RESEARCH CENTRE

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2023 ACTIVITY REPORT

Project-Team MOSAIC

MOrphogenesis Simulation and Analysis In siliCo

IN COLLABORATION WITH: Réproduction et Développement des Plantes

DOMAIN

Digital Health, Biology and Earth

THEME

Computational Biology

Inria

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Project-Team MOSAIC

Creation of the Project-Team: 2019 July 01

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1 Team members, visitors, external collaborators

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- François Parcy [CNRS, HDR]
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2 Overall objectives

Our general aim in MOSAIC is to identify key principles of organism development in close collaboration with biologists by constructing a new generation of models based on explicit mathematical and computational representations of forms. For this we will develop a dual modeling approach where conceptual models will be used to identify self-organizing principles and realistic models will be used to test non-trivial genetic and physical hypotheses *in silico* and assess them against observations. This will contribute to extend the domain of systems biology to developmental systems and help interpret where possible the vast amount of geometric, molecular and physical data collected on growing forms. The main originality of the project lies in its integrated approach: we want to face the complexity of living organisms by developing an integrated view of form development, relying on the study of the interaction between coupled processes.

While our approach will mainly focus on plant development at different scales, the MOSAIC project will also consider the morphogenesis of model animal systems, such as ascidians [1], to cross-fertilize the approaches and to open the possibility to identify abstractions and principles that are relevant to morphogenesis of living forms in general. Our work will focus on how physical and chemical processes interact within the medium defined by the form and feedback on its development. We will seek to integrate both mechanistic and stochastic components in our models to account for biological variability in shape development. In the long run, the team's results are expected to contribute to set up a new vision of morphogenesis in biology, at the origin of a new physics of living matter, and based on a more mechanistic understanding of the link between genes, forms and their environment.

To achieve the team's objectives, we will develop over the next 12 years a project focused on the definition of a consistent mathematical framework to formalize form growth and on the development of corresponding computational algorithms. The mathematical framework will extend classical dynamical systems to dynamical systems with a dynamical state-structure, i.e. to dynamical systems whose state is represented as a graph of components that may change in time. A similar approach was successfully developed in the last two decades in the restricted context of branching organisms and plant development. We now want to extend it to more general forms, and address the diversity of associated new and stimulating computational challenges. For this, we will organize our research program into three main research axes.

[1] A large class of marine animals (also called sea-squirt) in the phylum of Tunicates that is close to vertebrates, shares a particularly well conserved developmental program and that is a good model to study the development of chordates.

3 Research program

3.1 Axis 1: Representation of biological organisms and their forms *in silico*

The modeling of organism development requires a formalization of the concept of form, *i.e.* a mathematical definition of what is a form and how it can change in time, together with the development of efficient algorithms to construct corresponding computational representations from observations, to manipulate them and associate local molecular and physical information with them. Our aim is threefold. First, we will develop new computational structures that make it possible to represent complex forms efficiently in space and time. For branching forms, the challenge will be to reduce the computational burden of the current tree-like representations that usually stems from their exponential increase in size during growth. For tissue structures, we will seek to develop models that integrate seamlessly continuous representations of the cell geometry and discrete representations of their adjacency network in dynamical and adaptive framework. Second, we will explore the use of machine learning strategies to set up robust and adaptive strategies to construct form representations in computers from imaging protocols. Finally, we will develop the notion of digital atlases of development, by mapping patterns of molecular (gene activity, hormones concentrations, cell polarity, ...) and physical (stress, mechanical properties, turgidity, ...) expressions observed at different stages of development on models representing average form development and by providing tools to manipulate and explore these digital atlases.

3.2 Axis 2: Data-driven models of form development

Our aim in this second research axis will be to develop models of physiological patterning and biophysical growth to simulate the development of 3D biological forms in a realistic way. Models of key processes participating to different aspects of morphogenesis (signaling, transport, molecular regulation, cell division, etc.) will be developed and tested *in silico* on 3D data structures reconstructed from digitized forms. The way these component-based models scale-up at more abstract levels where forms can be considered as continuums will also be investigated. Altogether, this will lead us to design first highly integrated models of form development, combining models of different processes in one computational structure representing the form, and to analyze how these processes interact in the course of development to build up the form. The simulation results will be assessed by quantitative comparison with actual form development. From a computational point of view, as branching or organ forms are often represented by large and complex data-structures, we aim to develop optimized data structures and algorithms to achieve satisfactory compromises between accuracy and efficiency.

3.3 Axis 3: Plasticity and robustness of forms

In this research axis, building on the insights gained from axes 1 and 2 on the mechanisms driving form development, we aim to explore the mechanistic origin of form plasticity and robustness. At the ontogenetic scale, we will study the ability of specific developmental mechanisms to buffer, or even to exploit, biological noise during morphogenesis. For plants, we will develop models capturing morphogenetic reactions to specific environmental changes (such as water stress or pruning), and their ability to modulate or even to reallocate growth in an opportunistic manner.

At the phylogenetic scale, we will investigate new connections that can be drawn from the use of a better understanding of form development mechanisms in the evolution of forms. In animals, we will use ascidians as a model organism to investigate how the variability of certain genomes relates to the variability of their forms. In plants, models of the genetic regulation of form development will be used to test hypotheses on the evolution of regulatory gene networks of key morphogenetic mechanisms such as branching. We believe that a better mechanistic understanding of developmental processes should shed new light on old evo-devo questions related to the evolution of biological forms, such as understanding the origin of *developmental constraints* [2] how the internal rules that govern form development, such as chemical interactions and physical constraints, may channel form changes so that selection is limited in the phenotype it can achieve?

[2] Raff, R. A. (1996). The Shape of Life: Genes, Development, and the Evolution of Form. Univ. Chicago Press.

3.4 Key modeling challenges

During the project lifetime, we will address several computational challenges related to the modeling of living forms and transversal to our main research axes. During the first phase of the project, we concentrate on 4 key challenges.

3.4.1 A new paradigm for modeling tree structures in biology

There is an ubiquitous presence of tree data in biology: plant structures, tree-like organs in animals (lungs, kidney vasculature), corals, sponges, but also phylogenic trees, cell lineage trees, *etc.* To represent, analyze and simulate these data, a huge variety of algorithms have been developed. For a majority, their computational time and space complexity is proportional to the size of the trees. In dealing with massive amounts of data, like trees in a plant orchard or cell lineages in tissues containing several thousands of cells, this level of complexity is often intractable. Here, our idea is to make use of a new class of tree structures, that can be efficiently compressed and that can be used to approximate any tree, to cut-down the complexity of usual algorithms on trees.

3.4.2 Efficient computational mechanical models of growing tissues

The ability to simulate efficiently physical forces that drive form development and their consequences in biological tissues is a critical issue of the MOSAIC project. Our aim is thus to design efficient algorithms to compute mechanical stresses within data-structures representing forms as the growth simulation proceeds. The challenge consists of computing the distribution of stresses and corresponding tissue deformations throughout data-structures containing thousands of 3D cells in close to interactive time. For this we will develop new strategies to simulate mechanics based on approaches originally developed in computer graphics to simulate in real time the deformation of natural objects. In particular, we will study how meshless and isogeometric variational methods can be adapted to the simulation of a population of growing and dividing cells.

3.4.3 Realistic integrated digital models

Most of the models developed in MOSAIC correspond to specific parts of real morphogenetic systems, avoiding the overwhelming complexity of real systems. However, as these models will be developed on computational structures representing the detailed geometry of an organ or an organism, it will be possible to assemble several of these sub-models within one single model, to figure out missing components, and to test potential interactions between the model sub-components as the form develops.

Throughout the project, we will thus develop two digital models, one plant and one animal, aimed at integrating various aspects of form development in a single simulation system. The development of these digital models will be made using an agile development strategy, in which the models are created and get functional at a very early stage, and become subsequently refined progressively.

3.4.4 Development of a computational environment for the simulation of biological form development

To support and integrate the software components of the team, we aim to develop a computational environment dedicated to the interactive simulation of biological form development. This environment will be built to support the paradigm of dynamical systems with dynamical structures. In brief, the form is represented at any time by a central data-structure that contains any topological, geometric, genetic and physiological information. The computational environment will provide in a user-friendly manner tools to up-load forms, to create them, to program their development, to analyze, visualize them and interact with them in 3D+time.

4 Application domains

Our application domain is developmental biology (see overall objectives, research program above).

5 Highlights of the year

- The team published this year a work on seed size regulation in the journal Nature Communications [16], see 7.4 for more details. This publication bespeaks a new collaboration between the team and the seed development team of the RDP lab.
- How morphogenesis observed at an organ level is linked to cellular level properties, is at the heart of the team's research topics. In our work, published this year in SIAM Journal on Applied Mathematics [14], we establish and rigorously demonstrate links between microscopic (cellular level) properties and macroscopic (tissue level) properties in the context of a mechanical model of growing plant tissue, see 7.4 for more details.

6 New software, platforms, open data

6.1 New software

6.1.1 Gnomon

Name: Gnomon

Keywords: 4D, Modelization and numerical simulations, Finite element modelling, Computational biology, Data visualization

Scientific Description: Gnomon is a user-friendly computer platform developed by the Mosaic team for seamless simulation of form development in silico. It is intended to be a major tool for the team members to develop, integrate and share their models, algorithms and tools. In Gnomon, a developing form is represented at any time by a central data-structure that contains topological, geometric, genetic and physiological information and that represents the state of the growing form. Flexible components (plugins) make it possible to up-load or to create such data-structures, to program their development, to analyze, visualize them and interact with them in 3D+time.

Functional Description: Gnomon is a plugin-based computational platform for the analysis and simulation of morphogenesis. It relies on a scalable software architecture based on the dtk kernel developed by the group of software engineers (SED) from the Sophia-Antipolis Inria Center. The development of Gnomon aims at answering four main challenges:

* Provide an easily accessible computational tool for the exploration of morphogenesis, by focusing on the deployability of the software (using conda), on the ergonomics of the user interface and the availability of the documentation.

* Give access to powerful tools for the exploration of dynamical forms, through an interactive visualization framework allowing the exploration in space in time and the access to algorithmic resources developed by the team for image sequences of multicellular tissues or collections of branching forms.

* Ensure the interoperability of computational libraries within the platform and its extensibility by a generalized plugin-based architecture (facilitated by the dtk framework) for algorithms, visualizations and data structures, enabling the members of the team and future users to feed the platform with their own C++ and Python libraries.

* Bridge the gap between experimental data and computational simulations by offering the possibility to go from one to the other in the same platform in a nearly transparent way, thanks to a common dynamical system framework integrated to the core of the platform.

Gnomon project organization: * Project leader: Christophe Godin * Software development coordinator: Guillaume Cerutti * DTK coordinators: Julien Wintz, Thibaud Kloczko * Plugin coordinators: Jonathan Legrand, Romain Azais, Olivier Ali, Frédéric Boudon. * Diffusion coordinator: Teva Vernoux

This work is part of the Gnomon ADT project supported by the Inria centers of Grenoble Rhône-Alpes and Sophia-Antipolis Méditerranée.

Release Contributions: This version provides a first integration of a modelling framework, the branching-structure simulation engine LPy. It comes as a workspace with code editing facilities, a set of new parameter editors for 2D curves and rendering materials, and a visualization tool coupling the PlantGL graphical library with VTK. Other functionalities developed for this version include semi-automatic tracking of cells in 3D segmented images, extra menus and interactions in the 3D views, and a set of workspaces and plugins for the extraction and quantitative analysis of point clouds in images.

Contact: Christophe Godin

Participants: Olivier Ali, Frédéric Boudon, Tristan Cabel, Guillaume Cerutti, Christophe Godin, Jonathan Legrand, Arthur Luciani, Grégoire Malandain, Karamoko Samassa

6.1.2 TimageTK

Name: Tissue Image ToolKit

Keywords: 3D, Image segmentation, Fluorescence microscopy, Image registration, Image processing, Image filter

Scientific Description: TimageTK (Tissue Image Toolkit) is a Python package dedicated to image processing of multicellular architectures such as plants or animals and is intended for biologists, modellers and computer scientists.

Functional Description: TimageTK (Tissue Image Toolkit) is a Python package dedicated to image processing of multicellular architectures such as plants or animals and is intended for biologists and modelers. It provides grayscale or labeled image filtering and mathematical morphology algorithms, as well as image registration and segmentation methods.

Release Contributions: - Improve warning/error visibility - Improve image attributes - IO fixes - Add URL support for image IO - Improve 2D/3D visualization tools - Improve memory handling for some algorithms (topological_elements_extraction) - Improve manual landmark CLI - Integrate third-party library to predict cell membrane/wall (using CNN) before cell-based segmentation - Improve documentation & docstrings - Update the CI jobs - Update requirements - Fix some method and function names - Add ‘pyvista‘ 3D visualization methods - Add tools to generate Markdown and HTML reports - Add Docker image recipe

- Improve components module - Improve logging - Better notebooks - Add cluster matching methods - Add analysis reporting tools - Add synthetic data generation algorithms - Add seed detection & signal quantification algorithms - Better conda packaging

URL: https://mosaic.gitlabpages.inria.fr/timagetk/index.html

Contact: Jonathan Legrand

Participants: Guillaume Cerutti, Jonathan Legrand, Grégoire Malandain

6.1.3 TimageTK_geometry

Name: Tissue Image ToolKit - Geometry

Keywords: 3D, Computational geometry, Image analysis, Mesh generation

Functional Description: TimageTK - Geometry provides a suite of tools for the reconstruction and quantitative analysis of 3D multicellular tissues for which the common trait is to rely on meshes (essentially triangular meshes). The applications range from the estimation of tissue surface curvatures to the quantification of fluorescence microscopy image signal at the level of cell-cell interfaces, or the reconstruction of 3D simplicial complexes reflecting the topology of the tissue.

Release Contributions: The initial version incorporates the tissue mesh reconstruction functionalities from the draco_stem library (DRACO and GRIFONE algorithms) as well as other existing methods (extraction of surface mesh and estimation of L1 cell curvatures, extraction of cell interface meshes and quantification of image signal intensities and polarities) initially belonging to different projects.

The functions have been adapted to embrace more closely the TissueImage API of the TimageTK library, storing the computed features on cells and on walls in the data structure and making a better use of the existing methods for the construction of the mesh structures.

URL: https://mosaic.gitlabpages.inria.fr/timagetk_geometry

Contact: Guillaume Cerutti

6.1.4 dxtr

Name: dxtr

Keywords: Discrete exterior calculus, Computational geometry

Scientific Description: At the core of the dxtr library lie two main data structures implementing respectively the concepts of simplicial complex and cochain. The library also encompasses a collection of operators (differential, geometrical, topological) that can be applied to these data structures to simulate differential geometry problems, formalized through exterior calculus.

Functional Description: A Python library implementing data structures and algorithms to handle simplicial complexes and perform discrete exterior calculus.

Release Contributions: It is the beta version of the library at this stage, it is still in development and not open to the public.

News of the Year: This year we designed the major principles of the library: we implementation of the core data structures and algorithms and we set the general architecture. We wrote unit tests and proper documentation in parallel of this development. We also started to write detailed tutorials based on basic use cases.

Contact: Olivier Ali

Participants: Olivier Ali, Chao Huang

6.1.5 bvpy

Name: bvpy

Keywords: Finite element modelling, Python, Partial differential equation

Functional Description: Bvpy is a python library, based on FEniCS, Gmsh & Meshio, to easily implement and study numerically Boundary Value Problems and Initial Boundary Value Problems through the Finite Element Method.

News of the Year: The library has recently undergone updates to enhance its functionality and application range: (i) Integration of a PyVista-based module for advanced data visualization. (ii) Extension to support tetrahedral meshing for more complex geometries. (iii) Improved mesh import management from Gmsh, including integrity checks and enhanced labeling and naming of mesh entities. These enhancements make Bvpy more versatile and user-friendly for various scientific applications.

URL: https://gitlab.inria.fr/mosaic/bvpy

Contact: Olivier Ali

Participants: Olivier Ali, Florian Gacon, Elsa Gascon, Christophe Godin, Manuel Petit

6.1.6 plant-imager

Keyword: Robotics

Functional Description: As part of the Plant Imager control, the software allows you to scan a plant by: 1. planning the path of the robotic arm carrying the camera, 2. triggering the acquisition of a photo, 3. recovering the photo (WiFi), 4. transmitting it to a database (plantdb) bringing together the images and metadata.

In the case of the Virtual Plant Imager, the idea is to simulate the behavior previously described, this time in a virtual world. This requires generating a 3D representation of the plant beforehand. This is done using the LPY language and the PlantGL library.

URL: https://docs.romi-project.eu/plant_imager/

Contact: Christophe Godin

6.1.7 plant-3d-vision

Name: plant-3d-vision

Keywords: Photogrammetry, Phyllotaxis

Functional Description: From pictures of plants, obtained automatically by the 'Plant Imager', we reconstruct a digital twin in the form of a point cloud or triangular mesh as follows: 1. determination of camera poses (extrinsic parameters), 2. reconstruction of the volume occupied by the plant, 3. transformation into a point cloud and triangular mesh.

Then, we quantify the phyllotaxis of the plant, in particular the angles and distance between successive organs, according to: 1. computation of the plant skeleton, 2. identification of the main stem and organs, 3. computation of angles and distances between organs along the main stem.

URL: https://docs.romi-project.eu/plant_imager/

Contact: Christophe Godin

6.1.8 Riemannian L-systems

Name: Riemannian L-systems: modeling form development in curved spaces

Keywords: Differential geometry, Fractal, Curved spaces, Declarative language

Functional Description: Classical L-systems are a language model that makes it possible to construct a large variety of forms in a Euclidean space using a combination of (Euclidean) turtle geometry and rewriting rules. Riemannian L-systems can be seen as an extension of the concept of L-systems to curved spaces. With Riemannian L-systems, forms can be programmed as simply as in Euclidean space, but the instructions are automatically interpreted in specified curved spaces using built-in differential geometry operators.

News of the Year: First version of the software

URL: https://gitlab.inria.fr/cgodin-dev/RiemannianGeometry/riemannien-l-systems

Contact: Christophe Godin

Participants: Christophe Godin, Frédéric Boudon

Partner: CIRAD

7 New results

7.1 Dynamical characterization of morphogenesis at cellular scale

Participants: Guillaume Cerutti, Julien Derr, Ali Farnudi, Emmanuel Faure, Elsa Gascon, Christophe Godin, Annamaria Kiss, Jonathan Legrand, Manuel Petit.

- Related Research Axes: RA1 (Representation of biological organisms and their forms in silico) & RA3 (Plasticity & robustness of forms)
- Related Key Modeling Challenges: KMC3 (Realistic integrated digital models)

The modeling of morphogenesis requires to explore the interconnection of different spatial and temporal scales of developing organisms. Non-trivial questions such as whether the observed robustness of morphogenesis is rooted in some highly conserved properties at the cellular level or whether it emerges as a macroscopic phenomenon, necessitates precise, quantitative analyses of complex 3D dynamic structures. The study of dynamical properties at the cellular scale poses at the same time key technical challenges and fundamental theoretical questions such as: how to characterize and follow the change of shape of cells within tissues or of tissues within organs? how to couple this change with gene expression dynamics? how to define cell-scale variability of morphogenesis within and between species?

Our team has produced this year several results in this context:

Measuring cell volumetric growth in the Shoot Apical Meristem

The peripheral zone of the Shoot Apical Meristem (SAM) of *Arabidopsis thaliana* is the place where organogenesis takes place, which implies contrasted cellular growth rates between nearby tissue areas. Relying on the tools provided by the *TimageTK* library 6.1.2, we developed a computational pipeline to segment and track cells in confocal time-lapse sequences of tissues where the cell membranes are marked by a fluorescent reporter. This pipeline has been used to generate a complete map of cell volumetric growth and deformation across the SAM.

One of the findings evidenced by this quantitative analysis is that, within the organ-meristem boundary, a subpopulation of cells next to fast-growing cells experiences volumetric shrinkage, indicating water outflow. In order to understand this observation and to test the role of water fluxes in the emergence of the new organ, a mechanohydraulic model of the growing tissue was then constructed 7.4.

This work has been carried out in collaboration with the Mechanodevo team of RDP, headed by Olivier Hamant, and was included in an article submitted this year [22]. It appears as a nice example of the interplay between data extraction and analysis on the one hand and testing hypothesis using a modelling approach on the other hand in order to understand the basic processes that can drive morphogenesis.

Numerical reconstruction of cellular layers of plant seeds.

During morphogenesis, plant organs acquire very stereotyped shapes through complex biological processes including cellular growth, an irreversible expansion of the cell wall leading to tissue deformation. However, the importance of the cellular organization of multi-layered tissues for the mechanical control of growth directions, and thus the emergence of anisotropic shapes, is not fully understood. Taking as a model organ the seed of *Arabidopsis thaliana*, where various external layers are known to control the growth across development, we propose to study the contribution of the different cell layers to morphogenesis.

To investigate this question, we aim to reconstruct numerically the full 3D layered structure of Arabidopsis seeds at cellular level. To do so, we propose to develop a pipeline combining experimental and computational technics. The first step is to set up a protocol for imaging whole seeds at different stages of development. Similarly to the Flip-Flap imaging approach [43], we developed a method for multi-angle seed imaging of fixed and stained seeds. From two transverse stacks per seed, we could reconstruct 3D intensity images of the entire seed using a pointmatching algorithm with a manual initialisation

through surface landmark positioning, provided by the *TimageTK* library 6.1.2. The reconstructed 3D microscopy images are then segmented using a seeded watershed algorithm [32], and the robustness of the method assessed through the quantitative comparison [37] with published segmented data of similar tissues.

In order to perform mechanical simulations, simplicial complexes of cell adjacency, which form a natural discretization of the external surface of the tissue, are then extracted from the outermost layer of the seed coat, using tools from the *TimageTK-Geometry* library 6.1.3. The boundary value problem that consists of the seed loaded with internal pressure, and the seed coat set as an elastic material, can then be solved using the finite element method through the `bvpy` library 6.1.5. Moreover, the produced simplicial complexes will also serve as input for the `dxtr` library 6.1.4 currently in development within the team.

This work is part of the Inria AEx Discotik, and is carried out by Elsa Gascon, whose Ph.D. started in 2022.

Atlases of development at cellular scale: construction and update

Developing digital atlases of organism or organ development is a complex challenge for tissues that do not present a stereotyped cellular layout, as it is the case for most plant organs. For instance, to generate a cell-based atlas representing the development of a floral meristem of *Arabidopsis thaliana* we had to choose a single representative flower template, on which the spatio-temporal binary expression patterns of 27 genes was then introduced manually [9].

To proceed further, as the manual building of a cellular template remains a bottleneck of the method, we aim to automatize the construction of genetic atlases from several time-lapse image acquisitions displaying both cell interface markers and genetic reporters. In such case, we need to consider a pipeline where (1) time-lapse sequences from different individuals can be spatio-temporally registered and (2) genetic information can be projected from one sequence to another in a quantitative manner. Methods have been developed on these two aspects.

A previous work addressing the spatio-temporal registration of floral meristem time-lapses sequences [38] relied on the meristem size to perform the temporal alignment. This metric is not fully adapted to accurately compare developmental states, since important size variations can be observed from one individual to another. To overcome this limitation, we developed a method based on the surface curvature, a metric that captures all the morphological changes of the floral development. More precisely, curvature profiles are extracted from each image along the lateral symmetry plane of floral meristems, and then compared 2-by-2 to obtain a temporal alignment of the sequences. The method was evaluated on floral meristem datasets against the previous approach and showed improvement on the temporal alignment quality. Moreover, the comparison method naturally provides a spatial alignment between individuals that can be used to initialize an automatic spatial registration procedure. This spatial alignment has been validated for several pairs of individuals, enhancing the robustness of our method. The quality of the alignment was specifically evaluated by focusing on the alignment of organ structures, such as the alignment of sepals and epidermal tissues, ensuring a biologically relevant registration.

Superimposing organs with a similar developmental state enables the propagation of genetic information across different individuals. Since floral development is not stereotyped at the cellular scale, projection cannot be performed through a 1-to-1 cell mapping, but must be considered at the tissue level. We have developed methods to transfer gene expression information in various ways (lossless transfer of quantity/concentration). The main rationale behind these methods is to rely on the overlap of cells after registration to distribute the genetic information across individuals. This approach has been further validated by successfully transferring two genes from the acquisition of several individual sequences onto a reference sequence. Crucially, the spatio-temporal alignment of the sequences enabling this transfer was achieved using our new method, providing additional validation of its robustness. Moreover, by calculating statistics (mean, dispersion) on the transferred genetic information, we gain a better understanding of the variability within a population of individuals.

This work was made in collaboration with Grégoire Malandain from the Morphem team at Inria Sophia-Antipolis. It marks the end of the Ph.D. thesis of Manuel Petit, and an article is in preparation for a submission in 2024.

7.2 Reconstruction of macroscopic forms from images and characterization of their variability

Participants: Julien Derr, Christophe Godin, Annamaria Kiss, Jonathan Legrand, Lucie Poupardin.

- Related Research Axes: RA1 (Representations of forms *in silico*) & RA3 (Plasticity & robustness of forms)
- Related Key Modeling Challenges: KMC3 (Realistic integrated digital models)

To study the variability of macroscopic forms resulting from organ or organism development, it is necessary to be able to measure phenotypic traits on a large population. Our strategy is to create digital clones to then be able to quantify traits of interest, therefore requiring to develop acquisition and reconstruction methods. These digital reconstructions enable the identification of organs, the quantification of macroscopic features as well as their distribution in space and, potentially, in time. The development of algorithms to analyse the structure of the organism or quantify traits and the creation of data structure adapted to future modeling is thus a key challenge. Furthermore, it is important to develop metrics and statistical tools to define notions of distance or average between these forms in order to be able to compare the obtained reconstructions and generated models.

The use of prior knowledge can be very beneficial, and indeed, realistic synthetic models of forms can guide the reconstruction algorithms and/or assess their performances. The automatic inference of computational representations of forms or organ traits from images is therefore an essential step.

Computational representations of forms can then be used to analyze how forms vary at the scale of a population, of a species or between species, with potential applications in species identification and genetic or environmental robustness estimation.

Automatized characterization of 3D plant architecture.

The digital reconstruction of branching forms and the quantification of phenotypic traits (lengths of inter-nodes, angles between organs, leaf shapes) is of great interest for the analysis of plant morphology at population scale.

The ROMI project ended in 2022, but the work carried by the MOSAIC team, notably on the development of the 3D plant phenotyping platform adapted to single potted plants with the *Plant Imager* 6.1.6 (robot scanner) and the *Plant 3D Vision* tools 6.1.7 (reconstruction and analysis pipeline) is still ongoing.

As planned, we moved to larger scale acquisitions of *Arabidopsis thaliana* plants, thanks to a new biologist collaborator from our laboratory, to further test and improve our technology (acquisition and recontruction).

On the hardware side, few improvements were done. Mostly we quickfixed some of the obvious shortcomings we faced to perform the large scale acquisitions.

On the other hand, the software side, notably the plant-3d-vision library responsible for the 2D reconstruction of the plant from the set of 2D images, is still actively developped and improved.

In fact, as we acquired more data, new and unexpected problems arose. Using mutants that co-initiate organs, we indeed realized that the algorithm responsible for organ segmentation was not able to work with such data.

We are currently working on a solution and expect to be able to finalyze our analysis, even for the problematic data, with the aim of software and biology oriented publications.

Characterization of 3D plant shape and texture at the organ scale

Complementary to the full 3D reconstruction of plant architecture (ROMI project), we have developped a new platform to characterize plants in 3D at the organ scale coordinated by Julien Derr (typically at leaf scale). We can have access to the geometry and the texture of the leaf with high spatial (millimetric) and temporal (seconds) resolution. This will make it possible to quantify in 3D the rich spatio-temporal growth

patterns of leaves observed during unfolding[41, 29, 40], where “fast” elastic phenomena (buckling) or ample (nutation) motions are occuring.

In collaboration with computer vision scientists from Université de Strasbourg (Franck Hetroy-Wheeler and collaborators), we built a multicamera set up[42]. The set up is installed at ENS de Lyon in the new M8 building dedicated to plant growth.

Lucie Poupardin started her PhD in october 2022. During her first year, Lucie set up and calibrated the platform. Lucie is going to use this platform to research the kinematics of leaf unfolding.

7.3 Analysis and simulation of tree data

Participants: Romain Azaïs, Christophe Godin, Frédéric Boudon *(External Collaborator)*.

- Related Research Axes: RW1 (Representations of forms in silico)
- Related Key Modeling Challenges: KMC1 (A new paradigm for modeling tree structures in biology)

Tree-structured data naturally appear at different scales and in various fields of biology where plants as well as blood vessels for example may be described by trees. In the team, we aim to investigate a new paradigm for modeling tree structures in biology in particular to solve complex problems related to the representation of biological organisms and their forms in silico.

In previous years, we investigated the following questions linked to the analysis of tree data. (i) How to control the complexity of the algorithms used to solve queries on tree structures? For example, computing the edit distance matrix of a dataset of large trees is numerically expensive. (ii) How to estimate the parameters within a stochastic model of trees? And finally, (iii) how to develop statistical learning algorithms adapted to tree data? In general, trees do not admit a Euclidean representation, while most of classification algorithms are only adapted to Euclidean data. Consequently, we need to study methods that are specific to tree data.

Efficient algorithms on tree structures.

Complex queries on tree structures (e.g., computation of edit distance, finding common substructures, compression) are required to handle tree objects. A critical question is to control the complexity of the algorithms implemented to solve these queries. This year, we have explored the following strategies to this end.

- We study how the edit distance algorithm developed by Zhang in the 1990s can be implemented in an incremental way when comparing trees along a random walk. Random walks form an important class of stochastic processes, which can be used to explore a combinatorial space. We have shown that the time-complexity of Zhang's algorithm can be highly reduced using incremental computations. These very promising results, both in terms of theoretical and computational aspects, resulted in the paper [13] published this year (joint work with Farah Ben Naoum from the University of Sidi Bel Abbes, Algeria).
- One way to address the issue of the complexity of algorithms on tree structures is to approximate the original trees by simplified structures that achieve good algorithmic properties. One can expect good algorithmic properties from structures that present a high level of redundancy in their substructures. Indeed, one can take into account these repetitions to avoid redundant computations on the whole structure. After developments on topological trees through the approximation class of self-nested trees in the past years [26, 27], we now work on approximation of trees with geometrical attributes on their vertices. With Farah Ben Naoum and Salah Habibeche (University of Sidi Bel Abbes, Algeria), we have exhibited a lossy compression algorithm for such trees, with a control on the information loss. In particular, it can be used to detect (imperfect) symmetries of plant architectures, which helps to characterize the production and growth mechanisms that generated them, at least on simulated plants. This piece of work has been published in the international conference FSPM [20] and a longer version is in preparation.

- Recognizing when two trees are identical (isomorphic) is a crucial issue to reduce the complexity of algorithms and avoid repeating calculations. Assessing that two trees are topologically equal is a long-solved problem and can be done in linear time. When attributes (from a finite alphabet) are added to the nodes, two definitions exist for extending isomorphism definition: either attributes must be preserved through the topology, or it is rather their equivalence class that must be preserved, i.e., nodes with same labels in one tree are to be mapped to nodes with same labels on the other. The former can be solved easily by using the topological algorithm, but the latter can not. Actually, this problem is as difficult as graph isomorphism and seems to be open since the 1970s. In 2021, we published an algorithm that breaks the combinatorial complexity of the problem, reducing, on average from numerical simulations, the search space cardinality by an exponential factor within linear time [36]. Based on this previous work, we have developed a backtracking algorithm to explore the rest of the search space and either find an isomorphism if it exists, or certify that none exists. We use this technique to detect new types of patterns in tree data, namely subtrees with identical label distribution. We submitted a paper [11] on these questions in 2023, to be published in 2024.

Hierarchical Timeline Warping (HTW): a generic method to design realistic plant architecture models

Virtual models of plant architecture are needed for diverse applications in developmental biology, agronomy, botany or computer graphics. They can be used for hypothesis testing, data annotation and augmentation associated with deep-learning training or for producing photorealistic rendering of plants. To match the increasing needs of these applications in precision and realism, virtual plants with increasing realistic details are required. However, the design of such detailed models remains a complex task and new techniques are required to ease this process.

To address this complexity, we developed a timeline-based approach, where the hierarchy of plant parts is described by a corresponding hierarchy of developmental timelines. For each simple or composed organ, a reference (normalized) timeline is defined [21]. Different stages of development of the organ are associated with different time-points of this reference timeline between 0 and 1. These stages are characteristic morphological steps, which can be easily and reproducibly defined across different individuals, genotypes,or even species, but do not occur at identical time points.

We tested our HDTW strategy in order to reproduce realistic virtual architectures of the model plant Arabidopsis thaliana. For this, we grew real plants in standard indoor conditions and manually collected various quantitative information on the plant at different scales, focusing on the relative and absolute developmental dynamics of many plant parts and organs. Depending on the trait, hierarchical timelines were either calibrated by measuring the same plants over days, or from snapshot pictures, taking advantage of the repetition of the same developmental sequences along the plant axis. Models constructed with this strategy can reproduce precisely plant architectural dynamics at different scales.

This work is carried out in collaboration with Fabrice Besnard, biologist at RDP and was presented at the 10th conference on Functional-Structural Plant Models (FSPM), in Berlin [21]. The work will be published as a full paper in 2024.

7.4 Mechanics of tissue morphogenesis

Participants: Olivier Ali, Ibrahim Cheddadi, Andre-Claude Clapson, Ali Farnudi, Elsa Gascon, Christophe Godin, Annamaria Kiss, Guillaume Cerutti, Patrick Lemaire *(External Collaborator)*.

- Related Research Works: RW2 (*Data-driven models*) & RW3 (*Plasticity & robustness of forms*)
- Related Key Modeling Challenges: KMC2 (*Efficient computational mechanical models of growing tissues*) & KMC3 (*Realistic integrated digital models*)

Deformations supporting morphogenesis require the production of mechanical work within tissues. Such mechanical stresses cannot yet be experimentally quantified in living tissues; the ability to simulate

accurately the mechanical behavior of growing multicellular structures is therefore a mere need in developmental biology and consequently a critical objective of the MOSAIC project.

From a macroscopic perspective, tissues mechanics can be formalized through the framework of continuum mechanics. However, the fact that they are composed, at the microscopic level, by mechano-sensitive elements out of equilibrium (namely cells) offers genuine modeling challenges and opportunities. Integrating cellular behaviors such as mechano-sensitivity and cell division into a macroscopic mechanical picture of plant tissue morphogenesis is the topic of this section.

Antagonist cell responses to mechanical stress set organ size

Organ size and shape depend on complex biochemical and mechanical interactions between cells and tissues [31, 44]. In collaboration with biologists from the SEED-DEV team, we investigate the regulation of seed size and shape, key agronomic traits, by mechanical interactions between two compartments: the endosperm and the seed coat [33].

The first project on this theme started a few years back and aimed at understanding the complex mechano-sensitive regulation of seed size. By combining experiments with computational modeling, we tested a mechanosensitive incoherent feedforward loop (*ms-IFFL*) hypothesis in which pressure-induced stresses play two antagonistic roles; directly driving seed growth, but indirectly inhibiting it through mechanosensitive stiffening of the seed coat. We showed that our *ms-IFFL* model can recapitulate wild type growth patterns and explain the counter-intuitive small seed phenotype of the *haiku2* mutant. Our work further revealed that the developmental regulation of endosperm pressure is needed to prevent a precocious reduction of seed growth rate induced by force-dependent seed coat stiffening. This work has been published, this year, in Nature Communications [16].

This year we also started to work on a follow-up project from this initial joint-work on seed growth. Our aim is to complement the theoretical approach exposed in [16] with precise numerical simulations of seed morphomechanics. This project is part of the Discotik Aex and carried out by Elsa Gascon, a PhD student of the team who started in 2023. In this perspective, she has been working on a pipeline to generate FEM-ready meshes from confocal aquisitisions of growing seeds. Eventually, this will enable us to address two fundamental biological questions: how shape symmetry is broken during seed development and to what extend this symmetry breaking is related to seed coat inner stiffening.

Derivation of a formal expression of pressure-induced stresses.

In a growing tissue, mechano-sensitive cells relie on forces as guiding cues during morphogenesis [34]. From a signal processing perspective, one can wonder want kind of information can cells access to through mechanosensitivity? Within curved pressurized tissues such as the ones of growing organs, Experimental studies suggest that mechanical stresses could be a proxy for curvature, enableing growing cells to tune their expansion according to the shape of their embedding tissue.

However, from a theoretical perspective, considering smooth curved an closed surfaces, no formal relationship between pressure-induced stresses and curvature has been established. We derived such an expression in the case of symmetric and non-symmetric surfaces. In particular, we showed that pressure-induced stress fields main directions are tighly related to Killing vector fields in the case of symmetric surfaces and approximation of those in the case of non-symmetric ones. In order to assess the validity of these developments, we also conducted a numerical simulation campaign on a familly of closed surfaces of varying symmetry.

These results have been presented at the 7th Plant Computational Biology Workshop, held at the University of Cambridge this summmer. A manuscript is currently being written.

Multiscale modelling of growing plant tissues

How morphogenesis depends on cell wall rheological properties is an active direction of research, and we are interested in mechanical models of growing plant tissues, where microscopic cellular structure or even subcellular structure is taken into account. In order to establish links between microscopic and macroscopic tissue properties, we performed a multiscale analysis of a model of growing plant tissue with subcellular resolution. We used homogenization to rigorously deduce the corresponding tissue scale continuous model. Tissue scale mechanical properties are computed from all microscopic structural and

material properties, taking into account advection by the growth field. We then considered case studies and numerically compare the detailed microscopic model and the tissue-scale model, both implemented using finite element method in FreeFEM, code here. We found that the macroscopic model can be used to efficiently make predictions about several configurations of interest. Our work, published this year in SIAM Journal of Applied Mathematics [14], will help making links between microscopic measurements and macroscopic observations in growing tissues.

This project is a collaboration with Arezki Boudaoud (Ecole Polytechnique, Paris, France) and Mariya Ptashnyk (Heriot-Watt University, Edinburgh, UK).

Force inference

In the context of the HYDROFIELD ANR project and the postdoctoral contract of André-Claude Clapson, we are developing a force inference method in the SAM that derives wall stresses and cell turgor pressures from the geometry of the cells. Plant cells are inflating thanks to their turgor pressure, but this quantity cannot easily be measured. We have suggested a new indirect method inspired by foam mechanics: combining Laplace law (that relates pressure, wall curvature and stress) and the Gauss-Bonnet theorem (that expresses a geometrical constraint on cell shape), we develop a methodology to estimate stresses and pressures from observations of cells shapes in confocal images. Force inference is an active field of studies with recent publications [35], but mostly on animal tissues. Preliminary results with our method indicate that it compares well with the state of the art in the literature, while being more robust and better adapted to plant tissues. Our results will be compared to direct pressure measurements by our collaborators in Singapour (Yuchen Long team). Two publications are in preparation.

Coupling wall mechanics and water fluxes

Still in the context of Hydrofield and in collaboration with biologists from RDP (Olivier Hamant's group), we showed that a model that we have previously developed [3] is able to explain a set of apparently contradictory experimental facts in the growth of primordia at the SAM. An article [22] written with our colleagues biologists is under review; it could provide a seminal interpretation of the role of water in the SAM development.

By taking advantage of a more robust mathematical framework, we have improved the numerical resolution of the 2D coupled model, and have extended the description of fluxes to a more general situation that includes the so-called apoplasmic pathway, within the cell walls. We plan to extend the model to simple 3D geometries, and possibly full 3D tissues. Several publications are in preparation.

A mechanohydraulic model for cotton fiber growth

The cotton fiber is among the plant cells with the highest growth rates. In cultivars, a single fiber cell generally reaches a few centimeters in length. In order to understand this highly efficent growth process, we built a comprehensive mathematical model of fiber elongation, considering cell mechanics and water entry into the cell.

More precisely, in this model plant cell growth depends on turgor pressure, the cell hydrodynamic pressure, which drives expansion of the cell wall. On the other hand, turgor pressure regulation depends on several physical, chemical and biological factors, including: vacuolar invertases, which modulate osmotic pressure of the cell, aquaporins, which determine the permeability of the plasma membrane, cell wall remodeling factors, which determine cell wall extensibility, and plasmodesmata, which are membrane-lined channels that allow free movement of water and solutes between cytoplasms of neighbouring cells. The volume, the turgor and the osmotic pressures are dynamical variables, while all other above mentioned factors are considered as parameters of the model.

In this context we performed a sensitivity analysis to changes in values of model parameters and found that plasmodesmal permeability is among the most important factors for building up turgor pressure and expanding cotton fibers. Moreover, we found that non-monotonic behaviors of turgor pressure that have been reported previously in cotton fibers cannot be recovered without accounting for dynamic changes of the parameters used in the model. Therefore, model predictions agree with experimental observations, provided that we take into account active opening and closure of plasmodesmata. Altogether, our results suggest an important role for plasmodesmal permeability in the regulation of turgor pressure.

The results of this work are presented in the preprint [24] and is the fruit of collaboration with Arezki Boudaoud (Ecole Polytechnique, Paris, France).

Mechanics of tendrils

In the framework of the Dynavine project, we are investigating the force and torque generation of tendrils of climbing plants as a function of time and growth development. To do so, we have developed an experimental set up that we have been testing on synthetic rods.

- This preliminary work have lead us to discover a new and exciting result about rod mechanics : One can completely change the chirality of a helical rod by unwinding it. Doing so, the rod goes through a transition state involving two helices with opposite chiralities spatially connected by a so-called "perversion". In our work, we reported an experimental demonstration of this phenomenon. We monitored the axial torque and load upon such a transformation and revealed a phase transition like behaviour. We proposed a biphasic expansion of the elastic energy and reproduced the encountered behaviours. Our experiments also displayed hysteresis upon helical unwinding but numerical simulations seems to indicate that it is due to specific properties of our material. These results have been published in Physical Review Letters [17].
- Now that our set-up is ready, we are monitoring live plants. We are recording universal signatures of force and torque evolution as a function of writhing. Based on our experimental results, we are developing a phenomenological model of tendrils writhing.

Analysis of early pollen tube growth

Pollen grains are transported from flowers to flowers by wind or animals. They can germinate if they land on specific elongated cells, called papillae located at the tip of the stigma, the female organ of the flower. When they germinate, a pollen tube starts to grow out downward the papillae, and keeping at the papillae surface [39]. Papillae have roughly a pin-like structure, but may vary in shape within or between species and present either convex or non-convex forms. Biologists try to understand the possible physical or chemical clues that guide the growth of the pollen-tube downwards. One of the hypothesis is that the precise geometry of the papillae may play an important role in the guidance of the tube and that the tube could follow geodesics of the papillae surface.

To study this hypothesis, we constructed both a mechanical model to explore how pollen tube growth is guided on the stigma geometry. We found that in mutants stigmas, the WT tube tip moves freely on the curved papilla surface and follows geodesics, while the pollen tube growth deviates from geodesic trajectories on WT, suggesting an additional guidance mechanism. Based on a computational analysis of the magnitude of possible mechanical forces acting on the pollen tube during its growth, we show that these deflections can be explained by a mechanism based on the geometry of the papilla, cell wall elasticity and turgor pressure.

This work is made in collaboration with Isabelle Fobis-Loisy (RDP Lab, Lyon and Karin John, LIP, Grenoble) and Lucie Riglet (Sainsbury Lab, Cambridge, UK) and will be submitted for publication in early 2024.

Theoretical and numerical investigations of cell division orientation during tissue deformation

Early-developed biological structures such as animal embryos are highly complex systems within which shape dynamics at different locations are tightly coordinated. One essential process during development is the regulation of cell division orientation. In simple cases, the cell division orientation can be predicted by studying their geometrical shapes. The orientation of a cell's division plane (the direction orthogonal to the plane) often aligns with the longer geometrical axis of the cell during interphase, famously known as Errera's rule (1886) for plant cells and Hertwig's rule (1893) for animals. Cell division is also oriented in response to mechanical forces propagating in tissue. Therefore, states of anisotropic tension in multicellular systems can emerge from both geometry and external tension, as often experimentally found in living tissues.

As a part of the ANR cell whisper project, we strive to create a minimalistic mechanical model for cell division orientation in developing biological systems. By characterising the different intracellular

mechanisms at play through processes which minimise energy loss, we can investigate the trade-off between local and long-range mechanical signals. The consequences of this competition are explored in the epidermal morphogenesis of Ascidian embryos. As Ascidian embryos develop from the 64-cell stage (semi-oblate sphere) and go through gastrulation at ~ 200-cell stage (cup shape), they create a suitable canvas to study cell deformation and division orientation under various conditions.

Our efforts this year can be summarised as:

- Onboarded and trained the new team members on the theoretical background of the minimalistic mechanical model developed for the project. This was a model defined for flat geometrical shapes representing the apical surface of cells in tissue. Through shape deformation energy cost calculations, the model predicts the cell division orientation for 2D hypothetical cells.
- Developed an image analysis pipeline to extract the apical surface shape of cells on 3D time series images of Ascidian embryos. Model (I) and previously studied models in the literature were used to predict the cell division orientation, and the results were compared to the actual observed division orientation as a function of time.
- An open-source Tissue Deformation Quantifier (TDQ) software package was developed in Python and placed on the team's Gitlab repository to generalise this study to time series images of any biological tissue of interest.
- A set of discrete differential geometry tools were put together and developed to enable the characterisation of the embryo surface deformation in time. The tools were extended and applied to triangulated meshes.

We have made significant progress in characterising the cell apical surface deformation and modelling the division orientation. The surface of the embryo is a sophisticated manifold that deforms in time. The tools we developed allow us and the scientific community to accurately study cells on an evolving manifold. A paper on our results is expected to be submitted next year.

7.5 Signaling and transport for tissue patterning and growth

Participants: Jeanne Abitbol Spangaro, Romain Azaïs, Guillaume Cerutti, Landry Duguet, Christophe Godin, Jonathan Legrand, Teva Vernoux *(External Collaborator)*.

- Related Research Axes: RA1 (Representations of forms in silico) & RA2 (Data-driven models)
- Related Key Modeling Challenges: KMC3 (Realistic integrated digital models)

One central mechanism in the shaping of biological forms is the definition of regions with different genetic identities or physiological properties through bio-chemical processes operating at cellular level. Such patterning of the tissue is often controlled by the action of molecular signals for which active or passive transport mechanisms determine the spatial precision of the targeting. The shoot apical meristem (SAM) of flowering plants is a remarkable example of such finely controlled system where the dynamic interplay between the hormone auxin and the polarization of efflux carriers PIN1 governs the rhythmic patterning of organs, and the consequent emergence of phyllotaxis.

Using *Arabidopsis thaliana* as a model system, we develop an integrated view of the meristem as a self-organizing dynamical form by reconstructing the dynamics of physiological processes from living tissues, and by proposing computational models to study tissue patterning and robustness of biological shapes *in silico*.

Analysis and modelling of auxin transport at cellular level in the SAM.

Macroscopic model of organ interactions in plants have been particularly successful in explaining phyllotaxis patterns at the SAM. However, the details of the molecular processes allowing the spatiotemporal

coordination of the cells necessary to the maintenance of the regularity of the pattern is still a frontier question. Two main actors are thought to contribute to the emergence and maintenance of phyllotactic patterns. On the one hand, the plant hormone auxin accumulates at different sites of the SAM and triggers organ differentiation. On the other hand, polarized PIN1 proteins at the cell membranes directs auxin transport in the tissue. Recent experiments and methods developed in the team provided quantitative spatiotemporal data of auxin and PIN1 localization. These data have been analyzed at cell scale as discrete raw data, and at tissue scale as continuous data allowing to compare different individuals [4]. These observations question the mainly adopted interpretation of auxin transport in the SAM, mainly that PIN1 are polarized in the cell membranes according to the gradients of auxin in the tissue.

Our ongoing work consists of expanding the analysis of the mass of data collected in [4] and studying alternative explanations of the auxin accumulation patterns. In particular, we developed a rigorous analysis using discrete and continuous models to capture the essence of the interplay between the observed auxin and PIN1. We discovered a new correlation between the deflections in the PIN1 advection field and the auxin levels in the peripheral zone of the SAM, which could be a causality. We propose a new decomposition of PIN1 convergence into a change of direction and a change of intensity, and show that both components have equivalent significance. This highlights the importance of relying on quantitative data when analyzing PIN1 polarity patterns.

This work is part of a collaboration with Carlos Galvan-Ampudia and Teva Vernoux from the Signal team of the RDP, and has been presented at the 7th Plant Computational Biology Workshop, held at the University of Cambridge in August 2023. New experiments are currently being conducted to assess the conclusions of our analysis and modelling work, and the results will be gathered in an article to be submitted in the coming year.

Estimation of intercellular water transport capacities in the SAM.

Water fluxes are hypothesized to have a significant role in the patterning and organogenesis processes in the Shoot Apical Meristem (SAM). However, measuring how much water flows between cells in a living tissue is a highly challenging task. One way to get closer to this information is through monitoring the density and status of plasmodesmata, channels that connect the cytoplasms of adjacent cells, allowing for a symplasmic transport of water.

Using a co-visualization of a fluorescent protein marking the locations of plasmodesmata (MCTP, PDLP) with a dye staining of cell walls with propidium iodide (PI), we developed a method to quantify the estimated density of plasmodesmata at the level of every cell interface in the SAM epidermal layer from confocal images. This information can be interpreted as a potential symplasmic connectivity, and thus water conductivity, across the cellular network.

Building upon the methodology developed for the analysis of auxin dynamics in the SAM [4], we aim at gathering data quantified over a population of individuals and superimpose organs with a similar developmental state in order to reconstruct an average pattern of the symplasmic connectivity in the peripheral zone of the SAM. This would allow to corroborate whether the dynamic regulation of plasmodesmata could play a role in the early stages of organogenesis by modulating the water fluxes.

This work is carried out in collaboration with Géraldine Brunoud from the Signal team of the RDP, and is part of the Hydrofield ANR project.

Transport of auxin and branching patterns in mosses.

Branching patterns are omnipresent in plant architecture, but there still remains open questions about the molecular mechanisms that drive their emergence during plant development. In flowering plants, the shoot apical meristem (SAM) controls the plant architecture by inhibiting the initiation of new branches below it, through the action of the phytohormone auxin. Auxin is synthesized at the apex and is actively transported from cell to cell thanks to polar membrane transporters, generating a basipetal bulk flow and acting as a morphogen gradient.

Despite their different evolutionary paths, mosses show similar regulatory mechanisms. However, experimental evidence show that auxin transport is most likely not polarized in the shoot, and supplementary experimental and computational work led to the hypothesis that auxin transport was likely diffusive in the moss, through channels called plasmodesmata that link neighbouring cells.

In collaboration with Yoan Coudert (RDP Lab), we aim at modelling the moss development under the later hypothesis in order to test whether diffusion is sufficient to explain the branching patterns observed in the moss model species *Physcomitrium patens*. Through a multi-scale and quantitative approach, our model integrates biological data acquired at the cell level in order to deduce effective transport rates at the tissue level. In particular, we used electron microscopy to estimate the distribution of plasmodesmata densities in the tissues and showed how its heterogeneity affects the auxin spatio-temporal dynamics, and therefore the branching patterns. Our results so far are consistent with our working hypothesis.

This work is carried out in the context of the Ph.D. thesis of Jeanne Abitbol Spangaro (year 2 in 2023) and a publication is being prepared for a submission in 2024.

7.6 Regulation of branching mechanisms in plants

Participants: Christophe Godin, François Parcy *(External Collaborator)*.

- Research Axes: RA2 (*Data-driven models*) & RA3 (*Plasticity & robustness of forms*)
- Key Modelling Challenges: KMC3 (*Realistic integrated digital models*)

Branching in plants results from the development of apical meristems that recursively produce lateral meristems. These meristems may be more or less differentiated with respect to the apical meristem from which they originate, potentially leading to different types of lateral branches or organs. They also can undergo a more or less long period of inactivation, due to systemic regulation. The understanding of branching systems morphogenesis in plants thus relies on the analysis of the regulatory mechanisms that control both meristem differentiation and activation/inactivation.

The fractal nature of plants.

Inflorescence branching systems are complex and diverse. They result from the interaction between meristem growth and gene regulatory networks that control the flowering transition during morphogenesis. To study these systems, we focused on cauliflower mutants, in which the meristem repeatedly fails in making a complete transition to the flower and for which a complete mechanistic explanation was still lacking.

In collaboration with Eugenio Azpeitia (who started this project as a post-doc in the Virtual Plants team) and François Parcy's group in Grenoble, we have developed a model of the control of floral initiation by genes in *Arabidopsis thaliana*, refining previous networks from the literature so that they can integrate our hypotheses about the emergence of cauliflower phenotypes. The complete network was validated by multiple analyses, including sensitivity analyses, stable state analysis, mutant analysis, among others. It was then coupled with an architectural model of plant development using L-systems. The coupled model was used to study how changes in gene dynamics and expression could impact in different ways the architectural properties of plants. The model was then used to study how changes in certain parameters could generate different curd morphologies, including the fractal-like Romanesco. This work has been published in the Journal Science [2] in 2021 and received last year a price from the French Academie des Sciences, which in turn led us, this year, to write an overview of our findings in les comptes rendus de l'Académie des Science [12].

As a follow-up of this work, Mariana Juste, an undergraduate strudent from the University of Mexico supervised by Pr. Eugenio Azpeitia, came to France for a 3.5 months internship in the Mosaic team to work on extensions of the above inflorescence gene regulation network. In particular, she studies the role of transcriptions factors that transmit environmental signals to the plant.

7.7 New computational approaches for morphogenesis

Participants: Olivier Ali, Romain Azaïs, Christophe Godin, Chao Huang, Natacha Javerzat, Abdoullah Latreche.

- Research Axes: RA1 (Representations of forms in silico) & RA2 (Data-driven models)
- Key Modelling Challenges: KMC2 (Efficient computational mechanical models of growing tissues) & KMC3 (Realistic integrated digital models)

Theoretical and numerical investigations around Cellular Potts Model

The cellular Potts model can be used to describe tissues and cellular complexes. It emerged in bioinformatics as a derivation of statistical physics models (in particular, Ising model and Potts model). The cellular complexes σ described by this model are distributed according to the Gibbs measure $\mu(\sigma) \propto \exp(-\beta H(\sigma))$ where H denotes the energy function of the system.

To simulate this probability distribution, MCMC-type techniques are used, which tend to minimize the energy H. These techniques are difficult to analyze from both theoretical and numerical points of view. In particular, their convergence rate is complicated to obtain, and we know that the algorithm can be trapped in low-energy valleys that are not the global minimum.

As part of the ALAMO project, we are seeking to propose alternative algorithms to MCMC methods, and to better characterize existing methods so as to be able to precisely quantify the accuracy of the results obtained.

This year, as part of the start-up phase of the project, we have been working in three main areas: on small state spaces for which exact solutions are achievable by enumeration, we have carried out numerical analyses of several MCMC algorithms, enabling us to construct first numerical indicators of convergence. On the other hand, we have made significant progress on the proof of convergence of a cell division algorithm inspired by the Potts model. A paper on this subject is expected to be submitted next year. Finally, we have begun to explore new simulation techniques inspired by contour models.

Developing a python DEC-library for plant morphodynamics

Modeling morphogenesis of living organisms requires to numerically solve systems of ODEs and PDEs on cellularized domains. Currently, state-of-the-art approaches rely on classic *Finite Element Methods (FEM)* and require a precise triangulation[3] of the domains at stake [28]. This is a tedious task, for the natural cellularization of these domains must be preserved, even when cells are expanding and dividing.

To alleviate this difficulty, we got inspired by recent advances in the field of computer graphics, where a new method to solve differential systems has been developed: *Discrete Exterior Calculus (DEC)* [30].

Over the past years, in the context of the *Action Exploratoire Discotik* 8.2, we have been developing a `python` library, named *dxtr* (6.1.4), to adapt the tools of *DEC* within the context of plant morphodynamics.

Our objective with this library is to provide the community with efficient tools (data structures and algorithms) to estimate differential systems on simplicial complexes, inspired by developmental biology. After 18 months of development, a first version is currently being finalized and will be submitted for publication in the comming months. In parallel, a first usecase of this library has been explored this year in order to unravel the connection between tissue mechanics and geometric signal processing, see section 7.4, subsection “Theoretical and numerical investigations of cell division orientation during tissue deformation”, for details. More over, Elsa Gascon has been developing new technics (aquisition, segmentation and meshing) to extract from live microscopy imaging *DEC*-ready data structures to be used within the dxtr library, see 7.1, subsection “Numerical reconstruction of cellular layers of plant seeds”. Finally, this new library also enabled us to address more abstract questions, within the field of higher-order networks dynamics, see subsection below.

[3] or tetrahedrization in 3D

Genuine dynamical networks inspired by plant morphogenesis.

During morphogenesis, plant tissues are developing macroscopic shapes based solely on two cellular processes: growth and division. While the role of cell growth during morphogenesis is being under intense scrutiny, the influence of cell division remains far less understood.

Concomitantly, the question of emergent geometry within dynamical networks is a very active field of research that draws inspirations from a wide spectrum of scientific question (neurosciences, social media, quantum gravity...). However, so far, only dynamical rules based on aggregation of new nodes at the network margin have been studied.

In order to explore these two limitations, we implemented a new class of dynamical network where the evolution rule is inspired by plant cell division: an edge is substituting two existing nodes within the bulk of network.

This work is part of a project financed by IXXI (the institute for Complex Systems in Rhone-Alpes) and has been initiated by Chao Huang, a master 2 intern from the Universisty of Tokyo. In three month time, he managed to implement the evolution rule within the `dxtr` library 6.1.4 and started to run simulations.

Riemannian L-systems.

We are used to think of the development of forms in biology as a process that takes place in our 3-dimensional Euclidean space. However, various forms, patterns or processes in biology take naturally place in a non-euclidean space. The vein networks of leaves for instance grow within the leaf blade, which is in general a growing curved (non-euclidean) surface. Likewise, molecular signals are transported actively or passively within tissue layers (eptihelia) that are in general curved 2-D or 3-D domains. Modeling the growth or dynamics of these systems thus requires that we account for the curved nature of the underlying medium and involves the use of advanced geometric concepts (geodesics, curvature, parallel transport, etc.) coming from differential geometry and connected mathematical fields such as differential topology, algebraic topology ...

To address this issue, we developed over the last years a new major extension of L-systems, called Riemannian L-systems (6.1.8), that makes it possible to simulate the growth of patterns or the movement of molecules within curved 2-D domains. The framework provides a declarative language (as an extension of the L-Py language for modeling L-systems) high level primitives to develop models and simulations within curved spaces. In these models, growing structures follow in general geodesics. Deviation from these geodesic lines can be used or interpreted as resulting from extra forces due to various physical or chemical origins. A paper describing this new paradigm and its associated language will be submitted in the first semester of 2024.

7.8 Miscellaneous

Participants: Christophe Godin.

Post-transcriptional regulation of transcription factor codes in immature Neurons in drosophila.

Neuronal stem cells generate a limited and consistent number of neuronal progenies, each possessing distinct morphologies and functions. These two parameters, involving the precise production of neurons with distinct identities, must be meticulously regulated throughout development to ensure optimal brain function.

In this study, we focused on a neuroblast lineage in Drosophila known as Lin A/15, which gives rise to motoneurons (MNs) and glia. Interestingly, Lin A/15 neuroblast dedicates 40% of its time to producing immature MNs that are subsequently eliminated through apoptosis. Two RNA-binding proteins, Imp and Syp, play crucial roles in this process of neuronal elimination. We found that Imp+ MNs survive, while Imp-, Syp+ MNs undergo apoptosis.

Our results indicate that Imp promotes survival, whereas Syp promotes cell death in immature MNs. Furthermore, our investigations revealed that late-born motoneurons face elimination due to their failure

to express a functional code of transcription factors (mTFs) that control their morphological fate Late-born MNs possess a unique and distinct set of TFs compared to early-born MNs. By manipulating the expression of Imp and Syp in late-born motoneurons, we observed a shift in the TF code of late MNs towards that of early-born MNs, resulting in their survival. Additionally, introducing the TF code of early MNs into late-born MNs also promoted their survival. These findings demonstrate that the differential expression of Imp and Syp in immature MNs establishes a connection between generating a precise number of MNs and producing MNs with distinct identities through the regulation of mTFs. The Mosaic team developed the Positive Cell Cluster Detection procedure (PCCD) used to analyze the distributions of moto-neurons TF expression.

The Drosophila model, along with its genetic tools, provides a unique opportunity to further explore and decipher the functions of these RNA-binding proteins in neural stem cells versus immature neurons. The insights gained from these studies could shed light on the broader mechanisms of neurogenesis and neuronal identity determination in more complex organisms.

8 Partnerships and cooperations

8.1 International research visitors

8.1.1 Visits of international scientists

- Farah Ben-Naoum, Assistant Professor at the University of Sidi bel Abbes, Algeria. Farah visited the team in July 2023. She worked on tree-edit distance algorithms and on the approximate compression of trees.
- Eric Mjolsness, Professor at the University or Irvine, California, USA?. Eric visited the team in September 2023. He worked with Christophe Godin on differential geometry applied to plant modeling.
- Mariana Yuste, Master student from the University of Mexico (Prof. Eugenio Azpeitia). Mariana visited the team from October 2023 to January 2024. She worked on the development of genetic models of inflorescence growth.

8.2 National initiatives

Inria ADT - Gnomon / Naviscope (2021-2024)

Participants: Olivier Ali, Romain Azaïs, Guillaume Cerutti, Emmanuel Faure *(External Collaborator)*, , Christophe Godin, Jonathan Legrand, Arthur Luciani, Grégoire Malandain *(External Collaborator)*, , Karamoko Samassa, Teva Vernoux *(External Collaborator)*.

Gnomon is a user-friendly computer platform developed by the Mosaic team for the analysis and simulation of form development in silico. It is intended to be a major tool for the team members to develop, integrate and share their models, algorithms and tools. Flexible components (plugins) make it possible to load or to create such data-structures, to program their development, to analyze, visualize them and interact with them in 3D+time.

A first prototype 6.1.1 has been developed in collaboration with the software engineers (SED) from the Sophia-Antipolis Inria Center, relying on the *dtk* software kernel through the course of the previous ADT Gnomon (2018-2020). The current application is a highly interactive GUI that allows to manipulate 3D+t biological objects, and transform them using plugin-based algorithmic bricks, which implicitly composes a data processing pipeline.

The developments carried out in this ADT project aim to set up a complete ecosystem for the study of dynamical biological systems. Through Gnomon, users will have the possibility to carry out their own numerical experimentation project, relying on available plugins or developing new ones for their

applications, programming models to simulate developing forms, and dynamically visualizing the generated structures. The Gnomon application stands as a central tool to conceive intuitively both analysis and modelling pipelines, but it will interact with other software issuing from the Inria Défi Naviscope (2019-2023): BioImage-IT for batch-processing datasets with distributed computations, and MorphoNet for interacting with the computation results through a web-based 3D+t browser. The aim is to reach a software quality that will enable the diffusion of the platform, starting with the immediate collaborators of the partners.

Partners:

- SED Sophia Antipolis Inria Research Centre
- SED Rennes Inria Research Centre
- Serpico Inria project-team, Rennes, France
- Hybrid Inria project-team, Rennes, France
- Morpheme Inria project-team, Sophia Antipolis, France

ANR Cell Whisper (2020 - 2024)

Participants: Christophe Godin, Patrick Lemaire *(External Collaborator)*, , Grégoire Malandain *(External Collaborator)*.

Successful embryogenesis requires the differentiation of the correct cell types, in defined numbers and in appropriate positions. In most cases, decisions taken by individual cells are instructed by signals emitted by their neighbours. A surprisingly small set of signalling pathways is used for this purpose. The FGF/Ras/ERK pathway is one of these and mutations in some of its individual components cause a class of human developmental syndromes, the RASopathies. Our current knowledge of this pathway is, however, mostly static. We lack an integrated understanding of its spatio-temporal dynamics and we can imperfectly explain its highly non-linear (switch-like) response to a graded increase in input stimulus. This systems biology project combines advanced quantitative live imaging, pharmacological/optogenetics perturbations and computational modelling to address, in an original animal model organism, 3 major unanswered questions, each corresponding to a specific aim of the proposal:

- Aim 1: What is the spatio-temporal dynamic of intracellular signal transduction in response to FGF during embryogenesis?
- Aim 2: How is the switch-like response to graded extracellular signals controlled at the molecular level?
- Aim 3: Can the results be integrated into a predictive computational model of the pathway? Through this approach, in a simple model organism, we hope to gain an integrated molecular understanding of the spatio-temporal dynamics of this pathway and of its robustness to parameter variations.

Partners:

- UMR CRBM, CNRS Montpellier, France
- Morpheme Inria projec-team, Sophia Antipolis, France

ANR Netflux (2022 - 2025)

Participants: Christophe Godin, Ibrahim Cheddadi, Guillaume Cerutti.

The identification during the last decades of the molecular actors involved in guard cells signaling and ion transport highlights the fact that stomata opening or closure relies on the balanced control of ion fluxes across both plasma and vacuole membranes (PM and VM). However, how ion fluxes are coordinated between PM and VM membranes remains almost unknown. In this proposal, we hypothesize that the coupling between the ion transport at the PM and the VM is a major factor controlling stomatal aperture. Therefore, the main objective of the NetFlux project is to understand how cellular membranes are finely and tightly coordinated during cellular responses. For this purpose, we will use the guard cells from Arabidopsis thaliana as our cellular and biophysical model. To reach our goals the Netflux project will:

- characterize the ion flux across the PM and VM combining original genetic resources and highly resolutive techniques in living cells (refers to WP1 and WP2)
- develop mathematical and computational models of intracellular ion fluxes in GCs to quantitatively understand the coupling between ion transport across the PM and VM to control stomatal movements (refers to WP3)
- identify new regulators of ion transport in GCs using an original genetic screen based on a genetically encoded biosensor (refers to WP4).

Partners:

- BPMP Unit, Montpellier
- SAVE BIAM CEA, Cadarache

ANR Hydrofield (2021 - 2024)

Participants: Arezki Boudaoud *(External Collaborator)*, Christophe Godin, Ibrahim Cheddadi, Guillaume Cerutti.

Plant architecture continuously develop throughout their lifetime through the activity of the apical meristems located at the tip of growing axes. The genetic regulation of the shoot apical meristems (SAMs), which produces all plant aerial organs, has extensively been studied, various key molecular actors have been identified and their function in patterning the SAM has been mapped in space and time. In addition, recent work has established that these molecular actors not only regulate cell identities but also likely induce the physical deformation of tissues by modifying cell wall mechanical properties, in turn inducing leaf or flower primordia outgrowth. From these works progressively emerges a new mechanistic insight on the link connecting gene regulation, tissue deformation and organ growth in plants. However, despite these recent progresses, the contribution of turgor pressure and water fluxes regulation, that decisively contribute to tissue morphogenesis, is still elusive.

Partners:

- SIGNAL Team RDP, Lyon, (Teva Vernoux)
- Ecole Polytechnique, Saclay (Arezki Boudaoud)
- University of Singapour (Yuchen Long)
- University of Helsinky (Juan Alonso-Serra)

AEx Discotik (2021 - 2025)

Participants: Olivier Ali, Elsa Gascon, Chao Huang.

Computational morphomechanics is the study of living tissue morphogenesis through the scope of physics-based computational modeling. It has become a forefront tool to study organogenesis, where mechanical stresses play a paramount regulating role. At macroscopic scale, smooth living tissues can be described as Riemannian manifolds, subject to continuous mechanics. Concomitantly, at the cellular scale, they appear as networks of discrete effectors, where mechanics should be expressed in a combinatorial manner. Current state-of-the-art models, based on “classic” Finte Element Methods, struggle to efficiently integrate this cellular (discrete) / tissular (continuous) dichotomy. The Discotik project aims to alleviate this difficulty through the use Discrete Exterior Calculus to express the laws of mechanics. While classic FEM rely solely on simplicial meshing of manifolds, ”DEC” also exploits their dual structure, composed of cellular complexes. Strikingly, such cellular structures appear naturally in living tissues. Our goal is to assess this modeling approach on a specific, circumscribed problem: The morphomechanics of plant seed. We expect the “DEC” framework not only to enable faster computations but also to expose the deep connection between mechanical stress, tissue geometry and the corresponding cellular network topology.

Partners:

- Benoît Landrein, SEED team RDP, Lyon.
- Mathieu Desbrun, EPI Geomerix, Inria Saclay / Ecole Polytechnique.

AEx ALAMO (2023 - 2026)

Participants: Romain Azaïs, Natacha Javerzat.

Stochastic lattice models are of constant interest to the scientific community, both for their fundamental properties and the wide variety of applications they offer, notably in statistical physics, computational biology and population ecology. Their numerical simulation often requires the use of MCMC (Markov chain Monte Carlo) techniques. The ALAMO project aims at proposing alternative algorithms for the simulation of these models by studying and estimating the law of the contours formed by the nodes of the lattice having common characteristics. By controlling the error to the target distribution, these new simulation techniques will allow to fine-tune the MCMC algorithms or even to overcome some of their limitations and could therefore offer a credible alternative.

Partners:

- Benoît Henry, Institut Mines Télécom Nord Europe à Lille.
- Philippe Andrey, INRAE Versailles.

Appel à projets blanc BAP INRAe : Biomove (2022-2023)

Participants: Julien Derr, Mohammed Bendahmane *(External Collaborator)*.

In this proposal, we aim, to combine 3D tracking and quantification of plant movements using biophysical modeling. Our ambition is to better understand the very process of plant growth, and to discover the processes that regulate posture in plant development. To reach these goals, we will use the model plant Arabidopsis thaliana. A. thaliana is more suitable for the planed experiments, as all required tools and lines are available in the participating teams. The key point of this project is that these rich movements associated with plant development are essentially in 3D, and therefore must be quantitatively tracked in 3D. Our scientific program is broken into 4 interconnected tasks. In Task 1, we will set-up an experimental apparatus for 3D reconstruction. Task 2 we be devoted to data processing, and to the development of a new methodology to obtain a precise and fine growth field. In Task 3, we will use and apply our newly developed system (above) to study and compare movements in wild-type A. thaliana and in mutant lines affected in mitotic growth (cell division and proliferation) or

post-mitotic growth (cell expansion). The objective here is to assess the impact of slow or accelerated organ and plant growth on motion. In Task 4, we will use the above data and biophysical modeling to confront different mechanosensitivity scenarios in front of our experiments. By putting together three communities (physicist, computer scientists and biologists) we will achieve to quantify 3D plant motion to an extent which had never been done in the state of the art. Therefore, we expect the project to have strong scientific impact on plant biophysics. In particular, new mechanosensitivity lessons will be learned.

8.3 Regional initiatives

IXXI research project: Emergent geometry in simplicial complexes inspired by plant tissues. (2023 - 2024)

Participants: Olivier Ali, Chao Huang.

During morphogenesis, plant tissues are developing macroscopic shapes based solely on two microscopic processes: cell growth and cell division. The regulation of morphogenesis through directional and differential cell expansion rate has been extensively studied but the influence of cell division on shape emergence remains far less understood. Concomitantly, the question of emergent geometry within dynamical networks is a very active field of research that draws inspirations from a wide spectrum of scientific question (neurosciences, social media, quantum gravity...). However, so far, only dynamical rules based on aggregation of new nodes at the network margin have been studied. In this project, we propose to implement a new class of dynamical networks where growth is inspired by plant cell division: pairs of nodes are substituting existing ones within the bulk of the network. We will address the question of emergent curvature within such dynamical systems.

9 Dissemination

9.1 Promoting scientific activities

9.1.1 Scientific events: selection

Member of the conference program committees

- Christophe Godin
  - 10th conference on Functional-Structural Plant Models, Berlin (27-31 March 2023).
  - Plant Computational Biology Workshop, Sainsbury Lab, Cambridge (4-8 September 2023)

9.1.2 Journal

Member of the editorial boards

- Christophe Godin
  - Academic Editor in PLoS Computational Biology
  - Member of the Editorial Advisory Board of Plant in Silico
  - Associate Editor Frontiers in Plant Sciences, section Plant Biophysics and Modeling
  - Recommender of the Journal Peer Community In (PCI) Mathematical and Computational Modeling

Reviewer - reviewing activities

- Romain Azaïs
  - Advances in Data Analysis and Classification
  - Methodology and Computing in Applied Probability
  - International Conference on Learning Representations
  - Journal of Open Source Software
  - Annals of Statistics
- Olivier Ali
  - Journal of Open Source Software
- Julien Derr
  - Plos Computational Biology
- Christophe Godin
  - Science
  - New Phytologist

9.1.3 Invited talks

- Romain Azaïs
  - StatMod 2023, Bucarest, Romania (online)
  - Séminaire de Statistique de Toulouse
  - Journées DPEMS à Amiens
  - Séminaire de Statistique de Rennes
- Olivier Ali
  - 7th Plant Computational Biology Workshop, University of Cambridge, UK.
- Christophe Godin
  - Scientific day of the ENS Math department
  - ENS Computer Science Department, L3 series of weekly seminars
  - ISMB/ECCB Meeting in Lyon (23-27 July), symposium organized by HFSP on "Data science will determine the success of breakthrough research of the future"
  - Plant Computational Biology Workshop, Sainsbury Lab, Cambridge (4-8 September 2023).
  - Keynote Speaker at the congress 'Imaging the future', Montpellier, 17-19 Oct. 2023.
  - Invited speaker at an ANR workshop organized by Michalis Averof on tree-lineages, IGFL, 24 oct, Lyon
  - Invited speaker at the conference Mifobio (Functional microscopy for Biology), Presqu'ile de Giens, 9-17 Nov 2023.

9.1.4 Leadership within the scientific community

- Christophe Godin
  - Group leader of the Inria Mosaic project-team
  - Coordinator of the ANR project Hydrofield (2021-2024)
  - Scientific coordinator of the Gnomon computational platform project
- Guillaume Cerutti
  - Technical coordinator of the Gnomon computational platform project

9.1.5 Scientific expertise

- Christophe Godin
  - Member of selection jury for CRCN INRIA research positions
  - Member Member of the International Scientific Advisory Committee of the Plant Imaging and Phenotyping Research Centre (P2IRC) at the Global Institute for Food Security (GIFS), Saskatchewan, Canada
  - Member of the scientific committee of the INRAe BAP department
  - Expertize for the appreciation of a group leader activity in the Sainsbury Lab, Cambridge

9.1.6 Research administration

- Romain Azaïs
  - Elected member of the Comité de Centre du centre Inria de Lyon
- Olivier Ali
  - Member of the Conseil d'Analyse Numérique (CAN) of the SFR Biosciences lyon. Role of this council: coordinate digital knowledges and expertize between biology labs within the ENS Lyon site.
  - Elected member of Inria Evaluation Committee.
- Annamaria Kiss
  - webmaster of the hosting lab (RDP) website.
  - data management officer for the hosting lab (RDP).
- Christophe Godin
  - Member of the Inria Project-Team committee of the Inria Center of Lyon University.
  - Member of the management committee of the RDP lab, Lyon.
  - Correspondent for information and scientific editing (IES) at the Lyon Inria center

9.2 Teaching - Supervision - Juries

9.2.1 Teaching

- Romain Azaïs
  - Supervised classification at level Master 2 in Applied Mathematics (Univ. Lyon 1 and ENS Lyon)
  - Introduction to machine learning at level Master 1 in Biology (ENS Lyon)
- Guillaume Cerutti
  - Introduction to image processing, Master 1 Biosciences, ENS Lyon (6h)
- Landry Duguet
  - Introduction to signal processing, Master 1 Biosciences, ENS Lyon (4h)
- Elsa Gascon
  - TD introduction aux fondamentaux de biologie cellulaire, Licence de biologie, ENS Lyon (4h)
  - TP de neurophysiologie et de physiologie végétale, Licence de biologie, ENS Lyon (24h)
  - TD modélisation des systèmes biologiques, L3 biologie, ENS Lyon (16h)

  - TP de physique et chimie des systèmes biologiques, Licence de chimie, ENS Lyon (14h)
  - Cours Cellules et tissus biologiques, Master de chimie, ENS Lyon (3h)
  - TD de biologie moléculaire et génétique, Master de chimie, ENS Lyon (5h)

- Annamaria Kiss
  - Lectures for the "Modelling in biology" L3 level course at the ENS de Lyon, Department of Biology (4h).

- Julien Derr
  - in charge of the "Mathematics for biology" M1 level course at the ENS de Lyon, Department of Biology (8h course, exam). This teaching unit involves several members of our team : Jeanne Abitbol (8h tutorials), Guillaume Cerutti (6h lecture, tutorials), Landry Duguet (4h lecture, tutorials) and Romain Azaïs (6h lecture, tutorials).
  - in charge of the "Biostatistics" L3 level course at the ENS de Lyon, Department of Biology (16h tutorials, exam).
  - "Biophysics" M2 level course at the ENS de Lyon, Department of Physics (8h lectures, 12h tutorials, exam).
  - "Computational modeling for developmental biology" M1 level course at the ENS de Lyon, Department of Biology (10h projects, exam).
  - "Bio-modeling " M2 level course at the ENS de Lyon, Department of Biology (18h projects, exam).
  - participation in the "Developmental Biology" L3 level course at the ENS de Lyon, Department of Biology (12h).
  - In charge of the "Modelling in biology" L3 level course at the ENS de Lyon, Department of Biology (lecture, tutorials, exam, 11h).
  - Mentoring for L3 and M2 students (19h)

- Christophe Godin
  - Université ouverte, ENS de Lyon, March 2023 (2h)

9.2.2 Supervision

- Romain Azaïs
  - PhD supervisor of Natacha Javerzat
  - Internship supervisor of Abdoullah Latreche

- Olivier Ali
  - PhD supervisor of Elsa Gascon
  - Internship supervisor of Chao Huang

- Julien Derr
  - PhD supervisor of Sélène Jeammet
  - PhD supervisor of Camille Le Scao
  - PhD supervisor of Émilien Dilly
  - PhD supervisor of Lucie Poupardin

- Christophe Godin
  - PhD supervisor of Landry Duguet (co-supervision Teva Vernoux, RDP, Lyon)

  - PhD supervisor of Manuel Petit (co-supervision Grégoire Malandain, Inria, Sophia-Antipolis)
  - PhD co-supervisor of Jeanne Abitbol-Spangaro (with Yoan Coudert, RDP Lyon)
  - PhD co-supervisor of Corentin Bisot (with Tom Shimizu, AMOLF lab, Netherlands)
  - Internship supervisor of Lucas Mauboussin
  - Internship co-supervisor of Samara Gher (with Stefanie Wuhrer, Inria Grenoble)
  - Internship supervisor of John Thampi (with Landry Duguet and Teva Vernoux, RDP Lab)
  - Internship supervisor of Mariana Yuste (3.5 months from Mexico University)

9.2.3 Juries

- Romain Azaïs
  - Reviewer of Emilien Manent's PhD thesis at Université Rennes 2
  - Member of the HDR jury of Alexandre Genadot at Université de Bordeaux
- Julien Derr
  - President of the HDR jury of Benoit Landrein at ENS de Lyon
- Christophe Godin
  - Member of the Jury of Manuel Petit's PhD defense (as supervisor)
  - Member of the Inria-Academie de Science Awards Jury

9.3 Popularization

9.3.1 Animation

- Christophe godin and Jeanne Abitbol-Spangaro
  - Organization of bi-mensual Back-to-basics chalk talks in the RDP Lab.

9.3.2 Interventions

- Christophe godin
  - Lycée René Descartes, 4h for 2 classrooms, program 'Chiche' Inria, March 2023.

10 Scientific production

10.1 Major publications

[1] R. Azaïs and F. Ingels. 'The Weight Function in the Subtree Kernel is Decisive'. In: *Journal of Machine Learning Research* 21 (Apr. 2020), pp. 1–36. URL: https://hal.archives-ouvertes.fr/hal-02097593.

[2] E. Azpeitia, G. Tichtinsky, M. Le Masson, A. Serrano-Mislata, J. Lucas, V. Gregis, C. Gimenez, N. Prunet, E. Farcot, M. Kater, D. Bradley, F. Madueño, C. Godin and F. Parcy. 'Cauliflower fractal forms arise from perturbations of floral gene networks'. In: *Science* 373.6551 (2021), pp. 192–197. DOI: 10.1126/science.abg5999. URL: https://hal.archives-ouvertes.fr/hal-03291136.

[3] I. Cheddadi, M. Génard, N. Bertin and C. Godin. 'Coupling water fluxes with cell wall mechanics in a multicellular model of plant development'. In: *PLoS Computational Biology* 15.6 (20th June 2019), e1007121. DOI: 10.1371/journal.pcbi.1007121. URL: https://hal.archives-ouvertes.fr/hal-02196768.

[4] C. Galvan-Ampudia, G. Cerutti, J. Legrand, G. Brunoud, R. Martin Arevalillo, R. Azaïs, V. Bayle, S. Moussu, C. Wenzl, Y. Jaillais, J. U. Lohmann, C. Godin and T. Vernoux. 'Temporal integration of auxin information for the regulation of patterning'. In: *eLife* 9 (7th May 2020). DOI: 10.7554/eLife.55832. URL: https://hal.archives-ouvertes.fr/hal-02368529.

[5] C. Godin, C. Golé and S. Douady. 'Phyllotaxis as geometric canalization during plant development'. In: *Development (Cambridge, England)* 147.19 (12th Oct. 2020), pp. 1–45. DOI: 10.1242/dev.165878. URL: https://hal.archives-ouvertes.fr/hal-03014239.

[6] L. Guignard, U.-M. Fiuza, B. Leggio, J. Laussu, E. Faure, G. Michelin, K. Biasuz, L. Hufnagel, G. Malandain, C. Godin and P. Lemaire. 'Contact area-dependent cell communication and the morphological invariance of ascidian embryogenesis'. In: *Science* (10th July 2020). DOI: 10.1126/science.aar5663. URL: https://hal.inria.fr/hal-02903409.

[7] F. Ingels and R. Azaïs. 'Enumeration of Irredundant Forests'. In: *Theoretical Computer Science* 922 (27th Apr. 2022), pp. 312–334. DOI: 10.1016/j.tcs.2022.04.033. URL: https://hal.science/hal-02511901.

[8] B. Leggio, J. Laussu, A. Carlier, C. Godin, P. Lemaire and E. Faure. 'MorphoNet: an interactive online morphological browser to explore complex multi-scale data'. In: *Nature Communications* 10.2812 (2019), pp. 1–8. DOI: 10.1038/s41467-019-10668-1. URL: https://hal.archives-ouvertes.fr/hal-01938153.

[9] Y. Refahi, A. Zardilis, G. Michelin, R. Wightman, B. Leggio, J. Legrand, E. Faure, L. Vachez, A. Armezzani, A.-E. Risson, F. Zhao, P. Das, N. Prunet, E. Meyerowitz, C. Godin, G. Malandain, H. Jönsson and J. Traas. 'A multiscale analysis of early flower development in Arabidopsis provides an integrated view of molecular regulation and growth control'. In: *Developmental Cell* 56.4 (Feb. 2021), 540–556.e8. DOI: 10.1016/j.devcel.2021.01.019. URL: https://hal.inrae.fr/hal-03299500.

[10] F. Zhao, F. Du, H. Oliveri, L. Zhou, O. Ali, W. Chen, S. Feng, Q. Wang, S. Lü, M. Long, R. Schneider, A. Sampathkumar, C. Godin, J. Traas and Y. Jiao. 'Microtubule-Mediated Wall Anisotropy Contributes to Leaf Blade Flattening'. In: *Current Biology - CB* 30.20 (2020), p. 3972. DOI: 10.1016/j.cub.2020.07.076. URL: https://hal.archives-ouvertes.fr/hal-02370615.

10.2 Publications of the year

International journals

[11] R. Azaïs and F. Ingels. 'Detection of common subtrees with identical label distribution'. In: *Theoretical Computer Science* 988 (12th Mar. 2024). DOI: 10.1016/j.tcs.2023.114366. URL: https://hal.science/hal-04171279.

[12] E. Azpeitia, F. Parcy and C. Godin. 'Cauliflowers or how the perseverance of a plant to make flowers produces an amazing fractal structure'. In: *Comptes Rendus. Biologies* 346.G1 (2023), pp. 75–83. DOI: 10.5802/crbiol.120. URL: https://inria.hal.science/hal-04242307.

[13] F. Ben-Naoum, C. Godin and R. Azaïs. 'Characterization of random walks on space of unordered trees using efficient metric simulation'. In: *Discrete Applied Mathematics* 341 (31st Dec. 2023), pp. 290–307. URL: https://hal.science/hal-03910080.

[14] A. Boudaoud, A. Kiss and M. Ptashnyk. 'Multiscale Modeling and Analysis of Growth of Plant Tissues'. In: *SIAM Journal on Applied Mathematics* 83.6 (29th Nov. 2023), pp. 2354–2389. DOI: 10.1137/23M1553315. URL: https://hal.science/hal-04334494.

[15] M. Chaigne, S. Carpy, M. Massé, J. Derr, S. Courrech Du Pont and M. Berhanu. 'Emergence of tip singularities in dissolution patterns'. In: *Proceedings of the National Academy of Sciences of the United States of America* 120.48 (21st Nov. 2023). DOI: 10.1073/pnas.2309379120. URL: https://hal.science/hal-04316918.

[16] A. Creff, O. Ali, C. Bied, V. Bayle, G. Ingram and B. Landrein. 'Evidence that endosperm turgor pressure both promotes and restricts seed growth and size'. In: *Nature Communications* 14.1 (2023), p. 67. DOI: 10.1038/s41467-022-35542-5. URL: https://hal.science/hal-03927054.

[17] É. Dilly, S. Neukirch, J. Derr and D. Zanchi. 'Travelling Perversion as Constant Torque Actuator'. In: *Physical Review Letters* 131.17 (24th Oct. 2023), p. 177201. DOI: 10.1103/PhysRevLett.131.177201. URL: https://hal.science/hal-04067727.

[18] D. A. Hartasánchez, A. Kiss, V. Battu, C. Soraru, A. Delgado-Vaquera, F. Massinon, M. Brasó-Vives, C. Mollier, M.-L. Martin-Magniette, A. Boudaoud and F. Monéger. 'Expression of cell-wall related genes is highly variable and correlates with sepal morphology'. In: *Peer Community In Genomics* 3.93 (14th Sept. 2023). DOI: 10.24072/pcjournal.327. URL: https://hal.science/hal-04248384.

[19] N. Shourick, I. Cheddadi and P. Saramito. 'A new framework for shallow approximations of incompressible flows'. In: *Comptes Rendus. Mathématique* (2023). URL: https://hal.science/hal-04062098.

Conferences without proceedings

[20] R. Azaïs, S. Habibeche, F. Ben-Naoum and C. Godin. 'Exploring symmetries in plant architectures'. In: 10th International Conference on Functional-Structural Plant Models. Berlin, Germany, 2023. URL: https://hal.science/hal-04086650.

[21] C. Godin and F. Besnard. 'Hierarchical Developmental Timeline Warping: a generic method to design realistic plant architecture models'. In: 10th conference on Structural-Functional Plant Models. Berlin (DE), France, 27th Mar. 2023. URL: https://hal.science/hal-04392528.

Reports & preprints

[22] J. Alonso-Serra, I. Cheddadi, A. Kiss, G. Cerutti, C. Lionnet, C. Godin and O. Hamant. *Water fluxes contribute to growth patterning in shoot meristems*. 28th Aug. 2023. DOI: 10.1101/2023.08.27.554993. URL: https://hal.science/hal-04254674.

[23] W. Guan, Z. Nie, A. Laurencon, M. Bouchet, C. Godin, C. Kabir, A. Darnas and J. Enriquez. *The role of Imp and Syp RBPs in precise neuronal elimination by apoptosis through the regulation of TFs*. 17th Oct. 2023. URL: https://cnrs.hal.science/hal-04246082.

[24] V. Hernández-Hernández, O. Marchand, A. Kiss and A. Boudaoud. *A mechanohydraulic model supports a role for plasmodesmata in cotton fiber elongation*. 1st July 2023. DOI: 10.1101/2023.06.30.547211. URL: https://hal.inrae.fr/hal-04267489.

[25] A. Yadav, L. Hong, P. Klees, A. Kiss, X. He, I. Barrios, M. Heeney, A. M. D. Galang, R. Smith, A. Boudaoud and A. H. Roeder. *Growth directions and stiffness across cell layers determine whether tissues stay smooth or buckle*. 24th July 2023. DOI: 10.1101/2023.07.22.549953. URL: https://hal.science/hal-04334525.

10.3 Cited publications

[26] R. Azaïs. 'Nearest embedded and embedding self-nested trees'. In: *Algorithms* 12.9 (2019), pp. 1–16. DOI: 10.3390/a12090180. URL: https://hal.archives-ouvertes.fr/hal-01584078.

[27] R. Azaïs, J.-B. Durand and C. Godin. 'Approximation of trees by self-nested trees'. In: *ALENEX 2019 - Algorithm Engineering and Experiments*. San Diego, United States: SIAM, Jan. 2019, pp. 39–53. DOI: 10.1137/1.9781611975499.4. URL: https://hal.archives-ouvertes.fr/hal-01294013.

[28] G. Cerutti, O. Ali and C. Godin. 'DRACO-STEM: An Automatic Tool to Generate High-Quality 3D Meshes of Shoot Apical Meristem Tissue at Cell Resolution'. English. In: *Frontiers in Plant Science* 8 (Mar. 2017), pp. 13–15. DOI: 10.3389/fpls.2017.00353. URL: http://journal.frontiersin.org/article/10.3389/fpls.2017.00353/full?%5C&utm%5C_source=Email%5C_to%5C_authors%5C_%5C&utm%5C_medium=Email%5C&utm%5C_content=T1%5C_11.5e1%5C_author%5C&utm%5C_campaign=Email%5C_publication%5C&field=%5C&journalName=Frontiers%5C_in%5C_Plant%5C_Science%5C&id=233281.

[29] J. Derr, R. Bastien, É. Couturier and S. Douady. 'Fluttering of growing leaves as a way to reach flatness: experimental evidence on Persea americana'. In: *Journal of the Royal society interface* 15.138 (2018), p. 20170595.

[30] M. Desbrun, A. H. 4. I. International and 2003. 'Discrete exterior calculus for variational problems in computer vision and graphics'. In: *ieeexplore.ieee.org* ().

[31] D. Eder, C. Aegerter and K. Basler. 'Forces controlling organ growth and size'. In: *Mechanisms of Development* 144 (2017), pp. 53–61. DOI: 10.1016/j.mod.2016.11.005.

[32] R. Fernandez, P. Das, V. Mirabet, E. Moscardi, J. Traas, J.-L. Verdeil, G. Malandain and C. Godin. 'Imaging plant growth in 4D : robust tissue reconstruction and lineaging at cell resolution'. In: *Nature Methods* 7 (2010), pp. 547–553.

[33] D. Garcia, J. N. F. Gerald and F. Berger. 'Maternal Control of Integument Cell Elongation and Zygotic Control of Endosperm Growth Are Coordinated to Determine Seed Size in Arabidopsis'. In: *The Plant Cell* 17.1 (2005), pp. 52–60. DOI: 10.1105/tpc.104.027136.

[34] O. Hamant, M. G. Heisler, H. Jonsson, P. Krupinski, M. Uyttewaal, P. Bokov, F. Corson, P. Sahlin, A. Boudaoud, E. M. Meyerowitz, Y. Couder and J. Traas. 'Developmental Patterning by Mechanical Signals in Arabidopsis'. English. In: *Science* 322.5908 (Dec. 2008), pp. 1650–1655. DOI: 10.1126/science.1165594. URL: http://adsabs.harvard.edu/cgi-bin/nph-data%5C_query?bibcode=2008Sci...322.1650H%5C&link%5C_type=ABSTRACT.

[35] S. Ichbiah, F. Delbary, A. Mcdougall, R. Dumollard and H. Turlier. 'Embryo mechanics cartography: inference of 3D force atlases from fluorescence microscopy'. In: *Nat Methods* 20 (2023), pp. 1989–1999. DOI: https://doi.org/10.1038/s41592-023-02084-7.

[36] F. Ingels and R. Azaïs. 'Isomorphic unordered labeled trees up to substitution ciphering'. In: *International Workshop on Combinatorial Algorithms*. Vol. 12757. Lecture Notes in Computer Science. Conférence online. Ottawa, Canada: Springer International Publishing, July 2021, pp. 385–399. DOI: 10.1007/978-3-030-79987-8_27. URL: https://hal.archives-ouvertes.fr/hal-03227196.

[37] A. Kar, M. Petit, Y. Refahi, G. Cerutti, C. Godin and J. Traas. 'Benchmarking of deep learning algorithms for 3D instance segmentation of confocal image datasets'. In: *PLoS Computational Biology* 18.4 (Apr. 2022), e1009879. DOI: 10.1371/journal.pcbi.1009879. URL: https://hal.inrae.fr/hal-03659219.

[38] G. Michelin, Y. Refahi, R. Wightman, H. Jonsson, J. Traas, C. Godin and G. Malandain. 'Spatio-temporal registration of 3D microscopy image sequences of arabidopsis floral meristems'. In: *Proceedings - International Symposium on Biomedical Imaging* 2016-June (2016), pp. 1127–1130. DOI: 10.1109/ISBI.2016.7493464.

[39] L. Riglet, F. Rozier, C. Kodera, S. Bovio, J. Sechet, I. Fobis-Loisy and T. Gaude. 'KATANIN-dependent mechanical properties of the stigmatic cell wall mediate the pollen tube path in Arabidopsis'. In: *Elife* 9 (2020), e57282.

[40] M. Rivière, Y. Corre, A. Peaucelle, J. Derr and S. Douady. 'The hook shape of growing leaves results from an active regulatory process'. In: *Journal of Experimental Botany* 71.20 (2020), pp. 6408–6417.

[41] M. Rivière, J. Derr and S. Douady. 'Motions of leaves and stems, from growth to potential use'. In: *Physical biology* 14.5 (2017), p. 051001.

[42] V. Robin-Deleuze, H. Maziero, G. R. Krishnakumar, G. Devillers, M. Rivière, J. Pansiot, J. Derr, F. Bertails-Descoubes and F. Hétroy-Wheeler. 'Carambole'. In: ().

[43] L. Serra, S. Tan, S. Robinson and J. A. Langdale. 'Flip-Flap: A Simple Dual-View Imaging Method for 3D Reconstruction of Thick Plant Samples'. In: *Plants* 11.4 (2022). DOI: 10.3390/plants11040506.

[44] B. I. Shraiman. 'Mechanical feedback as a possible regulator of tissue growth'. In: *Proceedings of the National Academy of Sciences of the United States of America* 102.9 (2005), pp. 3318–3323. DOI: 10.1073/pnas.0404782102.