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Activity Report 2019

Project-Team MOSAIC

MOrphogenesis Simulation and Analysis In siliCo

RESEARCH CENTER
Grenoble - Rhône-Alpes

THEME
Computational Biology

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Project-Team MOSAIC

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1. Team, Visitors, External Collaborators

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Samuel Teva Vernoux [CNRS, HDR]

2. Overall Objectives

2.1. 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.

[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.

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. Axis1: Representation of biological organisms and their forms in silico

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

3.2. Axis2: Data-driven models of form development

Our aim in this second research axis will be to develop models of physiological patterning and bio-physical 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. Axis3: 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.

3.4.1. A new paradigm for modeling tree structures in biology

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

3.4.2. Efficient computational mechanical models of growing tissues

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

3.4.3. Realistic integrated digital models

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

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

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

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

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

4. Highlights of the Year

4.1. Highlights of the Year

- MOSAIC has been promoted to Inria project-team in July 2019.
- In collaboration with CNRS (LIRMM and CRBM units in Montpellier), the team published a new web browser-based computational tool, Morphonet, to interactively explore complex 3D+time biological structures in silico, [8].

5. New Software and Platforms

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

- Participant: Guillaume Cerutti
- Contact: Guillaume Cerutti

5.2. draco_stem

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 FUNCTIONAL DESCRIPTION: * Major refactoring, python3 compatibility * Addition of Draco2D functionalities

- Contact: Guillaume Cerutti
- Publication: DRACO-STEM: An Automatic Tool to Generate High-Quality 3D Meshes of Shoot Apical Meristem Tissue at Cell Resolution
- URL: https://gitlab.inria.fr/mosaic/draco_stem.git

5.3. 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 FUNCTIONAL DESCRIPTION: A major technical update has been carried out on the Gnomon platform with the switch of the platform core to dtk2, implying an upgrade of all involved Python code to python 3.6+. The newer version 0.13 displays a clearer and more customizable interface and all functionalities from the version 0.9. In terms of functionalities, a major effort has been put on recovering former applications of the team (LPy and PlantGL) and including them in a robust way in the scope of the platform. A release of the version 1.0 is planned for early 2020 including validated algorithms for the quantitative analysis of 3D images of tissue, a much more robust user interface and an extensive user and developer documentation made available online.

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

5.4. 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.

- Partner: CRBM - Centre de Recherche en Biologie cellulaire de Montpellier
- Contact: Emmanuel Faure
- URL: http://www.morphonet.org

5.5. TimageTK

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.

- Contact: Jonathan Legrand
- URL: https://mosaic.gitlabpages.inria.fr/timagetk/index.html

5.6. 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 FUNCTIONAL DESCRIPTION: 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.

- Participants: Romain Azais, Guillaume Cerutti, Didier Gemmerle and Florian Ingels
- Contact: Romain Azais
- Publication: treex: a Python package for manipulating rooted trees
- URL: https://gitlab.inria.fr/azais/treex

6. New Results

6.1. 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], Florent Papini, 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:

Cell-scale atlases of development. One fundamental question linked to morphogenesis is at which level and timescale tissue or organ development is reproducible and stereotyped. To answer this question, variability must be quantitatively assessed. In the team we have created to this end two morphogenetic atlases: the atlas of gene expression patterns in the Arabidopsis thaliana flower development and the atlas of early embryonic development of the ascidian Phallusia mammillata.

Thanks to the invariant cellular lineage of early development of *P. mammillata* embryos and to 3D reconstruction of their development at cellular resolution, quantitative comparison of their properties from cell to tissue scale has been performed. After fluorescent membrane labelling, several embryos have been imaged for several hours by light-sheet microscopy. These images were then reconstructed through the segmentation pipeline ASTEC, which also automatically tracked each cell over several rounds of cell division. This large amount of data allowed us to create an atlas of geometrical and topological properties at cellular resolution, which gives unprecedented depth of information on the variability of ascidian development. In addition this atlas, coupled to previous knowledge on gene-expression dynamics from the ascidian genetic database (ANISEED), made it possible for us to develop a mathematical and computational model to explore the main drivers of early ascidian development, identified as area-of-contact-mediated cell-cell communications. This model was also validated by experimental manipulations and mutations induced in ascidian embryos. This work is currently under review [26].

On the other hand, developing digital atlases of organism or organs development is a complex challenge for organisms presenting a strong variability in the cellular layout. Indeed contrary to C. Elegans or P. mammillata, for instance, that posses a very strict cell lineage in early phases, the development of most plant organs is under the influence of robust genetic patterns without a unique cellular layout. In that respect, proposing a cell-based atlas of flower development for instance is not straightforward and specific methods have been developed to choose a representative examples of the developing Arabidopsis thaliana flower. Using this representative flower we have generated an atlas in which we have introduced manually the expression patterns of 27 genes. The knowledge generated by the creation of this atlas makes it possible to have a first quantitative (correlative) view on the relation between gene activity and growth.

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 methods 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 a paper which is currently under review [26].

Robust extraction and characterization of cellular lineages. The quantification of temporal properties at cellular scale such as volumetric growth rate or strain patterns relies extensively on the identification of cellular lineages in time-lapse acquisitions of living tissues. In the case of plant tissues where the deformations between two consecutive time points can be very important in post-embryonic morphogenesis processes such as early flower development, it remains a real challenge to compute those lineages automatically, and manual user annotation is generally required to produce reliable results.

Building on the previous expertise of the team [25], [28] and on the state-of-the-art computational library for image analysis, timagetk, developed in collaboration with the Morpheme team, we currently develop a set of robust automatic cell lineaging methods for cases ranging from small to highly non-linear deformations. In the course of a M2 internship and the first months of a starting PhD work (Manuel Petit), a first so-called “naive” lineaging method has been implemented and validated on synthetic data with limited deformations. Methods involving optimal flow algorithms on graph structures and iterative image registration are being developed to provide robust results in the case of faster growing tissues. The output of these methods will allow to use the tools developed by the team for the analysis of spatio-temporal properties of growing cells at a much larger scale. This work is part of the Inria IPL Naviscope.

Reconstruction of Arabidopsis ovule development. The ovule is a relatively simple organ, with limited developmental variability, which makes it an excellent case study for the computational modeling of organ development. Given the technical difficulty of producing live-imaging acquisition sequences of ovules, we developed a method to perform a spatial registration of multiple individual ovules at various developmental states and in different global poses. Using the global cylindrical symmetry of the organ and the surface curvature as a key geometrical feature, we aligned individuals on their main axes and on their junction with the underlying placental tissue. Jointly with the 3D segmentation of cells in images, this will allow to evidence

the invariant features of ovule development at cellular scale, and to study the robustness of the dynamics of the megaspore mother cell (MMC) across indivduals. This work was part of the Imago project.

6.2. 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 development, it is necessary to both develop digital reconstruction methods, typically based on image acquisitions, and statistical tools to define notions of distance or average between these forms. The automatic inference of computational representations of forms or organ traits from images of different types is therefore an essential step, for which the use of prior knowledge can be very beneficial. Realistic synthetic models of forms can guide the reconstruction algorithms and/or assess their performances. 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 and organ 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. In collaboration with the ROMI partners from Sony CSL, Paris, we develop an automated processing pipeline that involves the 3D reconstruction of plant architecture from RGB image acquisitions performed by a robot, and the segmentation of the reconstructed plant into organs. We aim at releasing both hardware schematics and the developed software for image reconstruction to be used as cheap open-source solution to phenotype plants. In addition, to provide validation data for the pipeline, we designed a generative model of *Arabidopsis thaliana* simulating the development of the plant architecture at organ scale. This model was used to develop the method for the measurement of angles of organs and test its accuracy:

- RGB images were generated from the model and used as input of the pipeline;
- a physical version of the model has been obtained using 3D printing techniques;

In both cases, 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

The developed reconstruction and quantification pipeline is not made from scratch but aggregate a number of available third party libraries and codes in addition to three active research topics: spectral clustering, skeleton extraction, and ML segmentation. In a second phase, the model will be used to generate training data for machine learning techniques introduced in the reconstruction methods. This work is part of the *ROMI* project.

6.3. Analysis 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 2019, 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.

Approximation of trees by self-nested trees. 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. One way to address this issue 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. In the team, we think that the class of self-nested trees, that are the most compressed trees by DAG compression scheme, is a good candidate to be such an approximation class.

In [11], we have proved the algorithmic efficiency of self-nested trees through different questions (compression, evaluation of recursive functions, evaluation of edit distance) and studied their combinatorics. In particular, we have established that self-nested trees are roughly exponentially less frequent than general trees. This combinatorics can be an asset in exhaustive search problems. Nevertheless, this result also says that one can not always take advantage of the remarkable algorithmic properties of self-nested trees when working with general trees. Consequently, our aim is to investigate how general trees can be approximated by simplified trees in the class of self-nested trees from both theoretical and numerical perspectives. In [3], we present two approximation algorithms that are optimal but assume that the approximation can be obtained by only adding vertices to the initial data (or by only deleting vertices from the initial data). In [11], we have developed a suboptimal approximation algorithm based on the height profile of a tree that can be used to very rapidly predict the edit distance between two trees, which is a usual but costly operation for comparing tree data in computational biology. Another algorithm based on the efficient simulation of conditioned random walks on the space of trees is currently under development. This work should result in the submission of a paper next year.

It should be noted that the aforementioned strategy and algorithms can only be applied to topological trees. In 2019, we also began a new project on approximation of trees with geometrical attributes on their vertices and with possibly a controlled loss of information during the compression.

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 [5], 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 [5]. 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. The conditioning is a source of bias that must be taken into account to build efficient estimators of the birth distribution. This work should be submitted to a journal next year.

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 [17] 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. This work was presented at a national conference [15].

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 forest of subtrees with a uniform fringe. This work will be submitted for pre-publication early in the coming year.

6.4. Mechanics of tissue morphogenesis

Participants: Olivier Ali, Arezki Boudaoud [External Collaborator], Guillaume Cerutti, Ibrahim Cheddadi [External Collaborator], Florian Gacon, Christophe Godin, Bruno Leggio, Jonathan Legrand, Hadrien Oliveri, 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 [29] and a strain-based growth mechanism [24] 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. One key aspect we wanted to investigate was the effect of an heterogeneous stress-based stiffening mechanism on the overall dynamics: Starting from a given initial shape, can we get significantly different shapes by assuming the stress-based stiffening mechanism active only in specific parts of the structures?

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 is currently under review, see preprint version [23].

Influence of cell division during flat organogenesis in plants. One key limitation of our 3D modeling approach of leaf-like organogenesis is the lack of cell division implementation. This can be seen as a major flaw in the mechanical 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 developed a 2D modeling approach to complement the 3D one. This 2D model encompasses the same biophysical processes as the 3D one (described in the previous subsection): a stress-based stiffening and a strain-based growth mechanisms of cell walls; augmented with a cell division module. We used this 2D framework to investigate the flattening dynamics of structures mimicking ellipsoid cross sections of growing organs. Such cross section were described as vertex-based, multicellular and multilayered structures.

We first reproduced the results obtained with the 3D approach to ensure that both models agreed on similar situations, where no cell division was implemented. We tested then several rules of cell division orientation and check which one(s) produced the most efficient flattening process. 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 manuscript currently under review and available online in a preprint version [23].

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 and was presented in two international conferences: *Mechanobiology and Physics of Life* (Lyon) and *Developmental and Cell Biology of the Future* (Paris); and at the yearly *InriaBio* meeting in Lyon. A paper is currently under review and a preprint is available on bioRxiv [22].

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 mechanism of morphogenesis. We developed 2D computational models to investigate the morphological consequences of the interplay between cell expansion, water fluxes between cells and tissue mechanics. This interdisciplinary work, between experiments and modeling, address the influence of turgor pressure heterogeneities on relative growth rate between cells. We showed that the coupling between fluxes and mechanics allows to predict observed morphological heterogeneities without any *ad hoc* assumption.

This work was part of the Agropolis fundation project *MecaFruit3D* and Arezki Boudaoud's ERC *PhyMorph*. It resulted in a publication in PLoS Computational Biology [7] that introduces the theoretical model and studies some of its properties. Another paper [27] presents the comparisons with experiments and is currently under review.

Development of *de novo* finite element (F.E.) library dedicated to mechanical simulations performed on complex cellularized structures. In order to compute accurately the mechanical stress field borne by multicellular pressurized 3D structures (such as plant tissues), we needed to update our existing library (*tissueMeca*, see [24]). Three key aspects had to be upgraded (i) the control over the F.E. solver, (ii) tracking of its precision and (iii) integration of the F.E. framework with the rest of our pipeline.

To that end, we decided to switch from *Sofa* to *FEniCS* (https://fenicsproject.org/) as the core F.E. framework used within our simulation pipeline. We started to develop a dedicated library, called *CellFem*, to solve F.E. problems on *PropertyTopomesh* instances (the data structure we developed within the team to describe

multicellular plant tissues). *CellFem* provides a high level API to define and resolve variational problems to solve linear as well as non-linear elastic and elasto-plastic problems related to plant tissue morphogenesis.

In parallel, we also started the development of a meshing library (based on the GMSH library (http://gmsh.info/)) called *CellMesh* and dedicated to the triangulation of simplicial complexes. This work is currently under development.

6.5. Signaling and transport for tissue patterning

Participants: Romain Azaïs, Guillaume Cerutti, Christophe Godin, Bruno Leggio, 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 govern 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 integrating transport and signaling to study tissue patterning *in silico*.

Automatic quantification of auxin transport polarities. 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 functional fluorescent auxin transporter (PIN1-GFP) with a dye staining of cell walls with propidium iodide (PI), we developed an original method to quantify in 3D the polarization of auxin transport for every anticlinal wall of the first layer of cells in confocal images. The developed method [13] was thoroughly evaluated against super-resolution acquisitions of the same tissue obtained using radial fluctuations (SRRF), and show to provide highly consistent results (less than 10% incorrect polarities, 80% of cells with a polarity vector error lesser than 30°). The digitally reconstructed networks evidenced an overall stable convergence of PIN1 polarities towards the center of the meristem, with a local convergence and divergence pattern that could explain the dynamics of auxin distributions in the meristem [19].

Landmark-based registration for the averaging of meristem patterning. To perform statistics of meristem patterning at the scale of a population, we developed a series of tools to compute a rigid 3D transformation that registers any individual meristem into a common cylindrical reference frame in which point-wise comparison is meaningful. The orignal method relies on the identification of biological landmarks (apex and main symmetry axis of the meristematic dome, position of the lastly emerged organ primordium and direction of the phyllotactic spiral) to compute this transform. These landmarks can be extracted from image acquisitions of meristems carrying the right fluorescent bio-markers (*CLV3* central zone marker for the apex, *DIIV* auxin bio-sensor for the organ primordia) using an original method that relies on the computation of 2D continuous maps of epidermal signal from discrete point clouds. The use of this registration method allowed to evidence key features of the transcriptional response of mersitematic cells to auxin [19].

In a second time, we aim to generalize the method to images without specific bio-markers, using only the geometry of the tissue to identify the relevant landmarks. To do so, machine learning approaches making use of the data processed for [19] are being developed and evaluated. This new landmark-based registration method would drastically improve the ability of comparing different individual meristems, open the way to spatial statistics over of multiple genetic and molecular signals, and contribute to an integrated tissue-level view of meristem patterning.

Computational models of integrated transport and signaling. Guided by new discoveries on auxin patterning dynamics in the shoot apical meristem (SAM) of *A. thaliana*, we developed a theoretical model of active and passive auxin transport. This model, built on existing view of auxin active transport [30], [31], naturally integrates the role of deeper cellular layers in the SAM and the mutual feedbacks between different components of the auxin-transport machinery. Through numerical simulation, the consequences of competing theories on PIN polarisation mechanism on auxin dynamics were explored. These results will serve, in quantitative comparisons with *in vivo* observation, to validate hypotheses on molecular mechanisms of auxin transport and to provide information on the role of memory effects and information fluxes during patterning.

These works were part of the *BioSensors* HFSP project and are carried out in the *Phyllo* ENS-Lyon project. These works gave rise to a journal article which is currently under review and have been partly presented at the *International Worskhop on Image Analysis Methods for the Plant Sciences* in Bron in July 2019.

6.6. 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.

Analysis of the diversity of inflorescence architecture in different rice species. Rice is a major cereal for world food security and understanding the genetic and environmental determinants of its branching habits is a timely scientific challenge. The domestication, i.e., the empirical selection by humans, of rice began 10 000 years ago in Asia and 3 000 years ago in Africa. It thus provides a short-term model of the processes of evolution of plants.

Hélène Adam and Stéphane Jouannic from the group Evo-Devo de l'Inflorescence of UMR DIADE at IRD (Montpellier) have collected for years on the different continents an outstanding database of panicle-type inflorescence phenotypes in Asian and African, cultivated and wild, rice species. Classical statistical analysis based on the extraction of characteristic traits for each individual branching system were able to separate wild species from cultivated ones, but could not discriminate between wild species, suggesting that the entire branching structure should be used for classification methods to operate. For this, we are currently developing statistical methods on tree structures (see section 6.3) that should allow us to achieve better discrimination between panicles, based on their branching topology in addition to geometric traits. By coupling the quantitative study of the panicles to genomic analyses carried out by the IRD group, we should be able to highlight which regulation pathways have been selected or altered during the domestication process.

The role of sugars in apical dominance. The outgrowth of axillary buds is a key process in plant branching and which is often shown to be suppressed by the presence of auxin in nodal stems. However, local auxin levels are not always sufficient to explain bud outgrowth inhibition. Recent studies have also identified a contribution of sugar deprivation to this phenomenon. Whether sugars act independently of auxin or other hormones auxin regulates is unknown. Auxin has been shown to induce a decrease of cytokinin levels and to upregulate strigolactone biosynthesis in nodes. Based on rose and pea experiments, both in vitro and in planta, with our collaborators Jessica Bertheloot, Soulaiman Sakr from Institut de Recherche en Horticulture et Semences (IRHS) in Angers, we have shown that sucrose and auxin act antagonistically, dose-dependently, and non-linearly to modulate bud outgrowth. The Angers group provided experimental evidence that sucrose represses bud response to strigolactones but does not markedly affect the action of auxin on cytokinin levels. Using a modeling approach, we tested the ability of this complex regulatory network to explain the observed phenotypes. The computational model can account for various combinations of sucrose and hormones on bud

outgrowth in a quantitative manner and makes it possible to express bud outgrowth delay as a simple function of auxin and sucrose levels in the stem. These results provide a simple auxin-sucrose-cytokinin-strigolactone network that accounts for plant adaptation to growing conditions [6] and [10] for a review.

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 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 being written.

6.7. Miscellaneous

Participants: Romain Azaïs, Christophe Godin, Bruno Leggio.

Measurements and nonlocal correlations in quantum mechanics. Based on a long standing collaboration between Christophe Godin and Przemyslaw Prusinkiewicz from the University of Calgary on the analysis of connections between computer simulation paradigms and quantum mechanics, we theoretically investigated with the quantum mechanics expertize of Bruno Leggio in the team effects of measurements on quantum systems, mostly in connection with quantum non-locality and entanglement. At the same time, we exploit formal and conceptual analogies between quantum theory and biologically-inspired structures to study the latter under new paradigms.

One fruitful line of research deals with the inherent non-locality of correlations between measurement outcomes, characterizing the quantum world. These phenomena are described by the celebrated Bell inequalities. We study ways to generalize such inequalities to better capture non-local correlations, at the same time shedding light on the origin of the discrepancy between quantum and classical stochasticity. In parallel, we develop and profit from formal analogies between the theory of non-locality and the exploration of fractal structures in the context of simulation of arborescent systems.

Another research line sees the application of parameter-estimation techniques for piecewise deterministic Markovian 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 [21] 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.

Finally, a third research topic consists of the study of the structure of typical quantum correlations, called entanglement, and its relation to thermal noise induced in a quantum system by its unavoidable interaction with its surrounding environment. We show [9] that the quantitative amount of noise represents a tight upper bound on the amount of bipartite quantum correlation two systems can establish between them.

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.

7. Partnerships and Cooperations

7.1. Regional Initiatives

7.1.1. ENS de Lyon projets Emergents - Phyllo (2018 - 2019)

Participants: Christophe Godin, Bruno Leggio, Teva Vernoux [External Collaborator].

The aim in this project is to develop a model of phyllotaxis that would be compatible with the recent detailed and quantitative observations made by our group of the distribution of auxin in space and time at the SAM. In particular the work will seek at using the new quantitative data to estimate the parameters of the stochastic model previously developed of organ patterning.

7.1.2. 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.

7.2. National Initiatives

7.2.1. Inria ADT - Gnomon

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

7.2.2. Inria IPL - Naviscope

Participants: Guillaume Cerutti, Emmanuel Faure [External Collaborator], Christophe Godin, Jonathan Legrand, Grégoire Malandain [External Collaborator].

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.

7.2.3. ANR - Imago (2016 - 2019)

Participants: Guillaume Cerutti, Christophe Godin, Jonathan Legrand.

The goal of this project is to investigate the role of ovule growth constraints on germ cell fate establishment. This project is motivated by recent findings from the partners' groups suggesting that disturbances in cell divisions and expansion in early (pre-meiotic) ovules are sufficient to induce ectopic germ cells. These observations suggest novel routes to engineer apomixis in plants but remains poorly understood. Recent developments in high-resolution 3D imaging, image processing, and modeling offer a powerful combination of approaches to investigate this question. IMAGO proposes to elucidate patterning rules governing ovule growth, and their contribution to female germ cell fate acquisition. We use a combination of high-resolution static and real-time 3D imaging, quantitative image processing, cell-based growth models and functional approaches to (1) define cellular growth patterns in the ovule primordium using quantitative imaging (2) test patterning rules in silico by cell-based growth models (3) validate patterning rules in vivo using genetic, pharmacological and mechanical perturbations.

Partners:

- UMR DIADE, IRD, Montpellier, France
- Department of Plant and Microbial Biology, Zurich, Swisszerland
- RDP, ENS de Lyon, France

7.2.4. ANR DigEM (2015 - 2019)

Participants: Christophe Godin, Bruno Leggio, Patrick Lemaire [External Collaborator], Grégoire Malandain [External Collaborator].

In this project, we will use advanced ligh-sheet imaging of live embryos to quantitatively describe embryonic morphogenesis in ascidians, a class of animals that undergo very rapid genomic divergence, yet show an extraordinary stasis of embryonic morphologies, based on invariant early cell lineages shared by all studied species. The global aims of the proposal, which will bridge micro- and macroevolutionary scales of analysis, are: i) to provide a global systems-level description at cellular resolution of an animal embryonic program; ii) to use this description to characterize intra-specific and inter-specific patterns of morphogenetic variations; iii) to analyze possible molecular mechanisms explaining the unusual robustness of this program to environmental and genetic perturbations. To achieve these aims, we will combine advanced live light-sheet microscopy, computational biology, functional gene assays and evolutionary approaches.

Partners:

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

7.2.5. ERA-CAPS Genes2shape (2018 - 2021)

Participants: Olivier Ali, Guillaume Cerutti, Christophe Godin, 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

7.2.6. MITI - MISGIVING (2019)

Participant: 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

7.3. European Initiatives

7.3.1. FP7 & H2020 Projects

Program: H2020

Project acronym: ROMI

Project title: RObotics for MIcrofarms

Duration: November 2017 - October 2021

Coordinator: Sony

Other partners: Iaac, (Spain), FEI (France), Inria (France), CNRS (France), UBER (Germany), Chatelain (France)

Abstract: 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 the aerial drone N-E-R-O 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.

7.3.2. Collaborations with Major European Organizations

Laboratoire International Associé (LIA): Computing Plant Morphogenesis

The focus of this LIA headed by Teva Vernoux (RDP) and Ottoline Leyser (SLCU) is on plant morphogenesis i.e. the mechanisms allowing the generation of plant shapes at different scales. Both the RDP and SLCU Laboratories are leaders of this field. The scenario for morphogenesis that has recently emerged is that chemical signals controlling cell identities lead to changes in mechanical properties of cells, triggering changes in shapes feeding back on the gene regulatory network. This in turn affects the distribution of chemical signals and mechanical forces, thus channeling morphogenesis. However, our understanding of the molecular and physical basis of morphogenesis in plants or in any other eukaryotic system is still in its infancy due to the complexity and non-linearity of processes involved in morphogenesis dynamics (or Morphodynamics). Understanding morphodynamics requires a modeling environment for the explicit representation of forms at multiple scales and for incorporating complex data from different origins and nature (chemical, mechanical, geometrical). In addition to creating a unique scientific environment, this LIA will gather the critical mass and interdisciplinary expertise required to create such a computational platform and to generate the data to produce an integrated vision of how chemical and mechanical signals interaction drive morphogenesis.

Partners: Sainsbury Lab. University of Cambridge (SLCU)

7.4. International Research Visitors

7.4.1. Visits of International Scientists

- Farah Ben Naoum, associate professor in computer science at the University of Sidi Bel Abbes, Algeria, visited the team in March 2019 for 3 weeks and worked with Romain Azais and Christophe Godin on the definition of a strategy to make efficient random walks in spaces of trees.
- Gabriela Mosca was a visiting researcher from Celia Baroux's Lab (U. Zurich, Switzerland) in the context of the ANR project IMAGO. She spent 3 weeks in the team working with Guillaume Cerutti, Jonathan Legrand, Olivier Ali and Christophe Godin to set up a protocol to reconstruct ovule development from confocal imaging.

7.4.1.1. Internships

- Salah Eddine Habibeche is a PhD student supervised by Farah Ben Naoum from the University of Sidi Bel Abbes. The PhD subject of Salah consists of developing compressing schemes for semi-ordered trees. During his visit, he will study methods of compression of trees with loss of information.
- Caro Chavez Hernandez is a PhD student from Elena Alvarez-Buylla, UNAM University, Mexico. Caro visited the MOSAIC group to work with Christophe Godin to integrate the extensive gene regulatory network she assembled of key molecular processes involved at different phases of plant development into a model of plant architecture development written in LPy.

8. Dissemination

8.1. Promoting Scientific Activities

8.1.1. Scientific Events: Organisation

8.1.1.1. Member of the Organizing Committees

- Romain Azaïs was a member of the organizing committee of the Journées de Statistique 2019 in Nancy.
- Romain Azaïs organized with Hélène Leman (NUMED) the second InriaBio@Lyon day, which gathered 6 teams of the Inria center interested in biological questions.

8.1.2. Scientific Events: Selection

8.1.2.1. Reviewer

- Romain Azaïs: NeurIPS 2019.

8.1.3. Journal

8.1.3.1. Member of the Editorial Boards

- Christophe Godin:
  - Asssociate editor in Plant biophysics and modeling of the journal Frontiers in Plant Sciences.
  - Member of the Editorial Advisory Board of the journal in silico Plants.
  - Member of the board of the functional-structural plant modeling (FSPM) series of conferences (next to come at fall 2020).

8.1.3.2. Reviewer - Reviewing Activities

- Olivier Ali: Frontiers in plant sciences.
- Romain Azaïs: Stochastic Processes and their Applications, Journal of Statistical Theory and Practice, Bernoulli.
- Christophe Godin: Frontiers in plant sciences, Annals of Botany, Bulletin of mathematical Biology (co-coordination of a special issue).
- Bruno Leggio: Physical Review Letters, Physical Review A, Physical Review B, Physical Review E, Frontiers in Plant Science, Entropy, Symmetry, Energies.

8.1.4. Invited Talks

- Oliver Ali was invited to give a seminar at the UPSC Lab in Umea (Sweden) in December 2019.
- Romain Azaïs was invited to give a presentation at the UTC in Compiègne, at the Laboratoire Paul Painlevé in Lille, and at the Laboratoire de Biométrie et Biologie Evolutive in Lyon.
- Christophe Godin was invited to give presentations at the research unit IGFL (Lyon), University of Calgary (Canada), University of Heidelberg (Germany) and ENS de Lyon.

8.1.5. Scientific Expertise

- Christophe Godin
  - is a member of the International Scientific Advisory Committee of the Plant Phenotyping and Imaging Research Centre (P2IRC), Saskatchewan, Canada.
  - is a member of the Scientific Board of the Plant Biology and Breeding Department of INRA (BAP).

8.1.6. Research Administration

- Christophe Godin:
  - is a member of the Project Committee at Grenoble Rhone-Alpes Research Center.
  - is a member of the Steering Committee of the RDP Lab., Lyon.

8.2. Teaching - Supervision - Juries

8.2.1. Teaching

- Olivier Ali:
  - Jury for the evaluation of a practical course on computational modeling for developmental biology (Licence 3 Biology ENS Lyon).
  - Course (3h) and practical course (3h) about mechanical modeling of plant morphogenesis (Master plant biology for sustainable production, Umea university and Swedish University of Agricultural Science, Sweden).
- 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).
  - Master Stem Cells and Development ENS de Lyon (3h): *Introduction to Phyllotaxis*.
- Florian Ingels:
  - Séances de TP Probabilités-Statistiques, Licence Mathématiques et Economie, Université Lyon 1
  - Séances de TP Statistiques pour l'informatique, Licence Informatique, Université Lyon 1

8.2.2. Supervision

PhD (2016 – 2019): 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 in progress (2019 - 2022): Florian Ingels (MOSAIC, Université de Lyon). Supervisors: Romain Azaïs, Christophe Godin.

Hadrien Oliveri PhD (2015-2019) Montpellier University, co-supervision Christophe Godin, Jan Traas,

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

Manuel Petit PhD (2019-2022), ENS de Lyon, co-supervision Christophe Godin, Grégoire Malandain.

Master 2 (6 months): Florian Ingels. Statistical learning from trees: toward the definition of an optimal kernel for tree data. Supervisor: Romain Azaïs.

Master 2 (6 months): Florent Papini. Tracking cells in confocal images of meristems. Supervisor: Christophe Godin.

8.2.3. Juries

Christophe Godin was a member (as a supervisor) of the PhD defense of Hadrien Oliveri - University of Montpellier (May 2019).

Christophe Godin was the President of the PhD defense of Valeria Hernandez at ENS de Lyon (December 2019).

8.3. Popularization

- Olivier Ali:
  - Participated to the Declic initiative: Discussions about of scientific research to high school students (3h, Lycée Jean Perrin, Lyon).
  - Invited conference about mechanical modeling of plant morphogenesis for the Université Ouverte in Lyon.
- Christophe Godin participated to the Declic initiative: Introductory talk and discussions about scientific research to high school students (3h, Lycée Frédéric Fays, Villeurbanne).

8.3.1. Interventions

- Christophe Godin gave:
  - a lecture at Inria Grenoble in the context of a training program for Informatique et Sciences du Numérique dedicated to Math and Physics highschool teachers. see video (1h30)
  - a visio-seminar to highschool students of the French Lycée in Laos (1h30)

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