RESEARCH CENTRE

Grenoble - Rhône-Alpes

IN PARTNERSHIP WITH:

Ecole normale supérieure de Lyon, CNRS, INRAE

2021 ACTIVITY REPORT

Project-Team MOSAIC

MOrphogenesis Simulation and Analysis In siliCo

DOMAIN

Digital Health, Biology and Earth

THEME

Computational Biology

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Project-Team MOSAIC

Creation of the Project-Team: 2019 July 01

Keywords

Computer sciences and digital sciences

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A6.1. – Methods in mathematical modeling

A6.2. – Scientific computing, Numerical Analysis & Optimization

A6.3. – Computation-data interaction

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1 Team members, visitors, external collaborators

Research Scientists

- Christophe Godin [Team leader, Inria, Senior Researcher, HDR]
- Olivier Ali [Inria, Researcher]
- Romain Azaïs [Inria, Researcher]

Faculty Members

- Ibrahim Cheddadi [Univ Grenoble Alpes, TIMC, Associate Professor, from Sep 2021]
- Julien Derr [École Normale Supérieure de Lyon, Professor, from Sep 2021, HDR]

Post-Doctoral Fellows

- Ayan Chaudhury [Inria , Fev 2019, until Jan 2021]
- Anuradha Kar [Institut national de recherche pour l'agriculture, l'alimentation et l'environnement, until Sep 2021]

PhD Students

- Jeanne Abitbol Spangaro [CNRS, from Oct 2021]
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- Landry Duguet [Inria, from Oct 2021]
- Florian Ingels [Inria, from Sept 2019]
- Katia Mirande [Inria, from Nov 2018]
- Manuel Petit [Inria, from Nov 2019]

Technical Staff

- Guillaume Cerutti [Institut national de recherche pour l'agriculture, l'alimentation et l'environnement, Engineer]
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- Jonathan Legrand [CNRS, Engineer]
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- Landry Duguet [Inria, from Mar 2021 until Sep 2021]
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- Emmanuel Faure [CNRS]
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- Patrick Lemaire [CNRS, HDR]
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- Jan Traas [Institut national de recherche pour l'agriculture, l'alimentation et l'environnement, HDR]
- Samuel Teva Vernoux [CNRS, HDR]

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 cauliflower development resulting from a longstanding collaboration with François Parcy's group in Grenoble on the analysis of how genetic perturbation in the inflorescence gene regulation network lead to transform inflorescences in conspicuous cauliflower curds. This work has been published in the journal Science [9] and is illustrated on the journal's cover [32].
- Julien Derr joint the team as a Professor at ENS de Lyon on an Inria Chair in September 2021.

6 New software and platforms

6.1 New software

6.1.1 cvmgof

Keywords: Regression, Test, Estimators

Scientific Description: Many goodness-of-fit tests have been developed to assess the different assumptions of a (possibly heteroscedastic) regression model. Most of them are "directional" in that they detect departures from a given assumption of the model. Other tests are "global" (or "omnibus") in that they assess whether a model fits a dataset on all its assumptions. cvmgof focuses on the task of choosing the structural part of the regression function because it contains easily interpretable information about the studied relationship. It implements 2 nonparametric "directional" tests and one nonparametric "global" test, all based on generalizations of the Cramer-von Mises statistic.

Functional Description: cvmgof is an R library devoted to Cramer-von Mises goodness-of-fit tests. It implements three nonparametric statistical methods based on Cramer-von Mises statistics to estimate and test a regression model.

News of the Year: New version available on CRAN website since Jan 11 2021

URL: https://cran.r-project.org/web/packages/cvmgof/index.html

Publication: hal-03101612

Contact: Romain Azais

Participants: Sandie Ferrigno, Marie-José Martinez, Romain Azais

6.1.2 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 focuses on the possibility for the user to use its own custom Python code as a temporary plugin within the application, and to compose it with the other available algorithmic bricks. This is achieved through a plugin development workspace, where an interactive GUI allows to simplify the writing of a new plugin by generating a skeleton of Python code. The user only has then to fill in the method performing the actual processing, and can interact with the output data, both in a 3D viewer and in a Python shell.

News of the Year: A new ADT project, designed in synergy with the partners from the Inria Défi Navicope, has been submitted with the ambition of proposing a complete ecosystem for the study of dynamical biological systems. It will focus on the possibility to conceive intuitively both analysis and modelling pipelines in the main Gnomon application, to use those pipelines to batch-process datasets with distributed computation, relying on the technical solutions developed in the BioImage-IT project, and to interact with the resulting objects through the web-based 3D+t browser MorphoNet. The project received a 3-year funding and started in 12/2021.

Contact: Christophe Godin

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

6.1.3 MorphoNet

Name: MorphoNet

Keywords: 3D web, Morphogenesis, Big data, 3D reconstruction

Functional Description: MorphoNet is an open-source web-based morphological browser. It consists of a web application, exploiting the Unity3D gaming engine, which offers the user a comprehensive palette of interactions with the data, in order to explore the structure, the dynamics and the variability of biological systems. Users can also project quantitative and genetic properties onto the morphological scaffold, allowing for instance to easily explore the correlation between shape dynamics and gene expression patterns. On top of that, datasets and associated information can be shared with other selected users or with entire groups. This possibility of directly sharing results within and between research communities, together with the use of a unified, human readable

format, makes MorphoNet a unique tool for multidisciplinary research. Its web-based, user-friendly and open-source structure is also ideal for science dissemination and teaching.

URL: http://www.morphonet.org

Contact: Emmanuel Faure

Partner: CRBM - Centre de Recherche en Biologie cellulaire de Montpellier

6.1.4 TimageTK

Name: Tissue Image ToolKit

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

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.

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

Contact: Jonathan Legrand

6.1.5 treex

Name: treex

Keywords: Graph algorithmics, Data structures, Combinatorics, Machine learning

Scientific Description: Trees form an expanded family of combinatorial objects that offers a wide range of application fields, especially in biology, from plant modeling to blood vessels network analysis through study of lineages. Consequently, it is crucial for the team to develop numerical tools and algorithms for processing tree data, in particular to answer questions about the representation of biological organisms and their forms in silico.

treex is a Python 3 library dedicated to the manipulation of tree objects, whatever they are ordered or not, with or without quantitative or qualitative labels.

Functional Description: The package provides a data structure for rooted trees as well as the following main functionalities: - Random generation algorithms - DAG compression for ordered or not, labeled or not, trees - Approximation algorithms for unordered trees - Edit distance for unordered labeled trees - Kernels for ordered or not, labeled or not, trees - Computation of coding processes (Harris path, Lukasiewicz walk and height process) - Visualization algorithms in Matplotlib or in LaTeX

Release Contributions: In 2019, treex has been published in JOSS (Journal of Open Source Software). In 2021, the architecture of treex has been deeply modified. In the new version, treex is made of a main module implementing the data structure and of several self-contained application modules: analysis, simulation, lossy or lossless compression, etc.

URL: https://gitlab.inria.fr/azais/treex

Publication: hal-02164364

Contact: Romain Azais

Participants: Romain Azais, Guillaume Cerutti, Didier Gemmerle, Florian Ingels

7 New results

7.1 Dynamical characterization of morphogenesis at cellular scale

Participants: Guillaume Cerutti, Emmanuel Faure *(External Collaborator)*, , Christophe Godin, Anuradha Kar, Jonathan Legrand, Grégoire Malandain *(External Collaborator)*, , Manuel Petit, Jan Traas *(External Collaborator)*.

- 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, necessitate 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 or how to define cell-scale variability of morphogenesis within and between species?

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

Comparison of image segmentation methods for cell identification

Accurately identifying cell regions in 3D images is a crucial first step in many biological analysis methods. For a long time, cell segmentation has been performed using techniques that required significant manual parameter tuning. Recently, a new class of algorithms based on deep learning have been proposed which have been shown to achieve high accuracy in identifying objects from images automatically and requiring minimum human intervention. These deep learning based algorithms usually have the structure of a sequential pipeline consisting of a deep learning model which can be trained for prediction of the segmented regions along with set of pre and post processing steps.

The current problem with deep learning based segmentation is the lack of homogeneous methods to analyze the quality of segmentations, and the diversity of pipelines, pre and post processing steps and training datasets that can be used. Due to these, it is currently not possible to evaluate and compare the relative performances of the deep learning segmentation algorithms and identify their strengths and weaknesses. To address this problem, we set up a global evaluation strategy that consisted in:

- Selecting several deep learning based pipelines from the literature which could be trained for 3D cell instance segmentation task.
- Using a common expertized dataset of 3D cellular images (confocal images of floral or shoot apical meristems) to train and test the pipelines.
- Applying the same set of metrics and visualisation tools to compare the performances of the pipelines and in depth evaluation of their segmentation quality.
- Comparing the performance of the deep learning based pipelines with an established watershed based non-deep learning segmentation method [27].

By evaluating segmentation acuracy, rates of and under and oversegmentation in the whole tissue or in individual cellular layers (L1, L2, inner), this analysis provides a deeper insight into the robustness of each of the segmentation pipelines and helps to test their sensitivity to different image artefacts.

A Gitlab repository has been created to make this segmentation evaluation framework publicly available, and a paper is currently under review. This work is part of the ERA-CAPS project Genes2shape.

Robust extraction and characterization of cellular lineages

The quantitative study of developing tissues is mainly based on the analysis of time-lapse image acquisitions, from which cell-level temporal properties such as volumetric growth rate or cell cycle duration can be recovered through the identification of cell lineages. In plant tissues, accurate and automatic construction of cell lineages remains a real challenge because of the large deformations taking place between consecutive time-points, especially during the post-embryonic morphogenesis processes. In contrast with animal embryogenesis [5], these constraints impose the use of a two-stage procedure where image segmentation and cell lineaging are done separately.

Building on previous tracking methods published by the team [27, 31] and on the *TimageTK* computational library (developed in collaboration with the Inria team Morpheme), we implemented several robust fully-automatic cell lineage methods in order to handle different range of non-linear deformations. For small deformations, an overlap-based tracking method was implemented and tested on synthetic data and expertized experimental data. We embedded this method in an iterative image registration procedure in order to use cell lineage information to refine the estimation of non-linear deformations. The validation on experimental data showed a significant improvement of the tracking accuracy in the regions presenting larger deformations.

On top of our iterative automatic tracking method we developed a *nudge* approach for fast and semi-automatic post-correction. Given a proposed cell lineage, a cell lineage quality map can be automatically inferred from the results and used to detect visually low lineage quality areas. Then, in these areas, the user can select a few landmarks to automatically correct locally the lineage.

The methods developed in the context of this work have been submitted as a paper to the IEEE-ISBI 2022 conference and included in a new Python library, built upon the *TimageTK* package 6.1.4. This work is part of the Inria Défi Naviscope.

Cells spatio-temporal properties and population statistics

Over the past few years, thanks to cell based segmentation and lineage tracking algorithms, we have achieved quantitative characterization of some of the cells spatio-temporal properties, such as cells volume, volumetric growth rate or strain pattern. To structure this data, we have implemented a spatio-temporal graph structure, thus formalizing the cell tissue network and its dynamics in a dedicated computational object. For practical use such as statistical analysis and data interaction, we implemented biologically relevant methods to explore the tissues trough an API with a biological semantics.

To characterize the tissue growth, we aimed at identifying cellular patterns by means of clustering. To that extent, we developed and implemented a method to combine a weighted selection of cellular features (including topology) into a pairwise distance matrix. We then used the Ward's metrics on a agglomerative hierarchical clustering method to detect cluster or groups of cells based on their properties. As it is important to evaluate the clustering quality and gain biological meaning, we implemented the appropriates tools and methods. Together with Principal Component Analysis, this finally enabled us to perform an exploratory analysis of a biologically relevant subset of the possible cell features combinations aiming at cellular patterns identification.

Batch processing, especially the time-consuming ones like segmentation, lineage and features computations are simplified by the use of a minimal data model relying on a single JSON and folder structure. With a simple and minimal setup time, it will later automatically augment and organize the (potentially large) sets of generated data. Visual representations of the computational objects (graph, cluster), biological data interaction and statistical charts are available (requires jupyter notebooks for interactive ones). It is now also possible to export meshes representation of the segmentations, lineages and cell features to MorphoNet, [6] 6.1.3, a publicly accessible online tool allowing 3D interaction and exploration of this type of spatio-temporal data.

All the previously described implementations are available in the *TimageTK* package 6.1.4. The source code of this work is accessible via the Inria GitLab and is available as python packages. It should be soon available as a Gnomon 6.1.2 plugin, a Naviscope project currently in development, to benefit from the GUI. A paper on the underlying methodology is currently being written.

Atlases of development: construction and update

Developing digital atlases of organism or organ development is a complex challenge for tissues presenting a strong variability in their cellular layout. The development of most plant organs is under the influence of robust genetic patterns without a unique cellular layout. To generate a cell-based atlas representing the development of a floral meristem of *Arabidopsis thaliana* for instance, we chose a representative flower template, on which the spatio-temporal expression patterns of 27 genes was then introduced manually. We combined growth and gene expression to construct a molecular network model that correctly predicts a large majority of 28 gene expression patterns. This model suggests hypotheses for the combined action of regulatory genes in morphogenesis [12].

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 time-lapse image acquisitions displaying both cell interface markers and genetic reporters. Starting from previous works addressing the spatio-temporal registration of floral meristem time-lapses sequences [31], we are currently developing a method that uses the geometry of organs to propagate genetic information across several individuals. A proof-of-concept has been implemented and tested on simple sythetic data, floral meristem and apical meristem images. In the case of apical meristems, a specific spatio-temporal registration method based on surface curvature was developed. Different methods of information transfer with various properties (lossless transfer, variation preservation, cell/voxel level) have been implemented. The validation of this approach is currently performed on a larger set of experimental data, and should be published in 2022. This work is part of the Inria Défi Naviscope.

Extraction of biological landmarks using Machine Learning

In order to superimpose similar organs coming from different individuals, it is possible to map biological landmarks to compute a geometrical transformation, instead of relying only on image-based registration. For instance, in the case of the shoot apical meristem, detecting the centers of the central zone (CZ) and of the youngest organ primordia allows to align a population with a great precision [3].

However, locating such landmarks often requires to acquire images with an additional biological marker, which adds experimental constraints. Focusing on the detection of the CZ center, we explored the possibility of using existing data of meristems imaged with both a geometry and a CZ marker to train Machine Learning models that would predict the position of the CZ center (and therefore avoid to modify imaging protocols).

This work, carried out in the context of the M2 internship of Anthony Scriven, showed that a Deep Learning model (2D U-Net), trained on downsampled 2D projections of the original images, was able to detect the CZ center with an error of less than 1 cell on other images acquired with the same settings. It still lacks robustness to the 3D pose and to the number of visible organs, but already constitutes a very promising direction to investigate in the coming year.

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

Participants: Ayan Chaudhury, Christophe Godin, Julien Derr, Jonathan Legrand, Katia Mirande.

- 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 develop acquisitions and reconstruction methods to generate the best digital clone possible. 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. We developed a reconstruction and quantification pipeline that aggregates a number of algorithms developed in three active research topics (and making use of extra third-party libraries):

- plant structure identification by means of spectral clustering (thesis work of Katia Mirande);
- plant structure reconstruction by means of skeleton extraction and improvement [24];
- organs and plant structure identification by means of trained CNN segmentation, with a first paper describing this work this year [14].

This work is part of the *ROMI* project.

In collaboration with the ROMI partners from Sony CSL, Paris, we are developing an inexpensive and open-source solution to address this challenge of plant architecture characterization:

- a plant scanner, based on inexpensive and widely available electronics, designed to simplify and automatise the acquisition of RGB pictures necessary to the 3D reconstruction;
- a database, following the Findable Accessible Interoperable and Reusable (FAIR) principles, to store and organize the datasets;
- a task-based, modular and highly configurable processing pipeline, to:
  - reconstruct the plant architecture (in 3D) from the a datasets of RGB images;
  - segment the reconstructed plant into organs, using trained Convolutional Neural Networks (CNN);
  - compute phenotypic traits from reconstructed plant.
- a virtual plant creator and scanner to generate training datasets and ground-truth to evaluate the quality of each step of our reconstruction pipeline;
- a web interface, developed in collaboration with DataVeyes, to navigate the database and visualize the 3D reconstructed objects (point-cloud, mesh, skeleton).

As stated before, we use a generative model of *Arabidopsis thaliana* simulating the development of the plant architecture at organ scale developed within the project to provide validation data for the pipeline. The generative model of *Arabidopsis thaliana* is based on Lpy and is based on a new hierarchical timeline warping technology developed by the team in the context of the ROMI project (deliverable 6.2). We here use it to generate biologically realistic plants, and we aim at making them photo-realistic using texture mapping and advanced 3D-scene rendering engines (Blender). Then, we developed a strategy to construct a 3D point cloud from the virtual plant models, thus mimicking the reconstruction of 3D point clouds from real 2D photogrametric images in the main pipeline [23]. Altogether, this produces as a virtual scanner, reproducing the behavior of the real scanner, to generate datasets of RGB images and export the known the phenotypic traits. Knowing the generated phenotypic traits or the model shape allow to test the pipeline ability to reconstruct the plant and quantify its traits of interest.

Finally, assess the obtained sequences of angles and inter-nodes, it is needed to compare a possibly erroneous predicted sequence of angles and internodes to ground truth sequences. For this we developed a new algorithm to align multivariate sequences using split-merge operations in dynamical time warping models (SM-DTW). Then, this enables us to analyze real plants phyllotaxis by providing precise information on sequences similarities. We currently scale up the method at a plant population level to characterize population variability. A paper will report on this work next year.

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

Complementary to the full 3D reconstruction of plant architecture (ROMI project), we have also started to develop a new platform to characterize plants in 3D at the organ scale coordinated by Julien Derr (typically at leaf scale). The objective is to 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[34, 25, 33], 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 decided to build a multicamera set up[35]. The set up is being installed at ENS de Lyon in the new M8 building dedicated to plant growth.

7.3 Analysis and simulation of tree data

Participants: Romain Azaïs, Farah Ben Naoum *(External Collaborator)*, , Christophe Godin, Salah Eddine Habibeche *(External Collaborator)*, , Florian Ingels.

- 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 90's 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 a paper submitted 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, we now work on approximation of trees with geometrical attributes on their vertices. We have exhibited a lossy compression algorithm for such trees, with a control on the information loss (joint work with Farah Ben Naoum and Salah Habibeche - PhD student - from the University of Sidi Bel Abbes, Algeria).

- 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. We have developed 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. This work has been published as a proceeding in an international conference [19].

Statistical inference. The main objective of statistical inference is to retrieve the unknown parameters of a stochastic model from observations. A Galton-Watson tree is the genealogical tree of a population starting from one initial ancestor in which each individual gives birth to a random number of children according to the same probability distribution, independently of each other.

In a recent work [20], we have focused on Galton-Watson trees conditional on their number of nodes. Several main classes of random trees can be seen as conditioned Galton-Watson trees. For instance, an ordered tree picked uniformly at random in the set of all ordered trees of a given size is a conditioned Galton-Watson tree with offspring distribution the geometric law with parameter 1/2. Statistical methods were developed for conditioned Galton-Watson trees in [20]. We have introduced new estimators and stated their consistency. Our techniques improve the existing results both theoretically and numerically.

We continue to explore these questions for subcritical but surviving Galton-Watson trees, which are a typical example of multi-type Galton-Watson trees where the types are unobserved. The conditioning is a source of bias that must be taken into account to build efficient estimators of the birth distribution. T, we have developed an estimation algorithm for surviving Galton-Watson trees, and we have proved a theorem that states its statistical efficiency. These results have been submitted for publication [16].

Kernel methods for tree data. Standard statistical techniques – such as SVMs for supervised learning – are usually designed to process Euclidean data. However, trees are typically non-Euclidean, thus preventing using these methods. Kernel methods allow this problem to be overcome by mapping trees in Hilbert spaces. However, the choice of kernel determines the feature space obtained, and thus greatly influences the performance of the different statistical algorithms. Our work is therefore focused on the question of how to build a good kernel.

We first looked in [1] at a kernel of the literature, the subtree kernel, and showed that the choice of the weight function – arbitrarily fixed so far – was crucial for prediction problems. By proposing a new framework to calculate this kernel, based on the DAG compression of trees, we were able to propose a new weight, learned from the data. In particular, on 8 data sets, we have empirically shown that this new weight improves prediction error in 7 cases, and with a relative improvement of more than 50% in 4 of these cases.

We then tried to generalize our framework by proposing a kernel that is no longer based on subtrees, but on more general structures. To this end, we have developed an algorithm for the exhaustive enumeration of such structures, namely the forests of subtrees. This makes us able to define a new feature extraction process from tree data, that, roughly speaking, brings the previous algorithm based on subtrees to any order. This work has been submitted for publication in 2020 and is currently under revision [18].

Simulating the growth of branching systems in curved spaces. The growth of biological structures or their functioning may occur on substrates that are not flat. This can be for example the case of molecules that diffuse between cells at the surface of organs, of teeth that migrate on curved epithelia in

some animals during their lifetime (like sharks), of primordia outgrowth in plants, of organ vasculature that connects growing organs with the rest of the plant's body following curved paths. Here, we extended the language of L-systems in order to model the growth of branching structures in curved spaces. The resulting language is called *Riemannian L-system*. The language makes it possible to define curved spaces using a variety of parametric models (sphere, torus, surface of revolution, nurbs patches, etc) and to simulated automatically the movements of the L-system's turtle (move forward, turn some angle, etc.) in the underlying curved space. This makes it possible to simulate various dynamic phenomena in curved spaces: random walks and diffusion, movements on geodesics, parallel transport, fractals, growth of branching systems and their interaction with the substrate, phyllotaxis, etc. This year we added the possibility for L-systems to simulate the growth of branching structure in abstract Riemannian spaces (in spaces of 2 or 3 dimensions intrinsically curved and not only in 2D-surfaces embedded in 3D spaces), with a metric field over the whole space. This makes it possible for instance to grow a plant in a 3D space curved by external actors, such as light. A paper is in preparation about this work.

7.4 Mechanics of tissue morphogenesis

Participants: Olivier Ali, Elsa Gascon, Christophe Godin, Guillaume Cerutti.

- 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 depends on complex biochemical and mechanical interactions between cells and tissues [26, 36]. In collaboration with biologists from the SEED-DEV team, we investigated the regulation of seed size, a key agronomic trait, by mechanical interactions between two compartments: the endosperm and the seed coat [28].

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 presented at two online international events: *(i)* The Cambridge Morphogenesis Seminar Series, in March 2021 and *(ii)* the Cell and Tissue Hydraulic Mini-Symposium, a international online conference organized by the Mechanobiology Institute of the National University of Singapore, in October. A paper is currently under review in a top tier generalist journal. The corresponding preprint is already available on bioRxiv [17].

Mechanical stresses guide the formation of tricellular junction during cell division

In most biological tissues, cells attach each other by forming stable tricellular junctions (*3CJ*) [29]. In plants, the emergence of these tricellular junctions during cell division remains poorly understood. However, the influence of mechanical stresses on cell division orientation has been recently highlighted [30, 21] and suggests that, as in animals [22], mechanical stresses could be central in defining such stable structures in plants.

Together with colleagues from the SICE team, we wandered how tissue topology produces mechanical patterns within cell walls leading to biochemical signaling involved in *3CJ* formation. Using high resolution imaging, we exposed the existence of two positions, at a conserved distance near an existing *3CJ*, where the newly formed cell wall could attach during cytokinesis. This mechanism appears under genetic control, as a mutant impaired in the metabolism of phospholipid produces ill-formed junctions. The number of these ill-formed junctions increases with the intensity of turgor-induced stresses, suggesting that mechanical stresses are involved in junction formation. Using mechanical simulations with subcellular resolution we unraveled a correlation between stress distribution and the phospholipid composition of the plasma membrane. These preliminary results suggest that indeed mechanical stresses could act as guiding clues during the formation of tricellular junctions.

This project is a new collaboration between the MOSAIC & SICE teams. It has been mostly carried out by Elsa Gascon, a young engineer shared between the two teams and supervised by Olivier Ali (MOSAIC) and Marie-Cecile Caillaud (SICE).

Development of a high-level Finite Element library dedicated to complex cellularized structures.

Quantitative modeling of morphogene fields (chemical and/or mechanical) require to compute accurately differential equations on complex domains (*i.e.* cellularized and / or non-manifold). To that end, we developed, last year, a *Finite Element* python library, named *BVPy* and based on FEniCS and GMSH. The library source code is fully accessible via the team gitlab page, the team conda channel and also on the conda-forge official channel.

BVPy provides a high level API to define and resolve wide range of linear and non-linear Boundary-Value Problems as well as Initial Boundary-Value Problems, on domains inspired by biological structures. Emphasis has been put during its development on *UX*; in order to promote its dissemination among modellers and to ease collaborations between model developers and users.

This year, the *BVPy* library has been used between our team and the SEED DEV team to investigate the putative role of mechanical stresses within the formation of tricellular junction during cell division. This interdisciplinary project is a great opportunity to test and strengthen the userfriendliness of our API. The library has also been published in the Journal of OpenSource Softwaress [10].

Organ geometry channels reproductive cell fate in the Arabidopsis ovule primordium

The team collaborated as an adviser in mechanical modeling of tissue growth in the following work (ANR/Swiss NSF project). In multicellular organisms, sexual reproduction requires the separation of the germline from the soma. In flowering plants, the female germline precursor differentiates as a single sporemother cell (SMC) as the ovule primordium forms. Here, we explored how organ growth contributes to SMC differentiation. 92 annotated 3D images at cellular resolution in Arabidopsis were generated. Tissue growth models based on the analysis of different mechanical interactions between tissue regions, uncovered plausible morphogenetic principles involving a spatially confined growth signal, differential mechanical properties, and cell growth anisotropy. This analysis revealed that SMC characteristics first arise in more than one cellbut SMC fate becomes progressively restricted to a single cell during organ growth. Altered primordium geometry coincided with a delay in the fate restriction process in katanin mutants. Altogether, this study suggests that tissue geometry channels reproductive cell fate in the Arabidopsis ovule primordium [11].

7.5 Signaling and transport for tissue patterning

Participants: 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 (see an introductory presentation in [15]). 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*.

Temporal integration of auxin signaling in meristem organ patterning.

Morphogenetic signals such as auxin define spatial distributions that are thought to control tissue patterning, but it has been proposed in animals that they also carry temporal information in their dynamics. A recent model developed by our group has postulated the existence of a stochastic mechanism to explain disturbed phyllotaxis patterns. As a consequence of its structure, this model predicts that organ initiation results from a temporal integration of a morphogenetic signal that buffers molecular noise. Using a quantitative analysis of the dynamics of auxin distribution and response, we provide evidence that organ initiation in the SAM is indeed dependent on the temporal integration of the auxin signal. The duration of cell exposition to auxin is used to differentiate temporally sites of organ initiation, and provide robustness to the rhythmic organ patterning. In addition, the automatically reconstructed networks of auxin transporter PIN1, quantified from microscopy images, evidenced a slowly evolving centripetal pattern with local convergence and divergence that could explain the temporal dynamics of auxin distributions in the meristem. This work gave rise to a journal article published in 2020 in eLife [3]. In the context of the PhD work of Landry Duguet that started in October 2021, we are currently investigating how these new, more accurate, observations on auxin and PIN dynamics could be explained by new transport models at the SAM (still in collaboration with the SIGNAL team).

Gibberelin signaling and internode specification in the Shoot Apical Meristem

Building upon the methodology developed for the analysis of auxin dynamics in the Shoot Apical Meristem (SAM) [3], we aim at studying the role of other signaling molecules in the patterning of the meristem, notably an active form of gibberelic acid (GA). Time-lapse imaging of living SAM tissues marked with various fluorescent proteins allows monitoring the dynamics of cell-level molecular processes. Using a co-visualization of a fluorescent GA biosensor with a dye staining of cell walls with propidium iodide (PI), we developed a method quantify GA levels for every cell of the epidermal layer from confocal images.

By computing cell growth and division features from manually determined cell lineages, we evidenced a role for gibberelins in the patterning of the meristem. The high values of GA signaling coincide with low-growth cells located between organ primordia regions, which are actually precursors of internodes. Furthermore, the cell division plane orientation is shown to be regulated by GAs to establish typical cell file patterns, highlighting the contribution of GA to internode specification in the SAM.

This work is part of an ongoing collaboration with the Signal team of the RDP and has been submitted to Nature Plants in summer 2021. After rejection, it is currently being revised for a re-submission at the beginning of 2022.

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 [9].

7.7 Miscellaneous

Participants: Romain Azaïs, Christophe Godin, Teva Vernoux *(External collaborator)*
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Review article on shoot morphogenesis: What shoots can teach about theories of plant form.

Plants generate a large variety of shoot forms with regular geometries. These forms emerge primarily from the activity of a stem cell niche at the shoot tip. Recent efforts have established a theoretical framework of form emergence at the shoot tip, which has empowered the use of modelling in conjunction with biological approaches to begin to disentangle the biochemical and physical mechanisms controlling form development at the shoot tip. Here, we discuss how these advances get us closer to identifying the construction principles of plant shoot tips. Considering the current limits of our knowledge, we propose a roadmap for developing a general theory of form development at the shoot tip [13]

Statistical analysis and stochastic modelling of penguin diving.

The activity at sea of penguins can be reconstructed from measurement devices equipped on the animals during their trips. We study the relative behavior of the time under water with respect to the time spent at the surface from a dataset of about 100 thousands dives of little penguins. We show that dives that

form a bout in which the penguin explores a patch of preys show a type of stationarity. We have built a mathematical model of sequences of dives that can be optimized in terms of number of preys catched by the animal under physiological constraints. This reproduces the stationary behavior observed in the data.

Goodness-of-fit tests in regression models.

Many goodness-of-fit tests have been developed to assess the different assumptions of a regression model. Most of them are "directional" in that they detect departures from a given assumption of the model. Other tests are said "global" because they assess whether a model fits a dataset on all its assumptions. In the paper [8] published in 2021, we focus on the task of choosing the structural part of the regression function because it contains easily interpretable information about the studied relationship. We consider 2 nonparametric "directional" tests and one nonparametric "global" test, all based on generalizations of the Cramér-von Mises statistic. To perform these goodness-of-fit tests, we have developed the R package cvmgof providing an easy-to-use tool for practitioners. A simulation study has been carried out in order to show how the package can be exploited to compare the 3 aforementioned tests.

8 Partnerships and cooperations

8.1 International initiatives

8.1.1 Participation in other International Programs

ERA-CAPS Genes2shape (2017-2021)

Participants: Christophe Godin, Anuradha Kar, Jonathan Legrand, Manuel Petit, Guillaume Cerutti, Jan Traas *(External Collaborator)*.

This project is aimed at understanding how molecular regulation integrates with mechanics to control overall plant shape, an unresolved problem with wide implications for both fundamental and applied biology. We will address this issue in the Arabidopsis flower, which, besides their obvious importance as reproductive structures, are amongst the best characterised systems in plant developmental biology. From a mechanistic point of view, it is widely accepted that regulatory molecular networks interfere with the properties of the structural cellular elements (cell wall, cytoskeleton) to induce particular growth patterns. How this occurs and how this is coordinated in space is not known. To obtain a mechanistic understanding of such a complex process, information from multiple scales, from molecular networks to physical properties and geometry have to be combined into a single picture. An integrated tool to do so is currently not available. Building on our complementary experience in interdisciplinary research on plant development, we will therefore develop a tool, called the "Computable Flower" that permits (i) integration of data on geometry, gene expression and biomechanics and (ii) the user to explore, interpret and generate hypotheses based on data supported by mechanistic modelling approaches. The tool therefore provides an integrated description in the form of a 3D dynamic template of the growing flower bud.

Partners:

- University of Cambridge (Sainsbury Lab.)
- California Institute of Technology
- MaxPlanck Institutes of Molecular Plant Physiology

8.2 European initiatives

8.2.1 FP7 & H2020 projects

H2020 - ROMI (2017-2022)

Participants: Romain Azaïs, Ayan Chaudhury, Christophe Godin, Florian Ingels, Jonathan Legrand, Katia Mirande, Teva Vernoux *(External Collaborator)*.

- Project title: RObotics for MIcrofarms
- Coordinator: Sony
- Partners: Sony-Paris (UK), Iaac (Spain), FEI (France), Inria (France), CNRS (France), UBER (Germany), Chatelain (France)

All over Europe, young farmers are starting small market farms and direct sales businesses. These farms can be found both in rural, peri-urban and urban areas. They grow a large variety of crops (up to 100 different varieties of vegetables per year) on small surfaces (0.01 to 5 ha) using organic farming practices. These farms have proven to be highly productive, sustainable and economically viable. However, a lot of work is done manually, resulting in physically challenging work conditions.

ROMI will develop an open and lightweight robotics platform for these microfarms. We will assist these farms in weed reduction and crop monitoring. This will reduce manual labour and increase the productivity through advanced planning tools. Thanks to ROMI's weeding robot, farmers will save 25 percents of their time. This land robot will also acquire detailed information on sample plants and will be coupled with a drone that acquires more global information at crop level. Together, they will produce an integrated, multi-scale picture of the crop development that will help the farmer monitor the crops to increase efficient harvesting. For this, ROMI will have to adapt and extend state-of-the-art land-based and air-borne monitoring tools to handle small fields with complex layouts and mixed crops. To achieve this, we will: (i) develop and bring to the market an affordable, multi-purpose, land-based robot, (ii) develop a weeding app for this robot that is adapted for organic microfarms, (iii) apply advanced 3D plant analysis and modelling techniques to in-field data acquisition, (iv) integrate these analysis techniques in the robot for detailed plant monitoring, (iv) integrate these techniques also in aerial drones for multi-scale crop monitoring, (v) extend the robot with novel, adaptive learning techniques to improve sensorimotor control of the plant monitoring app, and (vii) test the effectiveness of our solution in real-world field conditions.

8.3 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 6.1.2 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 ambition of the new ADT project, designed in synergy with the partners from the Inria Défi Navicope, is to propose a complete ecosystem for the study of dynamical biological systems. It will focus

on the possibility to conceive intuitively both analysis and modelling pipelines in the main Gnomon application, to use those pipelines to batch-process datasets with distributed computation, relying on the technical solutions developed in the BioImage-IT project, and to interact with the resulting objects through the web-based 3D+t browser MorphoNet, both projects being supported by Naviscope. 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

Inria IPL - Naviscope (2018-2022)

Participants: Guillaume Cerutti, Emmanuel Faure *(External Collaborator)*, , Christophe Godin, Jonathan Legrand, Grégoire Malandain *(External Collaborator)*, Manuel Petit.

In this project, we plan to develop original and cutting-edge visualization and navigation methods to assist scientists, enabling semi-automatic analysis, manipulation, and investigation of temporal series of multi-valued volumetric images, with a strong focus on live cell imaging and microscopy application domains. We will build Naviscope upon the strength of scientific visualization and machine learning methods in order to provide systems capable to assist the scientist to obtain a better understanding of massive amounts of information. Such systems will be able to recognize and highlight the most informative regions of the dataset by reducing the amount of information displayed and guiding the observer attention. Finally, we will overcome the technological challenge of gathering up the software developed in each team to provide a unique original tool for users in biological imaging, and potentially in medical imaging.

ANR Cell Whisper (2020 - 2023)

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 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,
- Ecole Polytechnique, Saclay
- University of Singapour (Yuchen Long)

MITI - MISGIVING (2019 - 2020)

Participants: Romain Azaïs.

The diving performance of lung-breathing vertebrates, such as seabirds, can be quantified using measurement devices equipped on animals that allow us to reconstruct their activity at sea. During a classic dive, diving animals are faced with a dilemma: on the one hand, they want to optimize the time spent in contact with prey and therefore increase the time spent in diving; but, on the other hand, they are forced to return to the surface to breathe and will want to minimize this duration which remains however constrained by physiological rules. In addition, the dives are gathered in sequences because the prey are generally grouped in patches. In this project, we propose to use specific mathematical models to understand the complexity of the multi-scale decision processes that condition not only the optimal duration of the dive but also dives within a bout and therefore the total duration of the bout.

Partners:

- Centre d'Etudes Biologiques de Chizé
- Inria team CQFD in Bordeaux

9 Dissemination

Participants: Olivier Ali, Romain Azaïs, Christophe Godin, Florian Ingels.

9.1 Promoting scientific activities

9.1.1 Journal

Member of the editorial boards

- Olivier Ali: Review editor for Frontiers in Plant Science, section plant biophysics and modeling.
- Christophe Godin: Associate editor for Frontiers in Plant Science, section plant biophysics and modeling and Review editor for Plant Systems and Synthetic Biology.

Reviewer - reviewing activities

- Olivier Ali has conducted a review for Cell Report.
- Romain Azaïs has conducted several reviews for ICLR 2021 (International Conference on Learning Representations).
- Christophe Godin has been a reviewer for the journals: PNAS, Plant Research Journal and New Phytologist.

9.1.2 Invited talks

- Olivier Ali:
  - Invited speaker at the Cambridge Morphogenesis Seminar series (March 1st 2021). The event was held online.
  - Invited speaker at the Cell and Tissue Hydraulics Mini-Symposium organized by the Mechanobiology Insititute of the National University of Singapore (20-22 October 2021). The event was held online.
- Christophe Godin:
  - Keynote speaker at the 22nd autumn school in mathematical biology, UNAM, Mexico.
  - Keynote speaker at the kickoff meeting of the national INRAe metaprogram DIGIT-BIO *Biologie numérique pour explorer et prédire le vivant*.
  - Invited speaker aux journées de la SFR QuaSav, Angers, France.

9.1.3 Scientific expertise

- Olivier Ali was an expert for the French National Agency of Research (ANR).
- Romain Azaïs was an expert for the French National Agency of Research (ANR).
- Christophe Godin was
  - a member of the International Scientific Advisory Committee of the Plant Phenotyping and Imaging Research Centre (P2IRC), Saskatchewan, Canada.
  - member of the scientific council of the Biology and Plant adaptation department at INRAe (43 units, 14 centres, 1150 permanent staff).
  - the external member of the evaluation committee of Dr. James Locke's group at the Sainsbury Lab Cambridge, UK.

9.1.4 Research administration

- Olivier Ali is a member of the Conseil d'Analyse Numérique (CAN) of the UMS Bioscience at ENS Lyon.
- Christophe Godin is:
  - a member of the Comité des projets du centre Inria Grenoble-Rhône Alpes
  - a member of the Conseil de Direction of the RDP Lab.

9.2 Teaching - Supervision - Juries

9.2.1 Teaching

- Christophe Godin:
  - Organization with Patrick Lemaire and Gregoire Malandain of a one day session on imaging and quantitative biology at the winter school 'Cell Dynamics in Developmental Systems', coordinated by Patric Charnay, ENS.
  - Master class Sysbio, U. de Lyon: A journey in Phyllotaxis. coord O. Gandrion (2h).
  - Master class 'Les plantes dans tous leurs états' for non-specialists, ENS de Lyon: Phyllotaxis. Coord A. Vialette (2h).
- Florian Ingels:
  - Travaux dirigés: Optimisation (L3 Informatique)
  - Travaux dirigés: Algorithmique Numérique (L3 Informatique)
  - Travaux dirigés: Optimisation et Recherche Opérationnelle (M1 Informatique)

9.2.2 Supervision

- Olivier Ali: Master2 (6 months): Elsa Gascon, Insa Lyon, characterization of cell junction formation during cytokinesis in *Arabidopsis thaliana* root meristem.
- Christophe Godin: Master2 (6 months): Landry Duguet, Insa Toulouse. Canalization can explain dynamic auxin accumulation in the shoot apical meristem.

9.2.3 Juries

- Olivier Ali:
  - Member of the jury for the evaluation of a practical course on computational modeling for developmental biology (Licence 3 Biology ENS Lyon).
  - Member of the jury for Master (1 & 2) internship defenses for the ENS Lyon Biosciences Master.
  - Reviewer for Master (1 & 2) internship reports for the ENS Lyon Biosciences Master.
  - Member of the jury for the attribution of PhD grants for the *IADOC* program of the Université De Lyon (UDL).
  - Member of the thesis supervisory committee of Rawen Ben Malek (supervisor: Grégory Mouille and Alain Tissier) for the graduate school 567 (Sciences du Végétal) of Université Paris-Saclay.
- Romain Azaïs was a member of the thesis supervisory committee of Bartholomé Vieille, Ph.D. student at INRAE Avignon.
- Christophe Godin:

- Chair of the Jury of recruitment of CRCN/ISFP researchers for The Inria Grenoble-Alpes center.
- Vice-Chair of the Jury for the recruitment of a Professor position at ENS de Lyon.
- Chair of the PhD thesis jury of Clément Douarre (U. Lyon),
- Chair of the PhD thesis jury of M. Boukhana (U. Strasbourg)
- Reviewer of Marion Gauthier PhD thesis (U. Paris-Saclay),
- Reviewer of Simon Rouet PhD thesis (2021, Université de Poitiers)
- Member of the thesis committee of Baptiste Tesson (ENS de Lyon)

9.3 Popularization

9.3.1 Articles and contents

- Christophe Godin (as a follow-up of the Science paper on cauliflower [9]:
  - Article in 'the Conversation' introducing the contents of the work presented in the paper to a wide audience.
  - Reportage-interview at France Region 3 (Juil 2021).
  - Interview on Instagram by ARTECHOUSE (ARTECHOUR Live Fractals: Art & Science) (Sept 2021).

9.3.2 Education

- Christophe Godin:
  - the Maths week with the french Lycée in Laos (on fractals in visio conference, 3h)
  - 2 hour seminar on phyllotaxis at the french Lycée in Laos (visio conference).
  - 'Captain' in the context of the National wide Declic program, Citée Scolaire internationale de Lyon (3h)

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] 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.

[3] 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.

[4] 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.

[5] 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.

[6] 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.

[7] 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

[8] R. Azaïs, S. Ferrigno and M.-J. Martinez. 'cvmgof: an R package for Cramér-von Mises goodness-of-fit tests in regression models'. In: *Journal of Statistical Computation and Simulation* (24th Oct. 2021). DOI: 10.1080/00949655.2021.1991346. URL: https://hal.archives-ouvertes.fr/hal-03101612.

[9] 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.

[10] F. Gacon, C. Godin and O. Ali. 'BVPy: A FEniCS-based Python package to ease the expression and study of boundary value problems in Biology.' In: *Journal of Open Source Software* 6.59 (Mar. 2021), pp. 1–6. DOI: 10.21105/joss.02831. URL: https://hal.inria.fr/hal-03175968.

[11] E. Hernandez-Lagana, G. Mosca, E. Mendocilla-Sato, N. Pires, A. Frey, A. Giraldo-Fonseca, C. Michaud, U. Grossniklaus, O. Hamant, C. Godin, A. Boudaoud, D. Grimanelli, D. Autran and C. Baroux. 'Organ geometry channels reproductive cell fate in the Arabidopsis ovule primordium'. In: *eLife* 10 (7th May 2021). DOI: 10.7554/eLife.66031. URL: https://hal.archives-ouvertes.fr/hal-03533741.

[12] Y. Refahi, A. Zardilis, G. Michelin, R. Wightman, B. Leggio, J. Legrand, E. Faure, L. Vachez, A. Armezzani, A.-E. Risson, F. F. Zhao, P. Das, N. Prunet, E. M. 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.

[13] T. Vernoux, F. Besnard and C. Godin. 'What shoots can teach about theories of plant form'. In: *Nature Plants* 7.6 (7th June 2021), pp. 716–724. DOI: 10.1038/s41477-021-00930-0. URL: https://hal.archives-ouvertes.fr/hal-03393502.

Conferences without proceedings

[14] A. Chaudhury, P. Hanappe, R. Azaïs, C. Godin and D. Colliaux. 'Transferring PointNet++ Segmentation from Virtual to Real Plants'. In: CVPPA-ICCV. Montreal, Canada, 11th Oct. 2021. URL: https://hal.archives-ouvertes.fr/hal-03540304.

Scientific book chapters

[15] J.-L. Dinh, C. Godin and E. Azpeitia. 'Introduction to to Computational Modeling of Multicellular Tissues'. In: *Plant Systems Biology*. Vol. 2395. Methods in Molecular Biology. Springer New York, 26th Nov. 2022, pp. 107–145. DOI: 10.1007/978-1-0716-1816-5_7. URL: https://hal.archives-ouvertes.fr/hal-03533746.

Reports & preprints

[16] R. Azaïs and B. Henry. *Maximum likelihood estimation for spinal-structured trees*. 14th Jan. 2021. URL: https://hal.archives-ouvertes.fr/hal-03109867.

[17] A. Creff, O. Ali, V. BAYLE, G. Ingram and B. Landrein. *Endosperm turgor pressure both promotes and restricts seed growth and size*. 14th Nov. 2021. DOI: 10.1101/2021.03.22.436392. URL: https://hal.archives-ouvertes.fr/hal-03427685.

[18] F. Ingels and R. Azaïs. *Enumeration of Unordered Forests*. 17th Dec. 2021. URL: https://hal.archives-ouvertes.fr/hal-02511901.

[19] F. Ingels and R. Azaïs. *Isomorphic unordered labeled trees up to substitution ciphering*. 17th May 2021. URL: https://hal.archives-ouvertes.fr/hal-03227196.

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[20] R. Azaïs, A. Genadot and B. Henry. 'Inference for conditioned Galton-Watson trees from their Harris path'. In: *ALEA : Latin American Journal of Probability and Mathematical Statistics* 16.1 (2019), pp. 1–45. DOI: 10.30757/ALEA.v16-21. URL: https://hal.archives-ouvertes.fr/hal-01360650.

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[23] A. Chaudhury, F. Boudon and C. Godin. '3D Plant Phenotyping: All You Need is Labelled Point Cloud Data'. In: *CVPPP-ECCV 2020 - Workshop on Computer Vision Problems in Plant Phenotyping*. Glasgow, United Kingdom, Aug. 2020, pp. 1–17. URL: https://hal.archives-ouvertes.fr/hal-03030004.

[24] A. Chaudhury and C. Godin. 'Skeletonization of Plant Point Cloud Data Using Stochastic Optimization Framework'. In: *Frontiers in Plant Science* 11 (June 2020). DOI: 10.3389/fpls.2020.00773. URL: https://hal.archives-ouvertes.fr/hal-03029993.

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[27] 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.

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[31] 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.

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