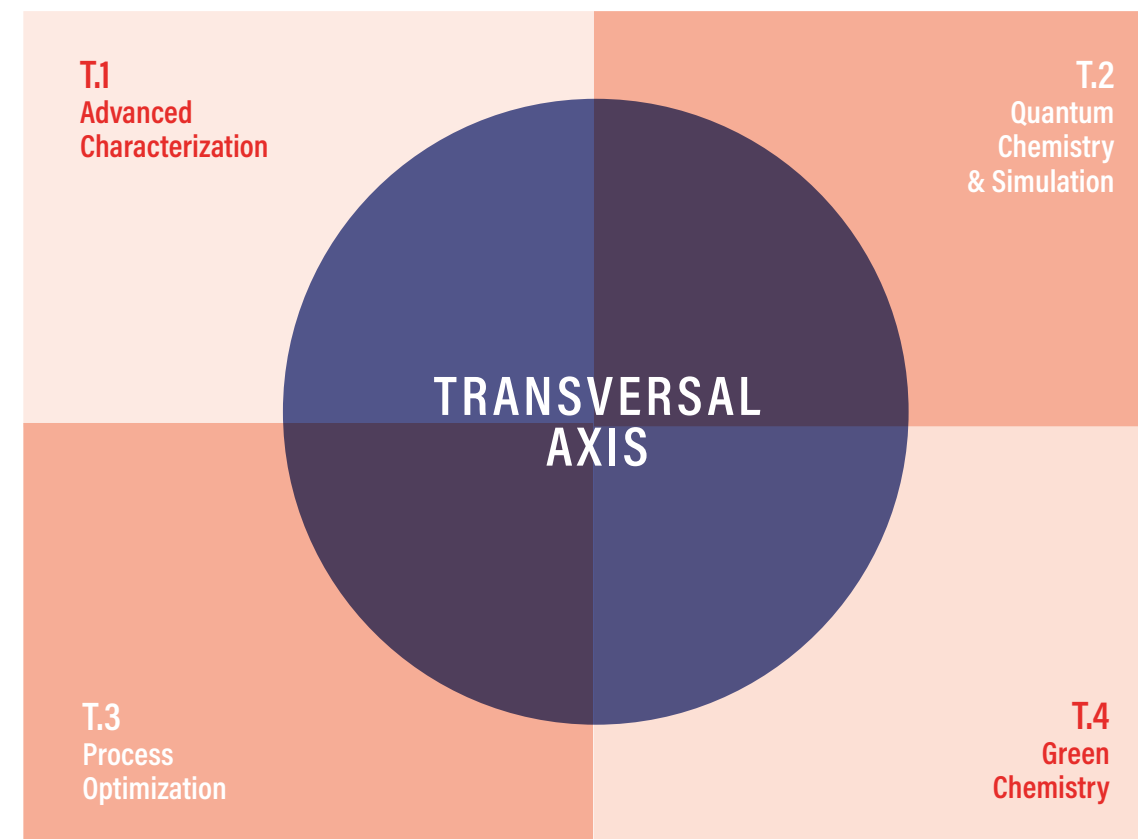
Molecular electrochemistry. In the field of molecular electrochemistry, our efforts will focus on both conceptual and practical advances. We aim to deepen our understanding of fundamental pathways, such as proton-coupled electron transfers that can be promoted by the presence of proton relays. We will explore catalytic mechanisms to achieve more efficient and sustainable electrochemically-driven transformations.

O-, C- and N-functionalization / Electrification & solarization of chemistry. Our primary goal is to develop efficient electrochemical, photochemical, and photoelectrochemical processes for a variety of applications, including artificial photosynthesis. A major focus will be on the reductive activation of CO₂, N₂, or water to produce fuels (such as H₂, CH₄, etc.) and O₂ for fuel cell applications. We also aim to achieve other chemical transformations, such as cycloisomerization and reductive activation of organic molecules, including those with recalcitrant C-H bonds.

Our targeted photo/electrocatalysts include natural or artificial metalloenzymes and (bio-inspired) synthetic metal complexes. We will concentrate on developing cascade reactions using dual catalysts, where the two different catalytic entities can be either of the same or different nature (enzymes or synthetic complexes) or incorporated into the same matrix (such as artificial metalloenzymes containing two active sites). Their tandem action is expected to drastically enhance efficiency, selectivity, and yield performance. Such ambitious processes will be particularly valuable for preparing bioactive and complex molecules.

Biofuel cells. Our research will focus on the development of enzymatic fuel cells, utilizing glucose and H₂ as substrates, H₂ and CO₂ bioelectrolyzers, enzymatic bioreactors, and microbial fuel cells. The general objective is to achieve more efficient and sustainable energy conversion technologies, including *in vivo* applications.

TRANSVERSAL AXES



Advancement of fundamental knowledge is critical to maintaining the flow of future breakthroughs and innovative ideas in molecular chemistry. This can only be achieved by maintaining and nurturing areas of underpinning science. Indeed, modern chemistry would not be possible without past and present advances in the development of analytical and computational tools.

Today, chemistry must answer challenges in the fields of health, energy, and environment, and understanding the mechanisms has never been more crucial to quickly and efficiently developing the new processes and catalysts needed for the paradigm shift we must face. Thus, the continuous improvement and development of characterization techniques, such as spectroscopy, spectrometry, microscopy, and imaging allow for more detailed and accurate analysis of molecular structures and behaviors in the bulk state. Advancements in *simulation and theoretical chemistry* provide powerful tools for predicting, modeling, and understanding chemical processes, enabling the exploration of complex systems and reaction mechanisms. Additionally, the functionalization of surfaces requires *specific techniques* with improved sensitivity to precisely analyze the surface modifications. The development of *in operando* techniques, which allow for real-time observation of chemical processes under operational conditions or *in vivo*, further enhances our ability to study molecular systems in their native or working environment. Equally important is to adopt *green chemistry* routes, to minimize environmental impact and promote the creation of safer, more efficient chemical processes. Together, these transversal methodological developments will support the molecular chemistry applications envisaged within Arcane 3.0, in view of more effective and sustainable solutions for key societal and environmental concerns.

T1. Advanced Characterization

Advanced techniques for surface characterization. For many targeted applications in the Arcane 3.0 scientific project, surface functionalization is required. It is thus of utmost importance to have access to and develop all the techniques required to precisely characterize these surfaces modified by molecules or molecular assemblies, specific to their size (from a single small molecule to a cell). These techniques include spectroscopic, imaging, and scattering techniques, *e.g.*, electron microscopy (Transmission Electron Microscopy-TEM, Cryo-Transmission Electron Microscopy-Cryo-TEM, or Scanning Electron Microscopy-SEM) and Atomic Force Microscopy-Infrared Spectroscopy (AFM-IR) that allows access to detailed chemical information at the nanoscale by combining the spatial resolution capabilities of AFM with IR.

Advanced NMR, EPR, and DNP methods require developments in instrumentation, method, data processing, and application-specific approaches to meet the expectations and needs of the researchers to investigate various molecular systems, including small molecules, functionalized surfaces, bio- and macromolecules, molecular and nanomaterials, organo- and bio-catalysts. The NMR sensitivity and resolution enhancement is crucial to address atomic-level chemical information for diluted, low abundant, and/or insensitive chemical species. DNP and HR-MAS NMR methodologies can offer a promising answer to these issues, allowing the identification of low-concentration compounds in complex mixtures with large dynamic ranges and access to cell-compartment-specific molecular descriptions of sub-cellular metabolomics. Besides, advanced EPR techniques are invaluable tools in the study of both (photo)-catalysts and key paramagnetic intermediates. These short-lived species will be generated *in situ* by coupling the EPR spectrometer with laser irradiation or proper electrochemical setup and detected with enhanced sensitivity by using the recently developed rapid scan technique. Pulsed EPR and high-field and high-(multi)frequency EPR advanced techniques will offer detailed information about the electronic properties of metal complexes.

Sensors, Electronic noses. In the context of health-related technology, we will develop advanced sensors, including electrochemical, electromechanical, and optical-based biosensors, *e.g.*, electronic noses, to detect and identify complex chemical compounds with high precision by greatly increasing the sensitivity and selectivity of the detection systems. By leveraging sensor technologies, we aim to enhance the accuracy and reliability of healthcare diagnostics and monitoring.

(Operando) spectroscopic, spectrometric & imaging techniques.

Our consortium has strong expertise in characterization techniques, including their further development, especially for the understanding of mechanisms through operando methodologies. Spectro-electrochemistry is one of these powerful techniques to investigate redox catalytic processes with a combination of electrochemistry with UV-vis, IR, EPR, and XAS spectroscopy. A special effort will follow these few axes:

- Regarding ^{57}Fe -Mössbauer spectroscopy, operando measurements will be developed to detect short-lived intermediates. It will allow measurements under constant irradiation or the investigation of batteries under working conditions, as well as experiments directly performed on cells to access iron distribution.
- Advanced NIR-I/NIR-II imaging and spectroscopy investigations will be pursued, *e.g.*, for non-invasive *in vivo* monitoring.
- Spectroscopic Bragg coherent diffraction imaging will be developed to characterize nanoparticles under photo- or electro-chemical conditions in liquid and gas phases. The aim is to access atomic-scale and time-resolved structural and chemical characterization of functional nanoparticles.
- X-ray Absorption Spectroscopy will be developed for *in vivo* and *in cellulo* structural characterization of metal sites in metalloenzymes, metalloproteins, coordination complexes, and nanoparticles. This will address the fate of metal-based complexes (*e.g.*, drugs, and nanoparticles) in biological systems.
- Advanced mass spectrometry techniques will be developed to allow metabolomic studies of natural products and to have access to kinetics, ion-molecule reactions, and mechanisms for different types of catalytic processes.

T2. Quantum Chemistry & Simulation

Combined experimental-computational approaches. The development of Density Functional Theory (DFT) methods is crucial for advancing applications relevant to the Arcane 3.0 project, for example:

- Investigation of *large molecules* such as macromolecules, interactions between molecules and nanomaterials, and solvated systems to provide chemical and biological interpretations necessitates developing high-performance computing (HPC) and sophisticated algorithms.
- *(Radical) Metal-based catalysis* is at the heart of intense research in our consortium. The optimization of their performance requires a deep understanding of the mechanism. DFT and ab initio methodologies will be the key to supporting the experiment by predicting the physical properties of the catalysts and intermediates, but also to predict the different potential catalytic pathways.

In parallel, QM calculations of inorganic complexes and/or organic systems in link with AI methodologies need to be further pushed for the determination and understanding of mechanisms, in view to improve the design of chemical systems.

Multiscale modeling methods. We will advance the field of QM/MM (Quantum Mechanics/Molecular Mechanics) for the modeling of proteins and transition metal complex catalysts in explicit solvent environments to investigate and tune their reactivity. This involves developing new workflows and approximations to enable efficient dynamics calculations, integrating both wavefunction-based methods and DFT within a multiscale modeling framework. Key developments will include ASH, a multiscale modeling program adapted to molecular chemistry, which will enable us to understand complex molecular systems at the level of atomic and electronic structure, and BigDFT, which can simulate large molecules in a complex environment on an HPC platform at the DFT level.

Reactivity: meta-dynamics, force-fields. We will utilize active learning of reactive Bayesian force fields to enhance our understanding of reactive adsorption, comparing these results with Bragg coherent diffraction imaging data, with the aim of improving the chemical description of large systems and predicting and analyzing complex interactions. The application of FLARE (Fast Learning of Atomistic Rare Events) will provide accurate predictions of forces, energies, and stresses. This method will allow us to quantitatively estimate principle uncertainty at each molecular dynamics (MD) simulation step.

Artificial Intelligence. AI is transforming chemistry, revolutionizing both theoretical chemistry and characterization and analysis methods. Significant methodological advancements driven by AI are anticipated in these fields in the coming years. We will focus on specific aspects:

- Developing AI methodologies for chemical reactivity: Our focus will be on improving the efficiency of training the deep neural network potentials (DNNPs) for chemical reactivity. Additionally, we will develop a hybrid version that combines a reactive component computed using DNNPs with molecular mechanics (MM) for the surrounding environment. A chemical system of interest for this method will be the Deep Eutectic Solvents (DES), especially because they are challenging to model with current state-of-the-art methods.
- Processing noisy NMR/DNP data resulting from insensitive or diluted species to improve the technique's detection limit for dilute systems.
- Processing *operando* coherent diffraction imaging data by improving phase retrieval, super-resolution, denoising, and phase unwrapping to accurately reconstruct in situ Bragg coherent imaging 3D datasets on highly strained and defective nanocatalysts.
- Enhancing electronic noses by improving their discrimination capacity through advanced data treatment techniques, leading to more precise and reliable detection of various substances.
- Investigation of macromolecular materials: AI will be used to study microstructure, transport phenomena, and mechanical properties, creating realistic models and determining molecule selectivity in macromolecular membranes. This complements experimental evidence and screens molecules under challenging conditions.

T3. Green Chemistry

Eco-compatible processes. In the quest for sustainable and environmentally friendly industrial practices, the development of eco-compatible processes has become a paramount objective. In this context, we will develop earth-abundant metal-based catalysts and artificial metalloenzymes for specific reactions, including converting biomass into valuable commodity chemicals and upcycling polyolefin plastics by transforming waste into useful materials. Innovative processes for the chemical modification of the surface of materials using eco-compatible techniques will also be investigated to reduce or eliminate the use or production of hazardous substances, as *e.g.*, the use of green solvents like supercritical CO₂, solvent-free vapor-phase, and water-based processes.

Bio-Sourced Molecules. For sustainable technological and industrial processes:

- *Surface grafting processes for catalysts and biocatalysts.* We will focus on new production methods for high-value molecules through (bio)catalysis using continuous flow production, combined with macro and microfluidics to enhance enzymatic reaction productivity.
- *Plastic material surface cleaning processes.* The goal is to move from «low-cost single-use analysis» to «competitive reusable multi-analysis.» This aims to eliminate chemical, biological (DNA, RNA, antibodies), and microbiological (bacteria) contamination of plastic surfaces by using supercritical CO₂ as a solvent and disinfecting agent.
- *Modification of bio-sourced polymers.* We will use natural molecules (cellulose, nanocellulose) for innovative renewable and biodegradable antimicrobial materials (bandages) functionalized through silanization with supercritical CO₂ or impregnation with bio-sourced molecules, like essential oils. We will also use bio-sourced aerogels (chitosan, alginate) as starting materials for synthesizing value-added bioactive molecules based on the catalytic conversion of CO₂, or to develop innovative materials for biological fluid sampling or the delivery of drug molecules *via* microneedles.

T4. Process Optimization

In the ever-evolving landscape of scientific research and industrial application, process optimization plays a pivotal role in enhancing efficiency, reducing costs, and driving innovation.

Chemometrics is a field within chemistry that applies mathematical, statistical, and formal logical methods to develop or select the best measurement procedures and experiments. It aims to extract the most relevant chemical information from the analysis of chemical data. This interdisciplinary science is applied to both descriptive and predictive applications, including identifying relationships and structures within systems, as well as modeling and optimization. The most important tools used in chemometrics are experimental design (DoE), multivariate statistical analysis, machine learning algorithms, and spectral analysis techniques.

Intensification. Developing equipment (reactors, sensors, etc.), tools, and methods for synthesizing, mixing, formulating, and implementing high-value molecules, biomolecules, and polymers is crucial in the current global economic context, especially post-COVID. This effort supports reindustrialization and French sovereignty while maintaining the competitiveness of chemical and pharmaceutical companies by aiming to «do more, better, and cheaper with less.» Key focus areas include scaling up surface functionalization processes for micro/milli fluidic reactors for biocatalytic synthesis and the development of sensors to improve bioproduction processes for vaccines and recombinant proteins. These advancements seek to enhance product quality, reduce energy and raw material consumption, minimize installation footprints, and boost production capacity.

In conclusion, the funding for these projects will hinge on the outcomes of future Arcane calls for proposals. Regardless of these outcomes, all initiatives will receive support from Arcane in some capacity. This continued backing ensures that our projects will advance the scientific and collaborative spirit of our community.

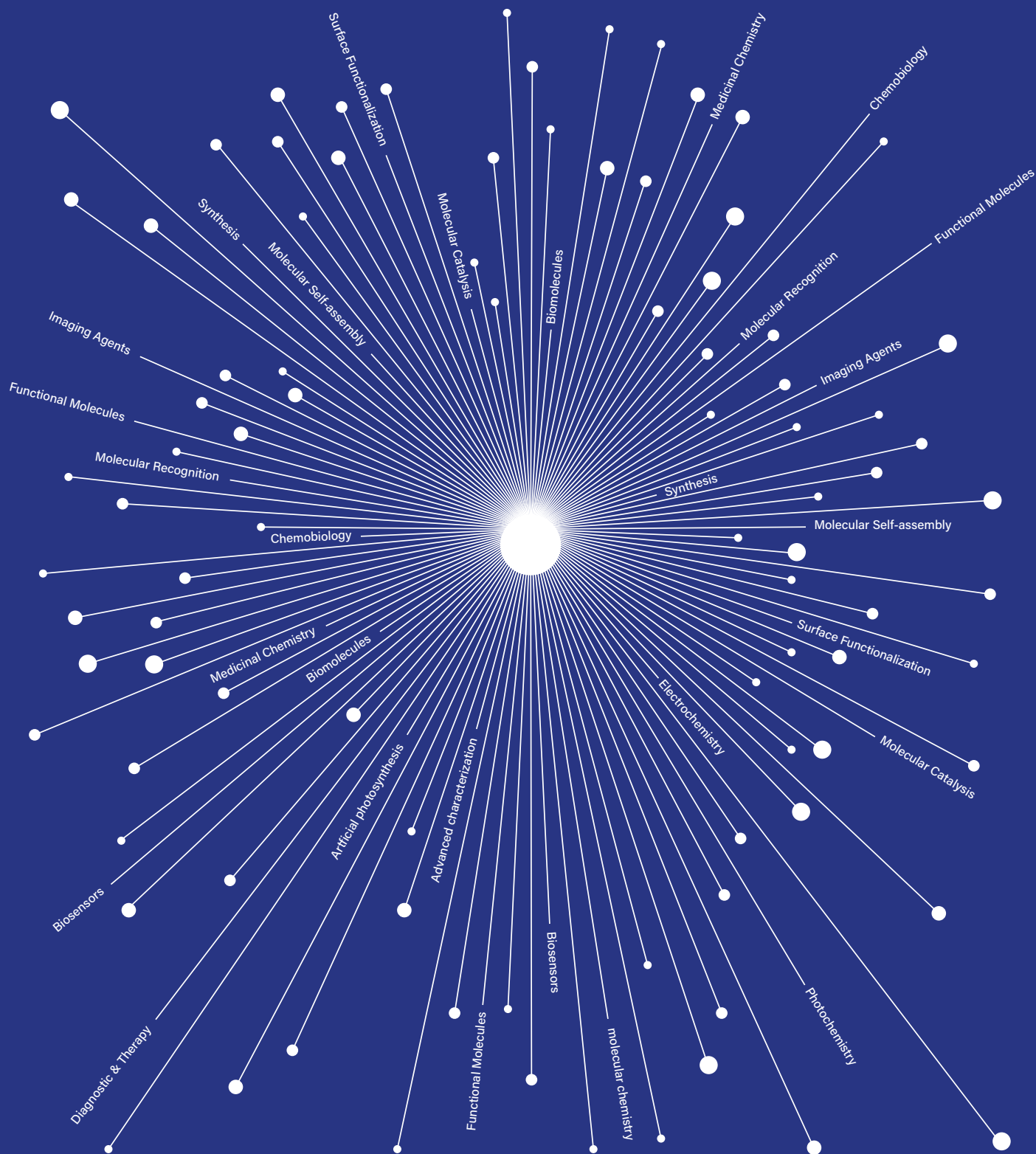
Arcane's evolution

The Arcane project has undergone a remarkable evolution over its three phases. Launched in 2012, Arcane 1 aimed to unite the molecular chemistry community around a common scientific project centered on bio-driven chemistry, with two main axes, bio-inspired chemistry and bio-targeted chemistry, supported by an emergence core with two axes, advanced characterization, and simulation. Initially, our consortium comprised seven laboratories spread across two sites with minimal interaction. Arcane 1’s primary objective was to create synergy among these labs by leveraging local expertise to tackle ever more ambitious challenges.

With its integration into the CBH-GS, we seized the opportunity to solidify our scientific program, especially by integrating in the emergence core synthetic methodology and surface functionalization. Amplify collective activities, including training initiatives, and enhance our visibility on local, national, and European stages.

Arcane 3.0 marks a substantial leap forward, broadening our scope to encompass all molecular chemistry in Grenoble. In this phase, our consortium will thus expand to 17 laboratories, integrating chemists working at the interface with biology, materials chemistry, and physics. Despite this significant expansion, the number of people involved will increase by only 10%, reflecting our strategic approach to growth. This enables us to build on a highly collaborative and interdisciplinary network, poised to pioneer innovative solutions to scientific challenges where molecular chemistry plays a pivotal role.

We aspire to achieve international recognition by leveraging the solid foundations our community has built over the past few years, ensuring robust local and national visibility. By strengthening our international scientific collaborations and working synergistically with UGA and its strategic international partners, we will unlock opportunities to spearhead ambitious projects with worldwide leaders in the field. This dynamic approach will also enable us to form powerful consortia that will propel our research to new achievements and secure European funding.



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