RESEARCH CENTRE

Grenoble - Rhône-Alpes

IN PARTNERSHIP WITH:

CNRS, Ecole normale supérieure de Lyon, INRAE

2020 ACTIVITY REPORT

Project-Team MOSAIC

MOrphogenesis Simulation and Analysis In siliCo

DOMAIN

Digital Health, Biology and Earth

THEME

Computational Biology

Contents

Project-Team MOSAIC 1

1 Team members, visitors, external collaborators 2

2 Overall objectives 3

3 Research program 3
3.1 Axis 1: Representation of biological organisms and their forms *in silico* . . . 3
3.2 Axis 2: Data-driven models of form development . . . 4
3.3 Axis 3: Plasticity and robustness of forms . . . 4
3.4 Key modeling challenges . . . 4
3.5 A new paradigm for modeling tree structures in biology . . . 4
3.6 Efficient computational mechanical models of growing tissues . . . 5
3.7 Realistic integrated digital models . . . 5
3.8 Development of a computational environment for the simulation of biological form development . . . 5

4 Application domains 5

5 Highlights of the year 5

6 New software and platforms 6
6.1 New software . . . 6
6.1.1 bvpy . . . 6
6.1.2 cellcomplex . . . 6
6.1.3 cvmgof . . . 7
6.1.4 draco_stem . . . 7
6.1.5 Gnomon . . . 8
6.1.6 MorphoNet . . . 8
6.1.7 TimageTK . . . 9
6.1.8 treex . . . 9

7 New results 10
7.1 Dynamical characterization of morphogenesis at cellular scale . . . 10
7.2 Reconstruction of macroscopic forms from images and characterization of their variability 12
7.3 Analysis and simulation of tree data . . . 13
7.4 Mechanics of tissue morphogenesis . . . 15
7.5 Signaling and transport for tissue patterning . . . 17
7.6 Regulation of branching mechanisms in plants . . . 18
7.7 Miscellaneous . . . 19

8 Partnerships and cooperations 19
8.1 Participation in other international programs . . . 19
8.2 International research visitors . . . 20
8.2.1 Visits of international scientists . . . 20
8.3 European initiatives . . . 20
8.3.1 FP7 & H2020 Projects . . . 20
8.4 National initiatives . . . 21
8.4.1 Inria ADT - Gnomon (2018-2020) . . . 21
8.4.2 Inria IPL - Naviscope (2018-2022) . . . 21
8.4.3 ANR Cell Whisper (2020 - 2023) . . . 21
8.4.4 MITI - MISGIVING (2019 - 2020) . . . 22
8.5 Regional initiatives . . . 22
8.5.1 IDEX Lyon Impulsion - MecaField (2019 - 2020) . . . 22

9 Dissemination **22**
9.1 Promoting scientific activities . . . 22
9.1.1 Scientific events: organisation . . . 22
9.1.2 Scientific events: selection . . . 23
9.1.3 Journal . . . 23
9.1.4 Invited talks . . . 23
9.1.5 Leadership within the scientific community . . . 23
9.1.6 Scientific expertise . . . 23
9.1.7 Research administration . . . 23
9.2 Teaching - Supervision - Juries . . . 23
9.2.1 Teaching . . . 23
9.2.2 Supervision . . . 24
9.2.3 Juries . . . 24
9.3 Popularization . . . 25
9.3.1 Internal or external Inria responsibilities . . . 25
9.3.2 Articles and contents . . . 25
9.3.3 Education . . . 25
9.3.4 Interventions . . . 25

10 Scientific production **25**
10.1 Publications of the year . . . 25
10.2 Cited publications . . . 26

Project-Team MOSAIC

Creation of the Project-Team: 2018 January 01

Keywords

Computer sciences and digital sciences

A3.4. – Machine learning and statistics

A6.1. – Methods in mathematical modeling

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

A6.3. – Computation-data interaction

A6.5. – Mathematical modeling for physical sciences

A7.1. – Algorithms

A8.1. – Discrete mathematics, combinatorics

A8.2. – Optimization

A8.3. – Geometry, Topology

A8.7. – Graph theory

A9.2. – Machine learning

Other research topics and application domains

B1.1.2. – Molecular and cellular biology

B1.1.3. – Developmental biology

B1.1.7. – Bioinformatics

B1.1.8. – Mathematical biology

B1.1.9. – Biomechanics and anatomy

B1.1.10. – Systems and synthetic biology

B1.1.11. – Plant Biology

B3.5. – Agronomy

B9.1.2. – Serious games

B9.5.1. – Computer science

B9.5.2. – Mathematics

B9.5.5. – Mechanics

B9.5.6. – Data science

1 Team members, visitors, external collaborators

Research Scientists

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

Post-Doctoral Fellows

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- Bruno Leggio [École Normale Supérieure de Lyon, until May 2020]

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- Florian Ingels [Inria]
- Katia Mirande [Inria]
- Manuel Petit [Inria]
- Anne Schneider [Unemployed, until Feb 2020]

Technical Staff

- Guillaume Cerutti [Institut national de recherche pour l'agriculture, l'alimentation et l'environnement, Engineer]
- Florian Gacon [Inria, Engineer, until Oct 2020]
- Jonathan Legrand [CNRS, Engineer]

Administrative Assistant

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Visiting Scientist

- Salah Eddine Habibeche [Bourse PROFAS B+ Ambassade France en Algér, until Oct 2020]

External Collaborators

- Arezki Boudaoud [École Normale Supérieure de Lyon, HDR]
- Frederic Boudon [Centre de coopération internationale en recherche agronomique]
- Emmanuel Faure [CNRS]
- Franck Hétroy-Wheeler [Univ de Strasbourg, HDR]
- Patrick Lemaire [CNRS, HDR]
- François Parcy [CNRS, HDR]
- 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.

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.

[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.

3.2 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?

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.

3.5 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.

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

3.6 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.

3.7 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.

3.8 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

- **Shouting or whispering: The embryonic cell dilemma, [6].** In this work, published in July and which results from a long-standing collaboration with the groups of Patrick Lemaire and Grégoire Malandain, we identified a new mechanism by which cells get their fates in living tissues during embryonic development. As cells divide, they take on increasingly precise roles in the body. Epidermal cells, muscular or neuronal, the different cell types that make up the embryo emerge little by little from a very fine orchestration of the positions of the cells, coordinated by the signals they exchange with each other. Like us, the cells "talk" to each other to make decisions.

  See also: Video, New York Times article, Le Monde article (in French).

- **Temporal integration of auxin information for the regulation of patterning, [4].** Several members of the team were involved in this article published in May 2020 in the biology journal eLife. It

finalizes a work that spanned over 6 years and lead to a novel view of key signaling mechanisms underlying plant organogenesis in the shoot apices, evidenced through an innovative computational pipeline for quantitative image analysis with cellular and subcellular resolution.

6 New software and platforms

6.1 New software

6.1.1 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.

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

Authors: Florian Gacon, Olivier Ali, Christophe Godin

Contact: Olivier Ali

6.1.2 cellcomplex

Name: cellcomplex

Keywords: Polyhedral meshes, 3D

Functional Description: The cellcomplex library is a Python library that allows manipulating 2D or 3D multicellular complexes, with the study of plant tissues as a main application. It is mostly structured around a data structure that is used to represent such complexes as incidence graphs of dimension 2 or 3, and provides several key functionalities:

* The creation of structures from more basic representation (polygons of points for instance), from some geometrical primitives (2D or 3D) and the generation of synthetic regular or irregular grids, allowing notably the simulation of tissues.

* The computation of topological and geometrical properties on the multicellular complex structures, including notably useful computations on triangle meshes, a specific case of complexes with simplicial faces (areas, normals, triangle eccentricity, curvature estimator).

* The edition of structures by local topological operations, notably in th case of triangle meshes (edge flip, subdivision, vertex insertion) and multi-criteria geometrical optimization processes and isotropic remeshing.

* The import and export in various standard file formats for geometries (.obj, .ply, .msh) and notably in the standard formad defined by the community of plant tissue modelling (PLY, Saisnbury Computational Workshop 2015).

Release Contributions: * Major restructuration involving a change of namespace and a simplification of module architecture. * Inclusion of 3D visualization functionalities based on VTK.

Contact: Guillaume Cerutti

Participant: Guillaume Cerutti

6.1.3 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 Preprint available on HAL since Jan 7 2021

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

Publication: hal-03101612v1

Contacts: Sandie Ferrigno, Romain Azais

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

6.1.4 draco_stem

Name: DRACO-STEM : Dual Reconstruction by Adjacency Complex Optimization & SAM Tissue Enhanced Mesh

Keywords: Meshing, Image segmentation, Computational biology, Optimization

Functional Description: Draco-stem provides a computational pipeline that allows going from multi-label segmented images of living tissue (typically resulting from a watershed segmentation of 3D microscopy image stacks) to topologically consistent, FEM-ready triangular meshes of all cell interfaces in the tissue.

It relies on an original topological optimization method that aims at reconstructing the simplicial complex of cellular adjacencies from the image, and on dualization and geometrical optimization to obtain a triangle mesh that satisfies simultaneously several quality criteria (triangle regularity, adequation to image, biological priors). The library provides implementations for 3D tissue reconstruction, single-layer 2.5D reconstruction and advanced 2D reconstruction.

Release Contributions: * Added a new reconstruction method : GRIFONE. This method relies on the extraction of vertices representing topological elements (cell interfaces, cell edges and cell vertices) from the image and their identification by a cell tuple. The algorithms connects this vertices by triangular faces in order to produce a topologically valid cellular complex.

URL: https://gitlab.inria.fr/mosaic/draco_stem.git

Publication: hal-01573521

Contact: Guillaume Cerutti

6.1.5 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 introduces a new major functionality: the generation of a pipeline on-the-fly. Based on the interactions within the application, algorithmic bricks are automatically connected by their inputs and outputs as the users perform their analysis. The resulting pipeline is then displayed as a workflow graph, which can be exported as a configurable Python script to be replayed outside the application.

Contacts: Guillaume Cerutti, Christophe Godin

Participants: Olivier Ali, Frédéric Boudon, Guillaume Cerutti, Florian Gacon, Christophe Godin, Jonathan Legrand, Grégoire Malandain

6.1.6 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

Contacts: Emmanuel Faure, Bruno Leggio

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

6.1.7 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

Contacts: Jonathan Legrand, Grégoire Malandain, Guillaume Cerutti, Christophe Godin

6.1.8 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). The subtree kernel has been released to accompany an article submitted to Journal of Machine Learning Research. In addition, the DAG class and the kernel class have been extensively redesigned to be more user-friendly.

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, Bruno Leggio, Jonathan Legrand, Patrick Lemaire *(External Collaborator)*, , 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. An example of the former category is how to characterize and follow the change of shape of cells within tissues and of tissues within organs, and how to couple this change with, for instance, gene expression dynamics; an illustration of the latter is how to define cell-scale variability of morphogenesis within and between species.

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

Robustness of ascidian embryonic development. The image segmentation pipeline ASTEC developed by the team in collaboration with the Inria Morpheme project-team in Sophia Antipolis and the CRBM team in Montpellier, allows the 3D reconstruction and tracking of each cell during early ascidian embryogenesis. This method allowed us to reconstruct over 50 ascidian embryos, both wild-type and mutants. Exploiting this large database and the fixed cellular lineage of ascidian embryos, we extracted and compared geometrical and topological cellular properties. This allowed us to compare the intra-embryonic (left/right) to the inter-embryonic level of variability of several properties, including cell volume, cell-cell contacts and the structure of the tree seeded by each cell. This study demonstrated that the genetic-induced variability is comparable to the stochastic one, quantitatively showing that ascidian embryonic development is highly canalized, and that the high reproducibility of shapes observed during embryogenesis is rooted in the robustness of cellular geometry and topology.

To look for the origin of this canalisation, we developed a mathematical model exploiting our quantitative geometric database and the previously-existing ascidian genetic database ANISEED. This model suggests that the main driver of ascidian development is the cell-cell communication mediated by direct physical contact, and hence dependent of the area-of-contact between neighbouring cells. This means that the robustness of cell topology and geometry is necessary for cell-cell biochemical interactions to give rise to the correct fate restriction events, which in turn we showed to be responsible for major changes of embryo geometry. We also tested and validated this feedback loop between cell contacts, fate restriction events and embryonic geometry predicted by the model by manipulations and mutations induced in ascidian embryos.

These results are reported in an article published in Science [6].

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 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 [19].

By evaluating cell accuracy, but also 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 is being created to make this segmentation evaluation framework publicly available, and a paper is being written which should result in a publication in 2021. 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 [6], 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 [19, 21] 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. However, the local scale of the overlap measure makes the iterative procedure prone to being trapped in local minima. In order to overcome this issue, we are currently developing a global graph-base tracking method based on optimal flow algorithm.

The methods developed in the context of this work are being included in a new Python library, built upon *TimageTK*, allowing tracking and analysis of large number of cells. This work is part of the Inria Défi Naviscope.

Cells spatio-temporal properties and population statistics. Over the past few years, we have achieved quantitative characterization of some of the cells physical properties, such as volumes or curvatures. Together with the robust cell lineaging described earlier, it also enables the quantification of temporal properties at cellular scale such as volumetric growth rate or strain patterns. To structure this data, we have implemented a dedicated spatio-temporal graph structure, formalizing the cell network and its changes over time.

To further characterize the tissue growth, we developed a method to combine a selection of cellular features into a pairwise distance matrix, including topology. This later enables the use of hierarchical clustering methods to identify cellular patterns. Since such data are highly structured, both in time and space, we developed two complementary approaches:

- space oriented: this approach uses the cell neighborhood and a selection of cell descriptors to create pairwise distance maps, later clustered by a distance-based method, such as Ward's hierarchical clustering.
- time oriented: this approach uses the lineage forest and a selection of cell descriptors to infer cell identities using Hidden Markov Tree (HMT) models.

Both approaches allow later characterization of the detected cluster or groups of cells based on their properties, and the first one should be published in 2021. The clustering method, as well as the cell features quantification tools are made available in the *TimageTK* package.

Information propagation and cell-scale atlases of development. 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 developement of a floral meristem of *Arabidopsis thaliana* for instance, we used specific methods to chose a representative flower template, on which the spatio-temporal expression patterns of 27 genes was then introduced manually.

Even though the automatic building of a cellular template remains a challenging task, 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 time-lapses sequences [21], we develop methods that use the geometry of an organ to propagate genetic information across several individuals. A proof-of-concept has been implemented and tested on simple sythetic data as well as on floral meristem images. It relies on volume overlapping between the cells in images to perform a lossless transfer of information between individuals. Improvement and validation of this approach are currently performed on a larger set of experimental data, and should be published in 2021.

This work is part of the Inria Défi Naviscope.

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

Participants Ayan Chaudhury, Christophe Godin, 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 modelling 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 internodes, 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;
- plant structure reconstruction by means of skeleton extraction;
- organs and plant structure identification by means of trained CNN segmentation.

This work is part of the *ROMI* project.

In collaboration with the ROMI partners from Sony CSL, Paris, we are developping 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 Interoperabile 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 dataset 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 evalutate 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 to provide validation data for the pipeline. The generative model of *Arabidopsis thaliana* is based on Lpy and is an available technology developed by Christophe Godin. 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 engins (Blender). Ultimately, this will be used in a virtual scanner, reproducing the behavior of the real scanner, to generate dataset 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.

7.3 Analysis and simulation of tree data

Participants Romain Azaïs, 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 and blood vessels 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 2020, 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 from incremental computations. These very promising results, both in terms of theoretical and computational aspects, should result in a paper submitted early in 2021.

- 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.

- 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 result should lead to a paper in the first semester of the next year.

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 [16], 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 [16]. 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. This year, 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 [14].

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 [15] and was presented in an international conference [11].

Simulating 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 work will be published in 2021.

7.4 Mechanics of tissue morphogenesis

Participants Olivier Ali, Arezki Boudaoud *(External Collaborator)*, , Guillaume Cerutti, Ibrahim Cheddadi *(External Collaborator)*, , Florian Gacon, Christophe Godin, Bruno Leggio, Jan Traas *(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*)

As deformations supporting morphogenesis require the production of mechanical work within tissues, the ability to simulate accurately the mechanical behavior of growing living tissues is a critical issue 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 active building blocks out of equilibrium (namely cells) offers genuine modeling challenges and opportunities. Integrating cellular behaviors such as mechano-sensitivity, intercellular fluxes of materials and cell division into a macroscopic mechanical picture of morphogenesis is the topic of this section.

Flattening mechanism during organogenesis in plants. Many plant species have thin leaf blades and axisymmetric elongating organs, such as stems and roots. From a morphoelastic perspective, such complex shapes are currently believed to emerge from the coordination between strain-based growth and stress-based stiffening at the cellular level.

To study the plausibility of such an hypothesis, we conducted numerical simulations where both a stress-based stiffening mechanism of cell walls [22] and a strain-based growth mechanism [17] have been implemented. We performed such simulations on multicellular and multilayered ellipsoidal structures and track their aspect ratio as they developed under various parametrization sets. Our results, in accordance with experimental measurements conducted simultaneously by biologist colleagues, showed that: (i) Stress-based stiffening was mandatory to grow flat and axisymmetric organs; (ii) in order to grow flat structures, stress-based stiffening should only be active on anticlinal inner walls.

This work was part of Jan Traas's ERC grant *Morphodynamics*. This work has been published in Current Biology [8].

Influence of cell division during flat organogenesis in plants. One key limitation of our 3D modeling approach is the lack of cell division implementation. This is a major flaw in our understanding of flattening since cell divisions, by increasing the number of load bearing walls, impact significantly the redistribution of mechanical stresses within the tissue.

To alleviate this limitation, we derived a 2D vertex-based model from the 3D one described above. This 2D model encompasses the same biophysical processes as the 3D one, augmented with cell division. We used this 2D framework to investigate the flattening dynamics of structures mimicking ellipsoid cross sections of growing organs. We were able to show that heterogeneity in the division rule between the epidermis and the inner tissues led to the more efficient flattening process and that a stress-based division rule was the most efficient to produce flat structure.

This analysis is part of the article [8] published this year in Current Biology.

Influence of mechanical stress anisotropy on the orientation of cell divisions in animal tissues. Tight regulation of cell division orientation is fundamental for tissue development. Recently, a great effort has been put into biophysical understanding of the *long-axis* division rules (Hertwig's rule for animal cells, Errera's rule for plant cells) and the systematic deviations from these rules observed *in vivo*. In both plants and animals, such deviations often correlate with anisotropic tensions within the tissue. To what extend these deviations are regulated or simply the result of stochasticity?

To address these questions in animal cells, we modeled theoretically and numerically cell division as an active process in a many-body system. We showed that under isotropic tension a cell's long axis emerges as the energetically optimal division orientation and that anisotropic stresses biased the energetics, leading to systematic deviations form Hertwig's rule. These deviations, as reported experimentally, are correlated to the main direction of stress anisotropy.

Our model successfully predicted division orientation distributions within two experimental systems: epidermis of the ascidian *Phallusia mammillata* (where deviations from Hertwig's rule have been so far eluding explanation) and of the pupal epithelium of the dorsal thorax of *D. melanogaster*.

This work was part of the *Digem* project. A paper preprint is available on bioRxiv [20].

Influence of water fluxes on plant morphogenesis. Since pressure appears as the "engine" behind growth-related deformation in Plants, its regulation by cells is a major control mechanis of morphogenesis.

We developed a 2D vertex-based model to investigate the morphological consequences of the interplay between cell expansion, water fluxes between cells and tissue mechanics. Combined with experiments conducted by biologist within our lab, this work demonstrated the anti-correlation between heterogeneities in turgor pressure and cell growth rate, a phenomenon new to the community. From a theoretical perspective it revealed the connection between the topology of the cell network and the regulation of the geometry of the corresponding tissue.

This work was part of the Agropolis fundation project *MecaFruit3D* and Arezki Boudaoud's ERC *PhyMorph*. The comparison between our model prediction and experimental measurements has been published this year in Current Biology [7].

This year, we have extended this hydraulic model [18] so that it includes now a finer description of apoplasmic flows (within the extracellular space), in parallel to symplasmic flows (directly between cells). A paper is in preparation on this topic. Thanks to that we will explore how the regulation of these two water pathways, as well as mechanical properties, relates to morphogenesis in the meristem.

Development of Fenics-based, high-level Finite Element library to estimate boundary-value problems on 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 a *Finite Element* python library, named *BVPy* and based on FEniCS (https://fenicsproject.org/) and *GMSH* (http://gmsh.info/).

Initially developed to compute mechanical equilibrium of living tissues, we extended the library to handle scalar and vector fields as well. In its current version, *BVPy* provides a high level API to define and resolve wide range of linear and non-linear Boundary-Value Problems as weel as Initial Boundary-Value Problems, on domains inspired by biological structures.

The library source code is fully accessible via the team gitlab page (https://gitlab.inria.fr/mosaic/bvpy). It is also available through the team conda channel (https://anaconda.org/mosaic/bvpy). The library is currently in review in the Journal of OpenSource Softwares (JOSS, https://github.com/openjournals/joss-reviews/issues/2831).

Cortical tension overrides geometrical cues to orient microtubules in confined protoplasts. In plant cells, cortical microtubules (CMTs) generally control morphogenesis by guiding cellulose synthesis. CMT alignment has been proposed to depend on geometrical cues, with microtubules aligning with the cell long axis in silico and in vitro. Yet, CMTs are usually transverse in vivo, i.e., along predicted maximal tension, which is transverse for cylindrical pressurized vessels. In [3], a microwell setup was adapted to test these predictions in a single-cell system. The protoplasts were confined laterally to impose a curvature ratio and modulated pressurization through osmotic changes. Using a combination of experiments and of mechanical models developed in the team, we showed that CMTs can be longitudinal or transverse in wallless protoplasts and that the switch in CMT orientation depends on pressurization.

7.5 Signaling and transport for tissue patterning

Participants Romain Azaïs, Guillaume Cerutti, 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*.

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 was part of the *BioSensors* HFSP project and gave rise to a journal article published in 2020 in eLife [4].

Automatic quantification of gibberelin signaling. Building upon the methodology developed in the previous project, 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, in order to evaluate its relationship with cell shape and growth features.

This work is part of an ongoing collaboration with the Signal team of the RDP and will be part of a publication to be submitted during the first half of 2021.

Theoretical modelling of self-organization in plants. The fact that in plants, lateral organs robustly form strikingly symmetric patterns (phyllotaxis), despite various sources of internal or external variability, illustrates the fundamental question of robustness in developmental biology. Part of the answer relies on the notion of developmental constraints: at any stage of development, morphogenetic processes are constrained to operate within the context of the current organism being built. One such universal constraint is the shape of the organism itself, which progressively channels the development of the organism toward its final shape. Through mathematical modelling, it can be argued that the spiral patterns in plants are progressively canalized from local interactions of nascent organs. The relative uniformity of the organogenesis process across all plants then explains the prevalence of certain patterns in plants, i.e. Fibonacci phyllotaxis.

This modelling work is a collaboration with Christophe Golé (Smith College, MA, USA), and Stéphane Douady (CNRS, U. Paris-Diderot) and led to a journal article [5].

7.6 Regulation of branching mechanisms in plants

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

- 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 is 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 first model of the control of floral initiation by genes, 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 normal and the fractal-like Romanesco. A paper reporting this work is currently under review.

7.7 Miscellaneous

Participants Romain Azaïs, Bruno Leggio.

Measurements and statistics in quantum mechanics. One interesting line of research deals with the application of parameter-estimation techniques for piecewise deterministic Markov processes (PDMP), developed by members of the team, to the special case of quantum dynamics: under certain conditions, the evolution of an open quantum system can be described as a PDMP, with a specific and non-trivial structure marking its departure from classical behaviour. We show [12] that approaches to appraise parameter values of the evolving systems, developed in the context of classical dynamics, can be successfully applied to the specific case of quantum systems.

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 preprint [13], 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 Participation in other international programs

ERA-CAPS Genes2shape (2018 - 2021)

Participants Guillaume Cerutti, Christophe Godin, Anuradha Kar, Bruno Leggio, 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 International research visitors

8.2.1 Visits of international scientists

- Salah Eddine Habibeche is a PhD student supervised by Farah Ben Naoum from the University of Sidi Bel Abbes (Algeria) and Christophe Godin, with co-supervision from Romain Azais. The PhD subject of Salah consists of developing compressing schemes for semi-ordered trees. During his visit in 2020 (1 year), Salah studied methods of tree compression with loss of information. This work should lead to a joint publication in 2021.

8.3 European initiatives

8.3.1 FP7 & H2020 Projects

H2020 - ROMI (2017-2022)

Participants Romain Azais, Ayan Chaudhury, Christophe Godin, Florian Ingels, 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.

8.4 National initiatives

8.4.1 Inria ADT - Gnomon (2018-2020)

Participants Olivier Ali, Romain Azaïs, Guillaume Cerutti, Florian Gacon, Christophe Godin, Jonathan Legrand, Grégoire Malandain *(External Collaborator)*, , Teva Vernoux *(External Collaborator)*.

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. 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.

Based on the past experience of the team with the OpenAlea platform, the goal of this ADT is to develop a more scalable software engineering solution based on the dtk kernel developed by the group of software engineers (SED) from the Sophia-Antipolis Inria Center.

Partners:

- SED Sophia Antipolis Inria Research Centre
- Morpheme Inria projec-team, Sophia Antipolis, France

8.4.2 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.

8.4.3 ANR Cell Whisper (2020 - 2023)

Participants Christophe Godin, Bruno Leggio, 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

8.4.4 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

8.5 Regional initiatives

8.5.1 IDEX Lyon Impulsion - MecaField (2019 - 2020)

Participants Christophe Godin, Bruno Leggio, Teva Vernoux *(External Collaborator)*.

In a previous work, we have shown that the coupling of mechanical and hydraulical descriptions in a 2D model of multicellular tissue growth induces the emergence of remarkable phenomena at tissue level. In particular, we have shown that the growth of an organ may induce a lateral inhibition surrounding the organ that prevents other organs to grow in its vicinity. The goal of this project is to estimate the hydraulic and mechanical parameters of such a model from confocal images of a growing SAM and to compare observations with the order of magnitude of the predicted inhibitory zones and of their amplitude at cellular resolution.

9 Dissemination

9.1 Promoting scientific activities

9.1.1 Scientific events: organisation

General chair, scientific chair

- Christophe Godin co-organized and co-chaired with Roeland Merks (U. Leiden), Mark Alber (U. Riverside, USA) et Philip Maini (U. Oxford, U.K.) a summer school at the Lorentz Center (Leiden, Netherlands) on Modeling shape and size in developmental biology (1 week online), 60 participants.

9.1.2 Scientific events: selection

Member of the conference program committees

- Christophe Godin was a member of the scientific committee of the IEEE International Conference on Functional-Structural Plant Modelling (FSPM 2020).
- Christophe Godin is a member of the Board of the FSPM conference since 2004.

9.1.3 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.
- Christophe Godin: Member of the editorial advisory board of the journal *In Silico Plants*.

Reviewer - reviewing activities

- Romain Azaïs: Computers and Electronics in Agriculture, NeurIPS 2020, ICML 2020, Mathematical Reviews.
- Olivier Ali: Biophysical Journal, European Physical Journal Plus.
- Christophe Godin: Journal of Plant Research, PNAS, Frontiers in Plant Sciences

9.1.4 Invited talks

- Romain Azaïs was invited to give a presentation at the 3rd congress of the French Mathematical Society (SMF) in Nancy (May 2020). The event was canceled because of the COVID-19 situation.

9.1.5 Leadership within the scientific community

9.1.6 Scientific expertise

- Romain Azaïs was an expert for the French National Agency of Research (ANR).
- Christophe Godin is a member of the International Scientific Advisory Committee of the Plant Phenotyping and Imaging Research Centre (P2IRC), Saskatchewan, Canada.
- Christophe Godin is a member of the scientific council of the INRAE department "Biologie et Adaptation de Plantes". (1134 employees, 42 research units in France).

9.1.7 Research administration

9.2 Teaching - Supervision - Juries

9.2.1 Teaching

- Olivier Ali:
  - Jury for the evaluation of a practical course on computational modeling for developmental biology (Licence 3 Biology ENS Lyon).

- Romain Azaïs:
  - Colles de mathématiques, CPGE PCSI, Lycée Jean Perrin, Lyon
  - Cours de Master 2 Apprentissage à partir de données arborescentes, Master Maths en Action, Université Lyon 1
- Christophe Godin:
  - Cours *Les plantes dans tous leurs états* pour non-specialistes, ENS de Lyon: *Phyllotaxis.* (2h).
  - Cours Master Sysbio, U. de Lyon: *A journey in Phyllotaxis.* (2h).
  - Lecture at the summer school from the Lorentz Center (Leiden, Netherlands) on Modeling shape and size in developmental biology (August 2020), 60 participants (3h). Supervision of modeling projects during the school week.
- Florian Ingels:
  - Séances de TD Algorithmique Numérique, Licence Informatique, Université Lyon 1
  - Séances de TD Optimisation, Licence Informatique, Université Lyon 1
  - Séances de TP Algorithmique et Programmation Récursive, Licence Informatique, Université Lyon 1
  - Séances de TD Techniques Mathématiques de Base, Licence Physique-Chimie-Science de l'Ingénieur, Université Lyon 1
  - Séances de TP Optimisation et Recherche Opérationnelle, Master Informatique, Université Lyon 1

9.2.2 Supervision

- PhD (2016 – 2020): Florine Greciet (IECL, Université de Lorraine and Safran). Régression polynomiale par morceaux pour la propagation de fissures. Supervisors: Anne Gégout-Petit (Inria team BIGS, IECL, Université de Lorraine) and Romain Azaïs. PhD thesis defended on January 22 2020.
- PhD in progress (2019 - 2022): Florian Ingels (MOSAIC, ÉNS de Lyon). Supervisors: Romain Azaïs, Christophe Godin.
- Katia Mirande PhD (2018-2021) Strasbourg University, co-supervision Franck Hetroy, Christophe Godin
- Anne Schneider PhD (2016-2020) Angers University, co-supervision Jesssica Bertheloot, Christophe Godin
- PhD in progress (2019 - 2022): Manuel Petit (MOSAIC, ENS de Lyon), co-supervision Christophe Godin, Grégoire Malandain, Guillaume Cerutti.
- Salah Habibeche (Université Sidi Bel Abbes), co-supervision Farah Ben Naoum, Romain Azais. Financement: Ministère Algérien de la Recherche (Bourse PROFAS +). Visite de 1 an dans l'équipe Mosaic en 2020.
- Master 2 (4 months): Margot Besseiche. Ecole Polytechnique. Deep learning strategies for detecting permutations in phyllotaxis sequences. Supervisor: Christophe Godin.

9.2.3 Juries

- Olivier Ali was president of an Inrae selection committee to hire an assistant engineer specialized in numerical simulations and image analysis.
- Romain Azaïs was a member (as a co-supervisor) of the PhD defense of Florine Greciet - Université de Lorraine, Nancy (January 2020).
- Christophe Godin was a member of a selection jury for a inter-department joint concours of Directeurs de Recherche at INRAE.

9.3 Popularization

9.3.1 Internal or external Inria responsibilities

- Christophe Godin was the Inria Ambassador at the French Science Festival 2020.

9.3.2 Articles and contents

- In collaboration with Patrick Lemaire, Christophe Godin produced a Video to illustrate the findings of Science paper for a large audience(see highlight of the year).

9.3.3 Education

9.3.4 Interventions

- Christophe Godin gave a seminar on Fractals for the maths week (march 2020) at the French Lycée in Laos in visio-conference (2h).

10 Scientific production

10.1 Publications of the year

International journals

[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] A. Chaudhury and C. Godin. 'Skeletonization of Plant Point Cloud Data Using Stochastic Optimization Framework'. In: *Frontiers in Plant Science* 11 (16th June 2020). DOI: 10.3389/fpls.2020.00773. URL: https://hal.archives-ouvertes.fr/hal-03029993.

[3] L. Colin, A. Chevallier, S. Tsugawa, F. Gacon, C. Godin, V. Viasnoff, T. Saunders and O. Hamant. 'Cortical tension overrides geometrical cues to orient microtubules in confined protoplasts'. In: *Proceedings of the National Academy of Sciences of the United States of America* 117.51 (2020), pp. 32731–32738. DOI: 10.1073/pnas.2008895117. URL: https://hal.archives-ouvertes.fr/hal-03063893.

[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] Y. LONG, I. Cheddadi, G. Mosca, V. Mirabet, M. Dumond, A. Kiss, J. Traas, C. Godin and A. Boudaoud. 'Cellular Heterogeneity in Pressure and Growth Emerges from Tissue Topology and Geometry'. In: *Current Biology - CB* 30.8 (Apr. 2020), 1504–1516.e8. DOI: 10.1016/j.cub.2020.02.027. URL: https://hal.archives-ouvertes.fr/hal-03029965.

[8] 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* (2020). DOI: 10.1101/604710. URL: https://hal.archives-ouvertes.fr/hal-02370615.

Conferences without proceedings

[9] Y. Boursiac, C. Pradal, F. BAUGET, S. Delivorias, M. Lucas, C. Godin and C. Maurel. 'Phenotyping and modeling of water transport in roots'. In: iCROPM 2020 - Satellite workshop : Phenotyping and modeling of plant anchorage and physiology. Montpellier, France, 3rd Feb. 2020. URL: https://hal.inrae.fr/hal-02935069.

[10] 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, 28th Aug. 2020, pp. 1–17. URL: https://hal.archives-ouvertes.fr/hal-03030004.

[11] F. Ingels and R. Azaïs. 'A Reverse Search Method for the Enumeration of Unordered Forests using DAG Compression'. In: Fourth International Workshop on Enumeration Problems and Applications. Online, France, 7th Dec. 2020. URL: https://hal.archives-ouvertes.fr/hal-03051733.

Scientific book chapters

[12] B. Leggio and R. Azaïs. 'Estimation of Piecewise-Deterministic Trajectories in a Quantum Optics Scenario'. In: *Statistical Topics and Stochastic Models for Dependent Data with Applications*. 2020. URL: https://hal.archives-ouvertes.fr/hal-02389225.

Reports & preprints

[13] R. Azaïs, S. Ferrigno and M.-J. Martinez. *cvmgof: an R package for Cramér-von Mises goodness-of-fit tests in regression models*. 7th Jan. 2021. URL: https://hal.archives-ouvertes.fr/hal-03101612.

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

[15] F. Ingels and R. Azaïs. *Enumeration of Unordered Forests*. 19th Mar. 2020. URL: https://hal.archives-ouvertes.fr/hal-02511901.

10.2 Cited publications

[16] 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.

[17] F. Boudon, J. Chopard, O. Ali, B. Gilles, O. Hamant, A. Boudaoud, J. Traas and C. Godin. 'A Computational Framework for 3D Mechanical Modeling of Plant Morphogenesis with Cellular Resolution'. In: *PLoS Computational Biology* 11.1 (Jan. 2015), pp. 1–16. DOI: 10.1371/journal.pcbi.1003950. URL: https://hal.archives-ouvertes.fr/hal-01142486.

[18] 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 (June 2019), e1007121. DOI: 10.1371/journal.pcbi.1007121. URL: https://hal.archives-ouvertes.fr/hal-02196768.

[19] 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.

[20] B. Leggio, J. Laussu, E. Faure, P. Lemaire and C. Godin. 'Multiscale mechanical model for cell division orientation in developing biological systems'. working paper or preprint. Nov. 2019. URL: https://hal.archives-ouvertes.fr/hal-02367600.

[21] 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.

[22] H. Oliveri, J. J. Traas, C. Godin and O. Ali. ‘Regulation of plant cell wall stiffness by mechanical stress: a mesoscale physical model’. In: *Journal of Mathematical Biology* (Sept. 2018), pp. 1–29. DOI: 10.1007/s00285-018-1286-y. URL: https://hal.inria.fr/hal-01691110.