Activity Report 2018

Team MOSAIC

MOrphogenesis Simulation and Analysis In siliCo

Inria teams are typically groups of researchers working on the definition of a common project, and objectives, with the goal to arrive at the creation of a project-team. Such project-teams may include other partners (universities or research institutions).

RESEARCH CENTER
Grenoble - Rhône-Alpes

THEME
Computational Biology

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Team MOSAIC

Creation of the Team: 2018 January 01

Keywords:

Computer Science and Digital Science:

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Other Research Topics and Application Domains:

B1.1.2. - Molecular and cellular biology
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1. Team, Visitors, External Collaborators

Research Scientists

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Ibrahim Cheddadi [INRA, Applied mathematician]
Emmanuel Faure [CNRS, Computer scientist]

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

The year 2018 was marked by the following events:

- **Creation of the team.** The team MOSAIC started in January 2018 at the Inria Grenoble Rhône-Alpes Research Center and is part of the laboratoire de reproduction des plantes (RDP research unit) at ENS de Lyon campus. Romain Azaïs joint the team in March 2018 and Guillaume Cerutti was hired as an Inra research engineer in September 2018.
- **Edition of *Statistical Inference for Piecewise-deterministic Markov Processes*.** Piecewise-deterministic Markov processes form a class of stochastic models with a sizeable scope of applications. Such processes are defined by a deterministic motion punctuated by random jumps at random times, and offer simple yet challenging models to study. The issue of statistical estimation of the parameters ruling the jump mechanism is far from trivial. Responding to new developments in the field as well as to current research interests and needs, the book "Statistical Inference for Piecewise-deterministic Markov Processes" edited by Romain Azaïs and Florian Bouguet [10] gather 7 chapters by different authors on the topic. The idea for this book stemmed from a workshop organized in Nancy in the 2016-17 winter.
- **Invited talk at the Jacques Monod conference in Roscoff**. Christophe Godin was invited in Sep 2018 at the prestigious Jacques Monod series of international conferences in Roscoff, France, to present an overview of the current research on phyllotaxis. The talk was entitled *Phyllotaxis at the era of molecular and computational biology: the revival of an old enigma* and prepared with Teva Vernoux.
- **First prototype of the software platform Gnomon**. A first, fully functional, prototype of the Gnomon software platform, dedicated to the modeling and simulation of plant and animal morphogenesis, was developed during a series of intensive coding sessions in Lyon and Sophia-Antipolis. This new concept of platform dedicated to the study of morphogenesis was presented in November 2018 to a panel of modelers and biologists at the RDP lab, who will contribute next year to the further testing and refining the platform. This prototype is a clear milestone and results from a strong collaboration between the Inria software engineering group from Sophia-Antipolis (who provides the software architecture kernel - DTK)) and the Mosaic team and is supported by Inria (Action de Developpement Tecnologique, ADT).

5. New Software and Platforms

5.1. treex

KEYWORDS: Graph algorithmics - Data structures - Combinatorics

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: treex is a Python library for manipulating rooted trees. The trees can be ordered or not, with or without labels on their vertices.

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 - Computation of coding processes (Harris path, Lukasiewicz walk and height process) - Visualization algorithms in Matplotlib or in LaTeX

Representations of trees. With treex, we aim to propose all the standard representations of trees as well as the one-to-one correspondences between them. Main coding processes (Harris path, Lukasiewicz walk, and height process), DAG representation, doubly-chained tree structures have been already coded. Standard exploration algorithms and editing methods have also been developed. Through these generic tools, treex enables the manipulation of trees from various application contexts.

Easy-to-use. We think that treex must be user-friendly to be adopted by collaborators from fields of biology. To this end, we develop high-level algorithms and provide an extensive documentation (with sphinx) as well as a simple installation method through conda.

Algorithms. The current version of treex provides edit distance algorithms, approximation algorithms (that can be used to control the complexity of the edit distance algorithms), and visualization algorithms (with an interface for TEX / LATEX and Matplotlib). A first statistical learning module is in progress.

RELEASE FUNCTIONAL DESCRIPTION: The first release of treex happened in the late 2018 after an intensive work to ease both installation and handling. A publication on treex is planned for the next early year. In addition, treex will be integrated in Gnomon in the following months.
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- Participants: Romain Azais, Guillaume Cerutti, Didier Gemmerle and FLORIAN INGELS
- Contact: Romain Azais
- URL: https://gitlab.inria.fr/azais/treex

5.2. 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 developed based on the past experience of the team with the OpenAlea platform, but moving towards 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. Gnomon development uses extensively an agile methodology and emphasizes three main aspects:

Deployable and extensible software architecture. The Gnomon platform is intended to become a perennial common resource for the members of the team as well as a tool to easily diffuse our methods to collaborators. It is a plugin-based architecture, relying on the dtk meta-platform developed by the SED at Inria Sophia-Antipolis. dtk eases the conception of a high-level C++ environment inside which added-value components are injected autonomously by the team members as Python plugins wrapping our scientific libraries. A significant effort is put on the packaging and deployability of this software (using conda), adding up unit testing, continuous integration and cross-platform installation.

Exploration of forms. The environment will provide tools to create and visualize forms, and explore them in space and time. Building on the algorithmic resources developed by the team for image sequences of multicellular tissues, user-friendly interfaces are being designed for the exploration of such structures. This gives the user the possibility to reconstruct computational representations from experimental data in an intuitive way, and to explore these spatio-temporal data in an interactive and visual manner.

Integrated form simulation framework. Within a general framework for the modeling of dynamical systems that the team is developing, a core component is the mechanical simulation engine that will handle the resolution of physical equations controlling form development. We want the simulation framework to be integrated within the Gnomon platform in a nearly transparent way for the user. To achieve this, we develop a high-level interface for a generic differential equation solver based on the *fenics* FEM library. Mapping the general concepts of morphogenesis modeling to this engine will allow the user to specify behavior rules of the system at high-level and easily design simulation scenarios directly in the Gnomon application.

Gnomon project organization:

- Project leader: Christophe Godin
- Software development coordinator: Guillaume Cerutti
- DTK backend coordinator: Thibaud Kloczko
- Plugin coordinators: Jonathan Legrand (TimageTK), treex (Romain Azais), Olivier Ali (Mechanics), Frédéric Boudon (L-Systems).
- Diffusion to end-users: 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 first, fully functional, prototype of the Gnomon software platform, dedicated to the modeling and simulation of plant and animal morphogenesis, was developed during a series of intensive coding sessions in Lyon and Sophia-Antipolis. This new concept of platform dedicated to the study of morphogenesis was presented in November 2018 to a panel of modelers and biologists at the RDP lab, who will contribute next year to the further testing and refining the platform. This prototype is a clear milestone and results from a strong collaboration between the Inria software engineering group from Sophia-Antipolis (who provides the software architecture kernel - DTK)) and the Mosaic team and is supported by Inria (Action de Developpement Tecnologique, ADT).
NEWS OF THE YEAR: A first, fully functional, prototype of the Gnomon software platform, dedicated to the modeling and simulation of plant and animal morphogenesis, was developed during a series of intensive coding sessions in Lyon and Sophia-Antipolis. This new concept of platform dedicated to the study of morphogenesis was presented in November 2018 to a panel of modelers and biologists at the RDP lab, who will contribute next year to the further testing and refining the platform. This prototype is a clear milestone and results from a strong collaboration between the Inria software engineering group from Sophia-Antipolis (who provides the software architecture kernel - DTK)) and the Mosaic team and is supported by Inria (Action de Developpement Tecnologique, ADT).

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

5.3. TimageTK: a Python package for image processing of multicellular architectures

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

- Related Research Works: **RA1** (*Representations of forms in silico*) & **RA2** (*Data-driven models*) & **RA3** (*Plasticity and robustness of forms*)
- Related Key Modeling Challenges: **KMC3** (*Realistic integrated digital models*)

Processing images of multicellular tissue architectures in plants and animals present difficult computational challenges, notably when dealing with heterogeneous data sources, temporal data. As for now, only limited computational tools exit to analyze these types of images efficiently. Based on our initial experience with the development of MARS-ALT, a pipeline for segmenting and tracking cell lineages, we have recently redesigned our software in order to develop a new high-level Python package named Tissue image ToolKit (TimageTK).

C/Python library. TimageTK is written in Python and is largely built on top of a C library (VT) developed by the Morpheme Inria team. Part of the C library was developed for MARS-ALT software by the Morpheme team. TimageTK provides high-level wrapping of these algorithms with additional functionalities directly written in Python, such as cell tracking.

Well documented, high-level image processing. TimageTK offer high-level methods, where few parameters are required to tune algotithms. They offer a safer use of function through well documented class methods. For experts in image processing, low-level functions and wrappings of C-functions are still accessible.

Easy deployment. TimageTK has simple and robust installation procedure based on conda (Conda is a package and environment management system that runs on Windows, macOS and Linux and allows to get rid of most installation issues, such as compilation or dependency errors). For now only macOSX and Linux version are packaged (x64 architecture) using Inria continuous integration tools.

Continuous integration. Using Inria continuous integration tools, TimageTK is regularly released through conda packaging mechanism. We also make use of these resources to regularly generate (sphinx) and publish updates in the documentation.

Compatibility with Gnomon. TimageTK is based on data structures representing images that are fully compatible with Gnomon. This makes it possible to use TimageTK as a plugin of the Gnomon software.

6. New Results

6.1. Dynamical characterization of morphogenesis at cellular scale

Participants: Guillaume Cerutti, Emmanuel Faure [External Collaborator], Christophe Godin, Bruno Leggio, Jonathan Legrand, Patrick Lemaire [External Collaborator], Grégoire Malandain [External Collaborator], Jan Traas [External Collaborator].

- Research Axes: **RA1** (*Representation of biological organisms and their forms in silico*) & **RA3** (*Plasticity & robustness of forms*)
- 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:

Cells spatio-temporal properties and patterns characterization. Over the past few years, we have achieved quantitative characterization of some of the cells physical properties, such as volumes or curvatures, in a developing tissue. Together with cell lineaging, it also enabled the quantification of temporal properties at cellular scale such as volumetric growth rate or strain patterns. To ease-up the analysis and to structure the previously described data, we have implemented a dedicated spatio-temporal graph structure, formalizing the cell network and its change in time.

To further characterize the tissue development, we developed clustering methods to identify cellular patterns based on a selection of quantified cell properties, including topology. Since such data are highly structured, both in time and space, we developed two complementary approaches:

1. spatial oriented: this approach use the cell neighborhood and a selection of cell descriptors to create pairwise distance maps latter clustered by a distance-based method, such as Ward's hierarchical clustering.
2. temporal 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 should be published during the first half of 2019.

Atlases. One fundamental requirement to understand morphogenesis is the creation of atlases of different properties and different species. This year we have started creating 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*.

Phallusia mammillata embryos develop with an invariant cellular lineage and with a relatively low number of cells (~ 700) up until the end of neurulation. This allows the creation of atlases with cellular resolution. Developing embryos from in-vitro fertilised dechorionated eggs have been injected with mRNA to fluorescently label their cell membranes and imaged by light-sheet microscopy for several hours of development. Automated image reconstruction through the segmentation pipeline ASTEC allowed to collect a large number of wild-type and mutated development with single-cell resolution and with a temporal resolution of two minutes. Based on this amount of data and on the invariant early ascidian lineage, we started curating an atlas of wild-type cellular, tissue and embryonic properties. Each cell, classified by its unique name, is identified in each wild-type embryo and analyzed through the dedicated computational pipelines. The result of this work provides a comprehensive view on the variability (in time, within and between embryos) of properties such as cell volume, cell surface, cell and tissue shape, cell topology, length of cell cycle, cell position within its tissue and globally within the embryo, orientation of cell's cleavage plane. This cellular networks have been coupled via cell names with genetic data coming from the the ascidian genetic database (ANISEED) and a specific tool, Morphonet, has been developed to explore these morphodynamic atlases seamlessly within a web-browser (paper in revision).

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, the development of most organisms or organs is under the influence of robust genetic patterns but 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 *A. 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.

Both these works should result in publications in 2019.

Robustness of ascidian embryonic development. The image segmentation pipeline ASTEC developed by the team allows the 3D dynamic reconstruction of early ascidian embryogenesis at cellular resolution. Based on the high-quality wild-type data of our ascidian morphogenetic atlas and on ANISEED, we investigated the robustness of ascidian embryonic development and established a model to explain its origin. Thanks to the

image-analysis pipelines we developed, we could extract relevant information from data and to perform cell-to-cell comparisons between different embryos of the same species (Phallusia mammillata). Since embryos developing from dechorionated eggs are left-right symmetric, we assessed the degree of cell-level variability between two embryos with different genomes (genetic variability) by comparing it to the intrinsic left-right variability in cellular properties within each embryo (stochastic variability). We showed that the same degree of variability is observed within and between embryos, demonstrating how ascidian embryonic development is highly canalised, and that the high reproducibility of shapes observed during embryogenesis is rooted in the robustness of cellular geometry and topology. Based on these observations, we studied the dynamics of embryonic patterning by developing a quantitative mathematical model for cellular fate-restriction events based on kinetic equations describing biochemical signalling. This model suggests that the robustness of cell topology and geometry is necessary for cell-cell biochemical interactions to give rise to the correct fate restriction events, a phenomenon which might represent a strong evolutive constraint to cell-scale variability in ascidians.

These results gave rise to a work which is currently under review and published as a preprint [16].

Digital reconstruction of developing *Arabidopsis* ovule. 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. In order to test various hypotheses of cellular growth, we reconstructed a first 4D digital tissue structure of a developing ovule as a triangulated cellular complex. It can be used as an input for FEM-based simulations, and will allow to compare quantitatively the results of growth models with actual ovule development.

This work was part of the *Imago* project.

6.2. Reconstruction of macroscopic forms from images and characterization of their variability

Participants: Guillaume Cerutti, Christophe Godin, Jonathan Legrand, Katia Mirande.

- Research Axes: **RA1** (*Representations of forms in silico*) & **RA3** (*Plasticity & robustness of forms*)
- 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. 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. 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. 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.

Identification of plant species from morphological traits. The description of morphological traits of the various organs of the plants (leaves, bark, flowers and fruits) is essential for the characterization of a phenotype, and is highly relevant in the context of species or variety identification. In the context of tree species identification from RGB images of their organs, we study methods to represent the morphological charateristics of the plant organs, and the way to combine those different sources of information to enhance the classification performance. We demonstrated that botany-inspired descriptors of bark improves tree species classification based on leaves [13]. We also explore the possibility of using deep learning techniques to train a system to extract botanically relevant information from images [3].

This work is part of the *ReVeRIES* ANR project, in which the team is not directly involved.

This work has led to a publication in *Ecological Informatics* and to a participation at the *International Worskhop on Image Analysis Methods for the Plant Sciences* in Nottingham in January 2018.

6.3. Analysis of tree data

Participants: Romain Azaïs, Christophe Godin, Florian Ingels, Clément Legrand.

- 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 2018, 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 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 [7], 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.

We conjecture that the problem of optimal approximation by a self-nested tree is NP-hard. Despite a substantial work in 2018 (internship of Clément Legrand), this remains an open question. Consequently, 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 [7]. Another algorithm based on the simulation of Gibbs measures on the space of trees is currently under development. This work should result in a publication 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 [12], 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 [19]. We have introduced new estimators and stated their consistency. Our techniques improve the existing results both theoretically and numerically. A simulation study shows the good behavior of our procedure on finite-sample sizes and from missing or noisy data.

In a very different context, a substantial work has been made on statistical inference for piecewise-deterministic processes [2], [9], [8].

Kernel methods for tree data. In statistical learning, one aims to build a decision rule of a qualitative variable Y as a function of a feature X (typically a vector of $\mathbb{R}^d$) from a training dataset $(X_i, Y_i)_{1\leq i\leq n}$. We assume that X is a tree, ordered or not, with or without labels. This framework is quite original since the state space of X is not endowed with a canonical inner product. Kernel methods are particularly adapted to this setting since they enable to transform the raw data into a Hilbert space. In this context, the main issue is related to the construction of a *good kernel*. A kernel function adapted to trees is the subtree kernel introduced [24]. While the literature has never been focused on the weight function involved in the subtree kernel, we have shown that this function is crucial in prediction problems. We have proposed a new algorithm for computing the subtree kernel. It has been designed to allow learning the weight function directly from the data. On some difficult datasets, the prediction error is dramatically decreased from $> 50\%$ to 3%.

This work is part of the *ROMI* project, that aims to develop an open and lightweight robotics platform for microfarms. This project requires to investigate advanced analysis and modeling techniques for plant structures. A main issue that arises in this context is to predict a feature of the plant (species, health status, etc) from its topology.

Invited talk on tree structures and algorithms Christophe Godin gave a invited talk entitled *Can we manipulate tree forms like numbers?* that was prepared with Romain Azaïs at the workshop on *Mathematics for Developmental Biology* organized at the Banff International Research Station for Mathematical Innovation and Discovery, organized by P. Prusinkiewicz and E. Mjolsness (Banff, Canada, December 2017).

Abstract: Tree-forms are ubiquitous in nature and recent observation technologies make it increasingly easy to capture their details, as well as the dynamics of their development, in 3 dimensions with unprecedented accuracy. These massive and complex structural data raise new conceptual and computational issues related to their analysis and to the quantification of their variability. Mathematical and computational techniques that usually successfully apply to traditional scalar or vectorial datasets fail to apply to such structural objects: How to define the average form of a set of tree-forms? How to compare and classify tree-forms? Can we solve efficiently optimization problems in tree-form spaces? How to approximate tree-forms? Can their intrinsic exponential computational curse be circumvented? In this talk, we presented a recent work to approach these questions from a new perspective, in which tree-forms show properties similar to that of numbers or real functions: they can be decomposed, approximated, averaged, and transformed in dual spaces where specific computations can be carried out more efficiently. We will discuss how these first results can be applied to the analysis and simulation of tree-forms in developmental biology (https://www.birs.ca/events/2017/5-day-workshops/17w5164).

6.4. Mechanics of tissue morphogenesis

Participants: Olivier Ali, Arezki Boudaoud [External Collaborator], Guillaume Cerutti, Ibrahim Cheddadi [External Collaborator], Christophe Godin, Bruno Leggio, Jonathan Legrand, Hadrien Oliveri, Jan Traas [External Collaborator].

- Research Axes: **RA2** (*Data-driven models*) & **RA3** (*Plasticity & robustness of forms*)
- 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. This section describes the team's efforts on integrating cellular behaviors such as mechano-sensitivity, intercellular fluxes of materials and cell division into a macroscopic mechanical picture of morphogenesis.

Mechanical influence of inner tissues. Mechanical stress patterns within plant tissues emerge from the balance between inner-pressure-induced forces and the elastic response of the cell wall [3] over the entire tissue. Being able to derive, from a specific cellular architecture, the corresponding pattern of stresses within a tissue is crucial for the study of morphogenesis. It requires a precise description of the tissue as a network of connected cells and the ability to run numerical simulations of force balance on such heterogeneous structures.

To that end, we developed numerical methods to generate finite element meshes from: i) 3D microscopic images with sub-cellular resolution (referred to as *bio-inspired* structures) and ii) 3D cellularized geometrical volumes (referred to as *artificial* structures). Combined with a FEM-based simulation framework previously developed within the team [20], we generated quantitative maps of stress distributions in multilayered reconstructed tissues. The combined analysis of stress patterns on *bio-inspired* and *artificial* structures showed how mechanical stresses experienced by cells convey geometrical information to cells about the global shape of the tissue as well as the local shape of cells.

This work was part of the *Morphogenetics* IPL and Jan Traas ERC grant *Morphodynamics*.

This work is currently under review in the *Bulletin of Mathematical Biology* and has been presented at the *19th International Conference of System Biology* held in Lyon at fall.

Shape regulation. Reproducible and robust morphogenesis requires growth coordination of thousands of cells. How such coordination can be "implemented" in living organism is a core question for *RA3*. One identified mechanism in plant to coordinate growth rely on cells mechano-sensitivity [4]. Combined with the geometrical dependency of mechanical stress (*c.f.* previous subsection), this suggests the existence of a feedback mechanism that regulates tissue shape changes. We have been investigating closely the consequences of such a mechanism.

To that end, we first modeled the bio-molecular pathway relating mechanical stress experienced by cells to actual modification of their mechanical properties (*e.g.* cell wall stiffness). This work enabled us to describe plant tissues as an active material featuring large-scale properties, such as stress stiffening [5], emerging from sub-cellular dynamics. This work has been published in *Journal of Mathematical Biology* [5].

In parallel, we modeled the influence of cell wall elasticity (value, orientation) on the growth dynamics of tissues. This was done in the context of plant organogenesis, in close collaboration with biologists investigating the effect of cell-wall-related mutations on plant organ initiation. Our modeling approach was based on our previously developed *strain-based growth* model [20]. This joint study has been published in *Development* earlier this year [1].

We then studied how initial spherical symmetry (e.g. dome-shaped primordia) can be potentially broken during development in such active tissues and lead to elongated or flat shapes. For this, we integrated the *stress feedback* model with the *strain-based growth* model to investigate how their interplay could influence the morphogenesis of 3D cellularized structures. In particular, we showed that a stress-based feedback mechanism can maintain the typical plant growth modes (*i.e.* axial elongation or 2D flat expansion) and amplify

[3] A thick protective exoskeleton surrounding plant cells
[4] the ability to probe mechanical stress around them and to modify accordingly their growth behavior
[5] the ability of the tissue to re-enforce itself in the directions of high mechanical solicitations

asymmetries. This computational approach to symmetry breaking in growing tissues has been developed in parallel to experimental investigations addressing the shape evolution of sepals [6].

This work was part of the *Mophogenetics* IPL and Jan Traas ERC grant *Morphodynamics*.

The whole story has been presented at the *9th International Plant Biomechanics Conference* in Montreal this summer. A journal article combining both our modeling approach and experimental work in the context of symmetry breaking during plant organogenesis is currently being written.

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, combining experiments and modeling, addresses the influence of turgor pressure heterogeneities on relative growth rate between cells. We showed that the coupling between fluxes and mechanics allows us to predict observed morphological heterogeneities without any *ad hoc* assumption. It also reveals the existence of a putative inhibitory action of organ growth on growth in immediatemy neighboring regions, due to the hydraulic coupling between cells during growth.

This work was part of the Agropolis fundation project *MecaFruit3D* and Arezki Boudaoud's ERC *PhyMorph.*

Two papers report the results of this work (one currently under review in *Nature Physics* [21] and a second one that is about to be submitted. These results have also been presented last summer at the *9th International Plant Biomechanics Conference* in Montreal.

Influence of dividing cells on tissue mechanics during morphogenesis in ascidians. The control of cell division orientation is of prime importance for patterning and shape emergence, especially in animal embryos where the first developmental stages happen at constant volume. In recent years, the Hetwig's rule appeared as a physical model accounting for orientation of cell division. Within animal tissues it has been shown that the coupling of externally induced strain and Hertwig's rule leads to the orientation of cell divisions with the main stress direction.

We investigated through modeling the consequences, in a multicellular context, of such stress-based regulation of cell division orientation. To that end, we developed a theoretical standpoint on the many-body energetic thermodynamics of cell divisions in the presence of external anisotropic stress. We showed that Hertwig's rule emerges as a limiting-case behavior and how anisotropic mechanical stresses can provide important cues to guide cell divisions. Our model accounts for the division pattern observed in the epidermis of the embryo of ascidian *Phallusia mammillata*, including those reproducible observed deviations from Hertwig's rule which have so far eluded explanation.

This work was part of the *Digem* project.

This work has been presented in two national conferences: the *IBC Scientific Days* and the *Cell Cycle Days* both held in Montpellier. A paper is currently being written.

Automatic quantification of adhesion defects in microscopy images. Direct measurements of mechanical stresses experienced by living tissues are not yet feasible. To circumvent this limitation, we developed an indirect method based on measurements of cracks in tissues: Our biologist colleagues developed cell-adhesion mutants in which strong connections between epithelial cells are impaired. As a consequence, mechanical stresses within the tissue produce cracks. Distribution and orientation of these cracks can be related to the main directions of the mechanical forces at play. We developed a 2D image analysis pipeline to detect and quantify these cracks in microscopy projections of epithelia, and deduce the magnitude and orientation of tensions in organs and tissues. This tool has been used to evidence new mechanical signaling mechanisms in *Arabidopsis*.

This analysis pipeline has been published in [6] and used by collaborators in the analysis performed in [26].

[6] leaf-like organs surrounding and protecting flowers

6.5. Signaling and transport for tissue patterning

Participants: Romain Azaïs, Guillaume Cerutti, Christophe Godin, Bruno Leggio, Jonathan Legrand, Teva Vernoux [External Collaborator].

- Research Axes: **RA1** (*Representations of forms in silico*) & **RA2** (*Data-driven models*)
- Key Modelling 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 patterning spatial precision. 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 during growth governs the rhythmic patterning of organs, and the consequent emergence of phyllotaxis. Using *Arabidopsis thaliana* as a model system, we developed 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 a method to quantify in 3D the polarization of auxin transport for every anticlinal wall of the first layer of cells. The digitally reconstructed network evidenced an overall stable convergence of PIN1 polarities towards the center of the meristem, with local front lines matching dynamic accumulations of auxin [15]. It also showed that the apparent crescent shape often thought to indicate polarities in cells might sometimes be misleading, and opens the way for a new view of how auxin transport is regulated.

Temporal 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. This model assumes that organ initiation results from a temporal integration of a morphogenetic signal that buffers molecular noise [22]. 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 [15]. The duration of cell exposition to auxin is used to differentiate temporally sites of organ initiation, and provide robustness to the rhythmic organ patterning.

Computational models of integrated transport and signaling. To interpret these new observations of auxin signaling and transport in the meristem, we investigate theoretical and computational models to study dynamic auxin distributions and the consequent organ patterning at the level of the meristem. Building on existing models of auxin transport [23], [25], we investigate different competing hypotheses on the auxin-PIN interplay, through numerical simulations based on rate equations for molecular transport and efflux carrier polarization. Quantitative comparisons with in vivo observations will provide cues on how the system responses are linked to memory effects and information exchanges between auxin and PINs.

These works were part of the *BioSensors* HFSP project and are carried out in the *Phyllo* ENS-Lyon project and gave rise to a journal article submitted for publication. These results have been presented at the *International Worskhop on Image Analysis Methods for the Plant Sciences* in Nottingham in January 2018 and in several invited talks given by Teva Vernoux and Christophe Godin.

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 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. A paper relating this work is currently under 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.

7. Bilateral Contracts and Grants with Industry

7.1. Bilateral Contracts with Industry

Participants: Frédéric Boudon [External Collaborator], Christophe Godin.

We started a collaboration with A.M.R. a start-up whose aim is to develop a web application to create social networks for project management. This application makes use of plant representations at different levels for which the expertize of the Mosaic group was required. In 2018, we hosted two internships during 6 months in co-supervision with Guillaume Asselot (founder of A.M.R.) to work on plant models for the web application. Guillaume Asselot is seeking to raise new funds to pursue the collaboration in the coming years.

8. Partnerships and Cooperations

8.1. Regional Initiatives

8.1.1. 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.

8.1.2. IDEX Lyon Impulsion - MecaField (2019 - 2020

Participants: Christophe Godin, 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.

8.2. National Initiatives

8.2.1. 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

8.2.2. 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.

8.2.3. ANR - ReVeRIES

Participant: Guillaume Cerutti.

The aim of ReVeRIES (Reconnaissance de Végétaux Récréative, Interactive et Educative sur Smartphone) is to make use of mobile technologies to transmit general knowledge and identification skills on the plant world to an urban audience who has little to no botanical background. Following the work of the ReVeS project and the development of the Folia mobile application, a major objective is to recognize automatically the species of trees and shrubs encountered in France using photographs of their leaves, fruits, flowers and barks, while providing the user the botanical vocabulary and the keys to learn how to identify species.

Partners:

- EVS Laboratoire Environnement Ville et Société, Saint-Etienne
- IRHS Institut de Recherches en Horticulture et Semences, Angers
- LIRIS Laboratoire d'Informatique en Image et Système d'Information, Lyon
- LISTIC Laboratoire d'Informatique, Système, Traitement de l'Information et de la Connaissance, Annecy
- LIUM Laboratoire d'Informatique de l'Université du Maine, Le Mans

8.2.4. 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

8.2.5. 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

8.2.6. 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

8.3. European Initiatives

8.3.1. 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.

8.3.2. Inria International Partners

8.3.2.1. Informal International Partners

8.3.2.1.1. 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)

8.4. International Research Visitors

8.4.1. Visits of International Scientists

8.4.1.1. Internships

Farah Ben Naoum, associate professor at the University of Sidi Bel Abbes, paid a one-month visit (July 2018) in the Mosaic group to work with Romain Azaïs and Christophe Godin on algorithms to compute incrementally tree-edit distances based on their directed acyclic graph representation. This visit was funded by Inria and will be followed by another one month visit in March 2019 to complete the writing a related paper.

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific Events Organisation

9.1.1.1. Member of the Organizing Committees

- Romain Azaïs is a member of the organizing committee of the *Journées de Statistique 2019* in Nancy.

9.1.2. Journal

9.1.2.1. Member of the Editorial Boards

- C. Godin is:
  - Associate Editor of the journal Frontiers in Plant Sciences, section Plant Biophysics and Modeling.
  - Review Editor of the journal Frontiers in Plant Sciences, section Plant Systems and Synthetic Biology.
  - Member of the Editorial Advisory Board of the new journal *in silico* Plants.
  - Associate Editor of a special issue of the Bulletin of Mathematical Biology on Multi-scale modelling of Tissue Growth and Shape.
- Olivier Ali: Review Editor in *Plant Biophysics & Modeling for Frontiers* since January 2018

9.1.2.2. Reviewer - Reviewing Activities

All team members are regularly involved in reviewer activities for academic journals from different scientific fields: Current Biology, Annals of Applied Probability, Journal of Theoretical Biology, Physical Review Letters, Journal of BioPhysics, Physical Review A, etc.

9.1.3. Invited Talks

- Romain Azaïs:
  - *Arbres de Galton-Watson conditionnés par la taille ou la hauteur : estimation via les modèles limites*. Journée de rencontres scientifiques autour de la statistique pour la biologie et la médecine, Poitiers, February 2018.
  - *Quelques pistes pour l'analyse de données arborescentes*. Rencontres Statistiques Lyonnaises, March 2018 (I/II) and May 2018 (II/II).
  - *Un nouvel éclairage sur le subtree kernel pour données arborescentes*. Séminaire de Probabilités et Statistiques de l'Université de Montpellier, September 2018.
  - *Average number of crossings and rupture detection for piecewise-deterministic processes*. International conference STODEP, Rouen, October 2018.
- Christophe Godin:

  - *Can we manipulate tree forms like numbers?*, co-authored with Romain Azaïs. Workshop on Mathematics for Developmental Biology, BIRS Center for Mathematics in Banff, Canada, Dec. 2017.
  - *Functional-Structural modeling of plants*, co-authored with Arezki Boudaoud. Phytobiom days in Lyon. France, April 2018.
  - *Phyllotaxis at the era of molecular and computational biology: the revival of an old enigma*, co-authored with Teva Vernoux. Jacques Monod series of international conferences in Roscoff, France, Sept 2018.
  - *Coupling mechanical and hydraulic processes in multicellular models of plant development*, co-authored with Ibrahim Cheddadi. Workshop on the Contribution of cell mechanics to cell fate determination and tissue integrity: from an interdisciplinary point of view. Fondation des Treilles, France, Oct. 2018.
- Bruno Leggio (with J. Laussu, E. Faure, C. Godin and P. Lemaire): *Reproducible epidermal morphogenesis in ascidians: an active-reactive mechanical model*. Cell Cycle Day 2018, Montpellier, September 2018.

9.1.4. Scientific Expertise

- C. 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).
  - has reviewed a project for the Strategic Basic Research programme of the Flanders fundation for research (FWO), Belgium.

9.1.5. Research Administration

- C. 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.
  - is a member of the Scientific board of the modeling axis of Labex NUMEV and a member of the direction board of the institut de biologie computationnelle (IBC) in Montpellier.
  - has been President of the 2018 CRCN Selection Jury at Inria Sophia Antipolis-Méditerranée

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

- Romain Azaïs:
  - *Colles de Mathématiques*, CPGE PCSI, Lycée Jean Perrin, Lyon.
  - One-day course on *Statistical learning*, Bioinformatics Summer School, Angers, July 2018.
- Guillaume Cerutti: *Practicals in modeling for Biosciences*, M2 ENS de Lyon (20h TP)
  Coordinator: Arezki Boudaoud, RDP, ENS de Lyon.
- Christophe Godin:
  - Co-organized with Patrick Lemaire the International Spring School on *Animal and Plant Morphogenesis*, one week in March, Paris ENS Master, Montpellier, France.
  - *Introduction to Microscopy image analysis*. Master Biology ENS de Lyon (2h).

- Bruno Leggio:
  - Conception and supervision of practicals for masters and PhD students during the 2018 *Interdisciplinary spring school on animal and plant morphogenesis*, Hameau de l'Etoile, Montpellier, France, March 2018.
  - One-day class for biophysics students at the University of Montpellier on the *modeling of morphogenesis*, December 2018.

9.2.2. Supervision

- PhD (2015 – 2018): Sarah Bertrand (LIRIS, Université Lumière Lyon 2). *Analyse d'images pour l'identification multi-organes d'espèces végétales*. Guillaume Cerutti. Supervisors: Laure Tougne (LIRIS, Université Lumière Lyon 2) and Guillaume Cerutti.
- PhD in progress (2015 – 2019): Florine Greciet (IECL, Université de Lorraine and Safran). *Modèles markoviens déterministes par morceaux cachés pour la caractérisation de contrainte admissible en fatigue des matériaux*. Supervisors: Anne Gégout-Petit (Inria team BIGS, IECL, Université de Lorraine) and Romain Azaïs.
- Master 1 (3 months in 2018): Florian Ingels. *Méthodes à noyau pour données arborescentes*. Supervisor: Romain Azaïs.
- Licence 3 (2 months in 2018): Clément Legrand. *A COMPLETER*. Supervisor: Christophe Godin.
- Niveau à completer (durée à compléter): Tony Vincent Ang. *A COMPLETER*. Supervisors: Christophe Godin and Frédéric Boudon.
- Niveau à completer (durée à compléter): Renan Berruex. *A COMPLETER*. Supervisors: Christophe Godin and Frédéric Boudon.
- Penser à Hadrien Oliveri, Katia Mirande, Anne Schneider

9.3. Popularization

9.3.1. Articles and contents

- Christophe Godin
  - made a presentation at *My team in 180 seconds*, June 2018 (in French).
  - wrote a paper *Pourquoi les Plantes font des maths* co-authored with Fabrice Besnard and Teva Vernoux, that was published in Pour La Science (Aug 2018) and in the hors-série issue on *La révolution végétale* (Nov 2018). (Nov 2018)

9.3.2. Interventions

- O. Ali has been an invited speaker for an art/science conference and debate organized by the modern art museum of Lyon, October 2018.
- Romain Azaïs won a special mention in the comics contest *Maths et Polar* organized by the website *Image des Mathématiques* of the CNRS, April 2018.
- Guillaume Cerutti, Christophe Godin and Jonathan Legrand have been involved in Déclics initiatives (presentation and discussion with high school students in order to promote science and research careers), October and December 2018.
- Christophe Godin gave an invited 2 hours seminar to 4 classes of high-school students for the Math week (March) at the Lyce ´e International de Valbonne, France.
- H. Oliveri took part in the Class'Code Initiative, a Mooc produced by Inria and OpenClassRoom providing supports and guidelines for people wanting to teach computer science to young childrens.

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