Modelling the regulation of biological systems at multiple scales: phenotypic variability and response to environmental changes

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Modelling the regulation of biological systems at multiple scales: phenotypic variability and response to environmental changes

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Introduction

Biological systems have a hierarchical organisation at different spatial and time scales, with multiple levels of regulation both within and between layers (Figure 1). At the cell scale, genetic and epigenetic mechanisms regulate the expression of genes, which code for enzymes, involved in the uptake and synthesis of metabolites, and regulatory proteins. In turn, these proteins can affect the expression of genes, giving rise to complex biochemical networks, with numerous feedback loops.
When moving to multicellular systems, the picture becomes even more complex, as additional regulatory mechanisms emerge at various spatial scales. In tissues, for instance, inter-cellular communication mechanisms exist via the diffusion of mechanical and chemical signals that are able to control important morphogenetic processes [Coen *et al.*, 2004]. At higher scales, transport through dedicated vascular systems regulate the delivery and accumulation of nutrients, hormones and other signalling molecules, coordinating developmental, physiological and stress-related processes at the scale of the whole organism [Lucas *et al.*, 2013].

The study of the mechanisms underpinning the regulation of biological system is the domain of system biology. The field arose during late 90s in opposition to the conventional biology as the study of large systems of interacting biological components. System biology, indeed, views biological processes and functions as emerging properties of the system, that cannot be reduced to the biochemical properties of the individual entities. Within this framework, system biologists initially focused on one single regulatory level. Methods were conceived to describe gene, metabolic or signaling networks, using adapted formalisms and approaches [Szallasi *et al.*, 2006]. In parallel important advancements in experimental, (bio)informatics and statistical tools considerably extended our capacity to quantify, analyse and visualize a large number of components.
Since a few years, system biology reached a new turning point. The challenge is now to scale up to multiple regulatory levels, understanding the way biological processes interact and coordinate across different organizational scales. This objective is accompanied by an increased awareness of the intrinsic variability of biological systems. As far as more complex system are concerned, indeed, phenotypic differences among cell types (gene expression, metabolic capacities, shape ..), tissues (mechanics..) and organs (structure, function..) become more and more evident, giving rise to a collection of systems within the system. Phenotypic (and genetic) variability has important consequences on the dynamics of the system and can shape the way it responds to changes in both abiotic and biotic conditions [Nicotra *et al.*, 2010, Heil, 2010]. Within this framework, my research project aims to investigate the interplay between different regulatory mechanisms [8], in relation to phenotypic diversity and environmental conditions.

In the objective of modelling, this calls for a multi-scale perspective that focuses on the interplay between molecular, cellular and macroscopic phenomena (Figure 2). From a theoretical point of view, multi-scale modelling means to explicitly integrate mechanisms of different nature, *e.g* biochemical, hydraulic, mechanical, that take place on distinct temporal or spatial scales [Southern *et al.*, 2008]. Molecular processes (metabolism, gene expression, protein synthesis, etc.) for instance take place in

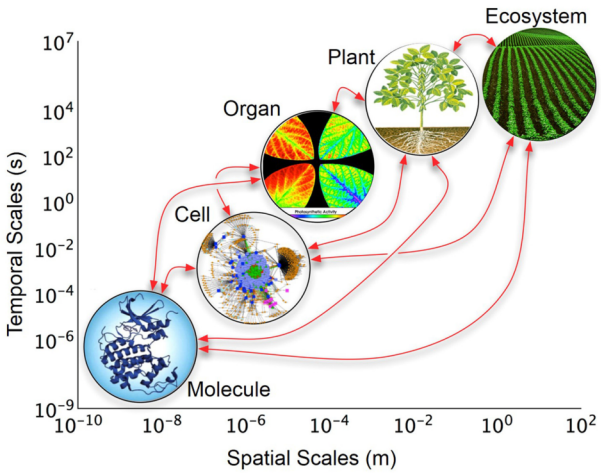


Figure 1: Layers of biological organisation across different spatial and time scales. Arrows indicate possible interactions between levels. Figure from [Marshall-Colon *et al.*, 2017].

a time window ranging from the second to a few minutes, while the timescale of interest in agronomy is of the order of the day or even the season. The challenge is then to select a reference timescale and then correctly simplify the processes that occur at different velocities, keeping the relevant information while reducing model complexity.

During my career, I had the opportunity to work on a variety of biological systems, using a panel of model formalisms. Although this variety of topics makes the writing of an HdR thesis a bit more complex, it offered me the possibility to explore different aspects of system biology and to make a "bridge" between modelling approaches originally developed in separate contexts. Based on my experience, two main approaches are possible for multi-scale integration. The first one relies on an intensive computational effort and is based on the numerical integration of multiple sub-models, each one describing a well-defined physiological mechanism. This leads to models that can be hybrid, linking mathematical formalisms and modelling strategies that differ both in their structure (1D, 2D vs. 3D, analytic vs numerical) and in their approach (qualitative vs. quantitative, deterministic vs. stochastic). Model reduction techniques may be used to simplify the mathematical structure of each sub-model, reducing the system size or the number of parameters to be identified [Snowden *et al.*, 2017]. This approach has the advantage of a direct connection with experimental data and an easier molecular interpretation that may facilitate the interaction with biologists and agronomic engineers. Indeed, within the plant sciences community, this approach is currently valued as a promising tool to improve plant management and breeding [Peng *et al.*, 2020, Benes *et al.*, 2020]. In practice, a number of limitations arise along with model complexity. Model parametrisation is often uncertain due to the large number of parameters (typically from 50 to 200 in whole-plant ecophysiological models) and strongly depends on the considered plant genotype. Moreover, an exhaustive analysis of possible model behaviours is generally difficult to obtain, hindering the identification of generic and robust mechanisms.

A second possible strategy, coming from the microbial community, involves a "multi-model" approach that aims at developing different models, at different levels of abstraction, for a *same* biological question. The idea here is that, given the intrinsic complexity of biological systems, it may be difficult for a single model to capture all the regulatory levels. In order to make the corresponding model tractable, a number of simplifying hypotheses can be made, resulting in different viewpoints for a same scientific question. A good example is offered by the study of microbial growth where a number of models have been developed at different degree of complexity, scaling from the description of steady-state metabolic reactions over a realistic biological network, possibly including thermodynamic or proteome allocation constraints, up to coarse-grained dynamical models, explicitly accounting for the non-linear dependence between biomass synthesis and growth over a small set of macroreactions [de Jong *et al.*, 2017, de Groot *et al.*, 2020]. Thanks to their simplicity, coarse-grained models can help to better understand fundamental principles of system functioning and are suitable to analyse

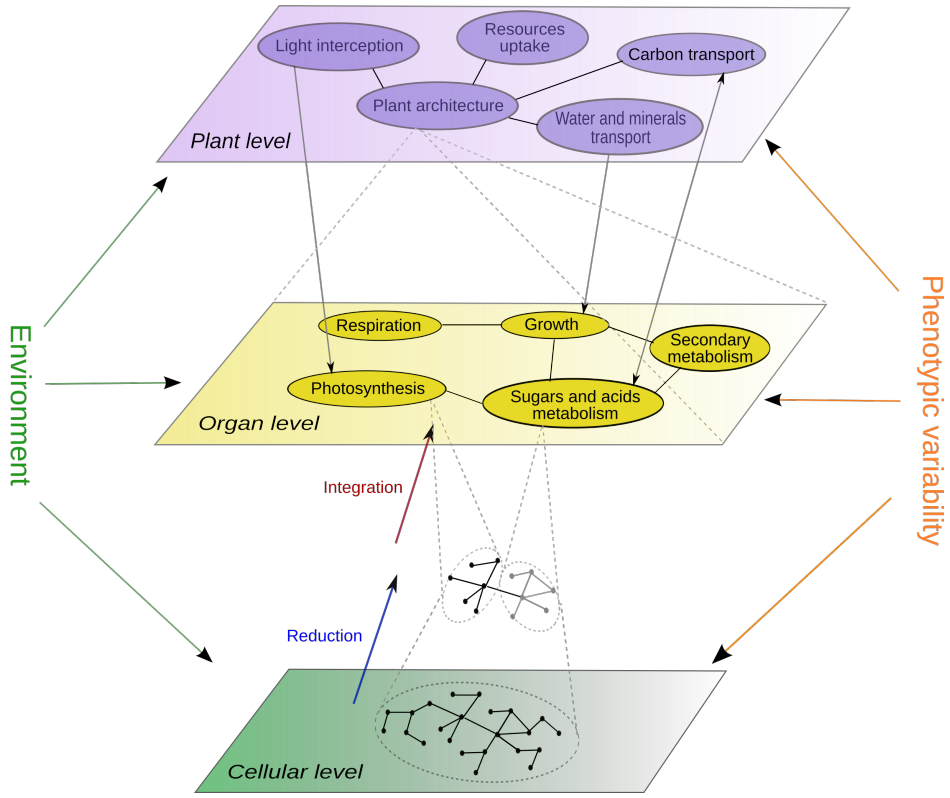


Figure 2: Regulatory levels and construction of a multi-scale plant model: overview. Methods from systems biology can be used to analyse and model cellular networks in order to get a simplified description of cellular functioning (reduction step). Once built, the reduced cellular model can be integrated into a higher-scale model (here exemplified by an organ model), following a multi-scale modelling approaches (integration step). In order to scale up to the phenotype of a whole plant, multi-scale modelling of selected processes can be combined into more macroscopic approaches, accounting for resource uptake and allocation among different plant organs.

global shifts in growth control following a change in the environment [de Jong *et al.*, 2017]. The drawback, of course, relies in the risk of excessive simplification and in a reduced correspondence with molecular data, both for parametrization and validation. In some cases, results obtained from simpler models can help identify key regulatory mechanisms, that can then be integrated into larger models [Cheng *et al.*, 2019].
Ultimately, both the integrative and the multi-model approaches can provide interesting insights into system functioning. The choice of the approach in not unique and strongly depends on the scientific question and the objective of the study. System size and data availability are also important determinants as integrative approaches usually require a lot of molecular information, which is not always available. In this sense, the study of multi-cellular systems having a long-development time, like plants, poses a number of technical constraints, reducing the quality and the quantity of available molecular data with respect to simpler unicellular systems. In my works, I mostly followed a multi-model approach, focusing on interactions between few (two, three at most) organizational layers at time. Depending on the context and available data, interactions could be described mechanistically or by means of data-derived inputs that acted as constraints on the possible dynamics of the model.

In the following I briefly present my past research activities, from my PhD thesis up to 2016, when I moved to Sophia-Antipolis and joined the Institut Sophia Agrobiotech and the Inria project-team Biocore. Current and future projects are detailed in the last chapter of this manuscript.

CHAPTER 1

Past research activities

This chapter is divided into two parts that roughly correspond to my Italian (2002-2007) and French (2007-ongoing) research period. In the first one, partly as a consequence of my formation as a physicist, the focus was set on individuals (either in isolation or as part of a larger system) and on how stochastic effects may affect their behaviour. In the second, the emergence of a robust, average behaviour of large biological systems was investigated as a consequence of the multiple interactions among their components and as a function of environmental conditions.
During my career, I had the chance to work with colleagues of many different backgrounds, including mathematicians, computer scientists, biologists and agronomists. Each of them has brought knowledge, data and a personal regard on the biological system under study. Indeed, although I may sometimes use the "I" form, all the results I will show in the following sections would not have been possible outside such an inter-disciplinary environment and without the contribution of all the people involved.

1.1 Italian period: stochastic, individual approaches

1.1.1 PhD: Mechanical statistics of DNA unzipping experiments

I made my PhD in the framework of a cotutelle project between the University of Rome "Tor Vergata" and the University of Strasbourg "Louis Pasteur", under the joint supervision of Dr. L. Biferale (University of Rome "Tor Vergata"), E. Marinari (University of Rome "La Sapienza") and Simona Cocco (University of Strasbourg "Louis Pasteur" & ENS Paris). My work set in the research field of theoretical biophysics and focused on the analysis of mechanical unzipping experiments in which the two complementary strands of a DNA molecule were pulled apart by the application of a force [Bockelmann *et al.*, 1998, Bockelmann *et al.*, 2002, Danilowicz *et al.*, 2003]. Experiments showed that the unzipping dynamics was strongly correlated to the underlying DNA sequence. Remarkably, the unzipping signal could be affected by the substitution of one single base pair, when adequately located along the sequence [Bockelmann *et al.*, 2002]. The aim of my thesis was to investigate the inverse problem *i.e.* whether one could get informations on the DNA sequence from unzipping data. For this aim, we proposed a method based on the use of statistical Bayesian inference and of Viterbi decoding algorithm [Viterbi, 1967].

At first, the reconstruction ability was studied under the hypothesis of an infinite spatial and temporal resolution. The effects of thermal fluctuations, intrinsic to any unzipping experiments, were analysed, setting an upper bound to the achievable sequencing accuracy [1]. We showed that the probability of misprediction decreases exponentially with the amount of collected data [1]. The decay rate was calculated as a function of biochemical parameters (binding free energies), the sequence

content, the applied force, the elastic properties of a DNA single strand and time resolution [1]. We then moved to a more realistic case where opening events were known to a very good, but not infinite, time resolution. In this case, the dynamic information available for the reconstruction was reduced, making the actual fork dynamics unknown. Numerical and theoretical analyses showed that DNA sequencing was still possible. In particular, we showed that multiple unzippings of the same molecule might be exploited to improve the quality of the prediction, and calculated analytically the number of required unzippings to discriminate between strong (C/G) and weak (A/T) bases or for a complete sequence recognition [3].

1.1.2 Post-doc: Computational immunology

After my PhD thesis, I was hired as a post-doc in the group led by M. Bernaschi and F. Castiglione, at the Istituto Applicazioni del Calcolo (IAC), in Rome. The team was developing an immune system simulator, called C-ImmSim, based on stochastic cellular automata. This was for me an opportunity to improve my programming skills, that I started to acquire during my PhD, working on a large and complex code. It also represented my first contact with the world of "system biology" *i.e.* the study of complex system in which the emergence of a biological behaviour derives from the interaction among many individual components.
At the time of my recruitment, the simulator included the description of different cells classes (T and B lymphocytes, macrophages, dendritic cells..), all living in a discrete lattice space, in which they randomly moved. Each cell class corresponded to a different automaton, with specific attributes. When on the same lattice site (*i.e.*, within the same unit of volume), cell entities could interact according to a probabilistic affinity function that depended on the values of their attributes. In its original formulation, the model used an homogeneous two-dimension triangular lattice with periodic boundary conditions. However, lymphocytes motility plays a central role in determining the efficiency of the immune response. In particular, within the lymphoid organs, diffusion and chemotaxis affect the cellular organization and the dynamics of interactions among immune cells.

The aim of my post-doc was to improve the description of the cell motion, accounting for differences in cell velocity and chemotactic response. To this purpose we first upgraded the simulator to a three-dimensional mesh having the typical ellipsoid shape of a lymph node [2]. Internally, the mesh was divided into 3 distinct regions, each one characterized by the secretion of specific chemotactic molecules, able to attract cells expressing the corresponding receptor.
In order to account for chemotaxis and time-scale difference between cell and molecule mobility, I developed a hybrid discrete/continuous approach, that combined a stochastic agent-based description of cell interactions with a continuous model of chemokine diffusion described by partial differential equations [4]. Once calibrated, the model reproduced the correct timing of an immune response, including the observed time delay between the duplication of T helper cells and of B cells in response to antigen exposure. Given its mechanistic nature, the model was then used to investigate the role of specific biological mechanisms on the emergence of the resulting immune response [4].

1.2 French period: average behaviour and environmental response

My arrival in France marked the broadening of my research themes towards the intra-cellular scale. During my post-doc at Inria, first, and then as a researcher at INRAE, I got interested on the molecular, biophysical and genetic mechanisms that allow biological systems to adapt to changes in their environment and that set the bases of the observed phenotypic differences. From the methodological point of view, this transition was accompanied by a change in modelling formalism. Stochastic approaches were replaced by an ODE formalism, more adapted to capture the *average* behaviour of a system composed of a large number of components. Indeed, although stochasticity may play an important role in several cellular and molecular processes, the experimental data I disposed of were not accurate enough to capture its potential effects. Measurements over an ensemble of individuals (plants, fruits, bacteria etc) were used instead, which made the ODE formalism more adapted. On

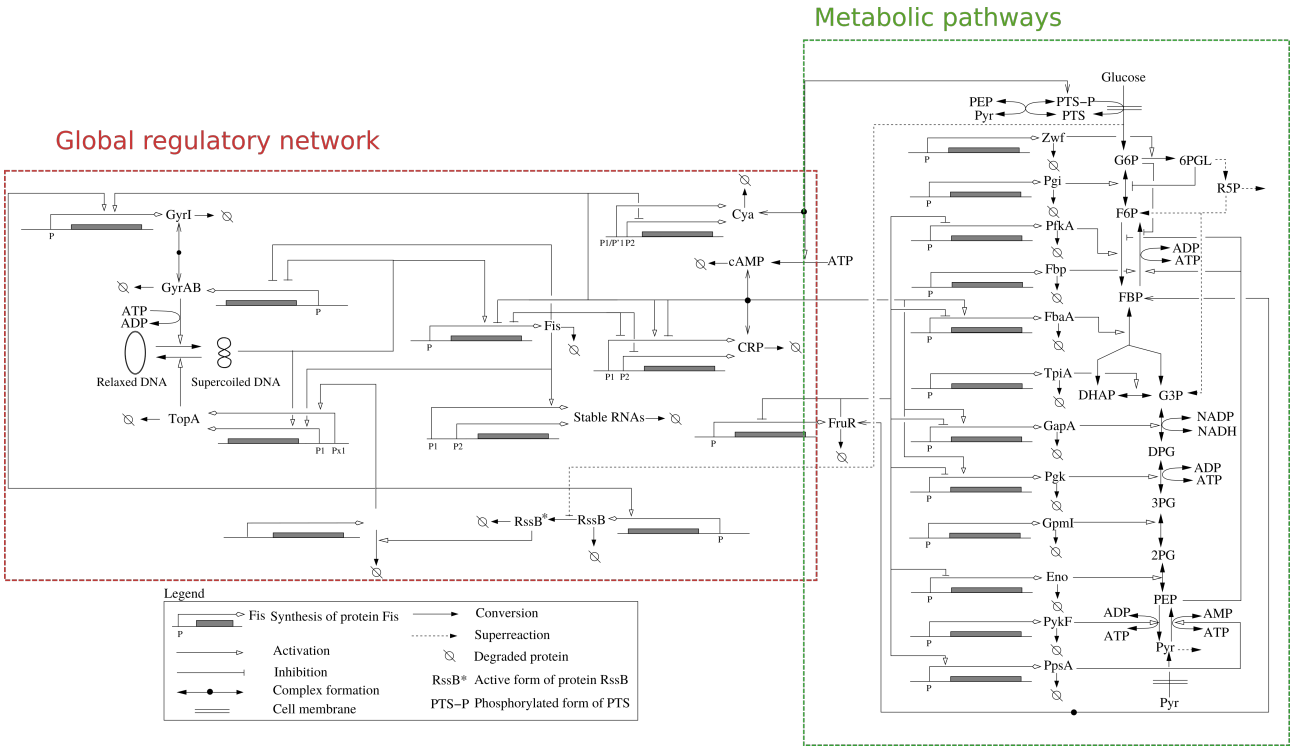


Figure 1.1: Upper part of the carbon assimilation network in *E. coli*, consisting of the glycolysis and gluconeogenesis pathways and their genetic and metabolic regulation [5]. On the left side, the red-bounded part represents the global regulatory network considered in [6]. The graphical conventions are explained in the legend.

the other hand, I had to face new kind of issues, related to the large number of variables, the absence of precise quantitative information on kinetic parameters and the presence of multiple time-scales that made these models difficult to handle both mathematically and computationally. Appropriate model reduction strategies had to be found to reduce the size and complexity of the models and to numerically estimate the parameter values needed to reproduce experimental observations.

1.2.1 The genetic control of metabolism

The carbon assimilation network in Escherichia coli

The biochemical network controlling the adaptation of the bacterium *E.coli* to changes in nutrient availability is a good example of a nonlinear, multi-scale system, that involves adjustments in the expression of genes coding for enzymes, regulators, membrane transporters, signalling molecules etc. When considering large biochemical networks, the interactions in the network may be direct, as in the case of a gene coding for a transcription factor regulating the expression of another gene. Most of the time, however, regulatory interactions are indirect, *e.g.* when a gene encodes an enzyme producing a transcriptional effector [Brazhnik *et al.*, 2002]. By ignoring indirect interactions mediated by metabolic and signalling pathways we may miss crucial feedback loops in the system.

For this aim, we developed a method for the systematic derivation of direct and indirect interactions in a gene regulatory network from the underlying biochemical reaction network, based on the assumption that the metabolic and signaling processes are fast on the time-scale of gene expression [5]. Briefly, we started from a kinetic model of the biochemical network of the form

$$\dot{x} = N\, v(x), \qquad x(0) = x_0. \tag{1.1}$$

where $x \in R_+^n$ denotes the vector of concentrations and $v : R_+^n \to R^q$ and $N \in Z^{n\times q}$ is the stoichiometry matrix of the system. We then introduced vectors of slow and fast variables, $x^s \in R_+^m$ and

$x^f \in R_+^{n-m}$, respectively ($m < n$), defined as linear combinations of the original variables x:

$$\begin{bmatrix} x^s \\ x^f \end{bmatrix} = T\,x, \tag{1.2}$$

with $T \in Z^{n\times n}$. The slow variables typically corresponded to total protein concentrations, whereas the fast variables included concentrations of metabolites and biochemical complexes. The QSS hypothesis stated that at the time-scale of the slow processes, the fast part of the system could be assumed to be at steady state, instantly adapting to the dynamics of the slow variables, *i.e.* $N^f\,v^f(x^s, x^f) = 0$, where N^f is stoichiometry matrix for the fast part and $v^f(x^f, x^s)$ the corresponding reaction rates . The resulting system at the slow time-scale had the following form

$$\dot{x}^s = N^s\,v^s(x^s, g(x^s)). \tag{1.3}$$

By studying the sign of the elements of the Jacobian matrix $\mathcal{J}$ of the system in Eq. 1.3, we could get information on the interaction structure of the gene regulatory network:

$$\mathcal{J} = \frac{\partial \dot{x}^s}{\partial x^s} = N^s\,\frac{\partial v^s(x^s, x^f)}{\partial x^s} + N^s\,\frac{\partial v^s(x^s, x^f)}{\partial x^f}\,\frac{\partial g(x^s)}{\partial x^s} \tag{1.4}$$

The Jacobian matrix indeed accounted for direct regulation of gene expression by transcription factors (first term) as well as indirect regulation through metabolism (second term).

Applied to the upper part of the carbon assimilation network in *E. coli* (Figure 1.1), this method leaded to three major insights. First, contrary to what was often assumed, the derived gene regulatory network was densely connected due to numerous feedback loops resulting from indirect interactions. Second, we found that the signs of the indirect interactions were largely fixed by weak information on flux directions of biochemical reactions, without explicit specification of kinetic rate laws or parameter values. Third, a change in environmental conditions might invert fluxes, and thus the signs of indirect interactions, resulting in a dynamic rewiring of the regulatory network. This leaded to a feedback structure that was at the same time robust to changes in the kinetic properties of enzymes and that had the flexibility to accommodate radical changes in the environment.

It remained an open question, however, to which extent the indirect interactions induced by metabolic coupling influenced the dynamics of the system. To address this issue, we used the topology obtained in [5] to build a piecewise-linear (PL) dynamic model of the gene regulatory network controlling carbon assimilation in *E. coli*, and used this model to study the changes in gene expression following a diauxic shift from glucose to acetate (see figure 1.2). Piecewise-linear (PL) differential equations encode the regulatory logic of the system by means of positive (s^+) or negative (s^-) step functions that abruptly change their value at a threshold value θ_j of the protein concentration x_j [26]:

$$s^+(x_j, \theta_j) = \begin{cases} 1, & \text{if } x_j > \theta_j \\ 0, & \text{if } x_j < \theta_j \end{cases}$$
$$s^-(x_j, \theta_j) = 1 - s^+(x_j, \theta_j)$$

By means of the threshold values, the phase space can be partitioned into hyper-rectangular regions in which the system behaves in an qualitatively homogeneous manner. As a result, the qualitative dynamics of the systems is much simpler to analyse as it depends only on the ordering of threshold parameters rather than exact numerical values, an information that can generally be inferred from experimental literature or by intuitive reasoning, even in the absence of quantitative information on parameter values. Moreover, we previously proved that PL-approximation were able to preserve the qualitative dynamics of the corresponding non-linear system, under a wide range of parameter values [6]. Qualitative models were therefore an appropriate tool for analysing if metabolic coupling could induce *major* changes in the gene expression dynamics, *i.e.* if they had an effect on both the quantitative and qualitative properties of the system dynamics. We built several qualitative models, corresponding to a network topology including all, some, or none of the indirect interactions

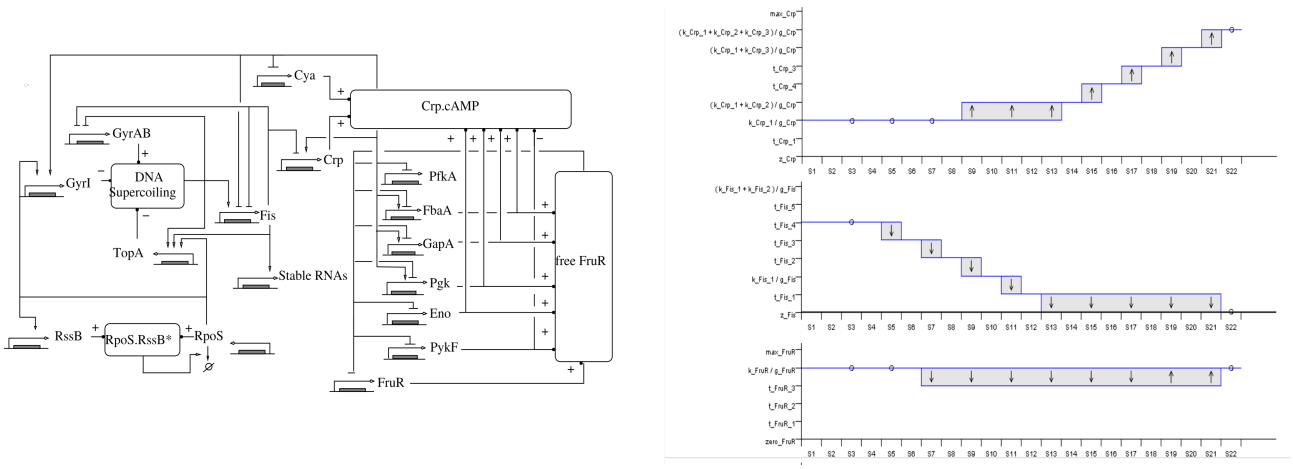


Figure 1.2: Left: Derived gene regulatory network for the glycolytic case [5]. The boxes represent fast coupling species, mediating the influence of metabolism and signal transduction on gene expression. The influence of the enzymes and other slow species on the concentration of the fast coupling species are represented by +/ signs. Right: Example of a qualitative simulation of the glucose–acetate diauxie [7]. The vertical axis shows the symbolic values of concentration variables, the horizontal axis indicates the qualitative states of the system (note that time is implicit in a qualitative model, given by the ordering of qualitative states). Transitions between qualitative states correspond to qualitative events, notably threshold crossings of the variables.

and compared their dynamics with available experimental data [7]. We found significant differences between the dynamics of the system in the absence and presence of metabolic coupling, confirming that indirect interactions were essential for driving the adaptation of gene expression to a change in carbon source.

Collaborations:

- H. de Jong, Inria, Grenoble
- D. Ropers, Inria, Grenoble
- H. Geiselmann, UGA, Grenoble
- D. Kahn, INRAE, Lyon

Associated projects:

- ANR project, MetaGenoReg
- EU project, EC-MOAN

Fruit sugar metabolism : intra-specific genetic variability

Sugar content is an important agronomic criterium for fruits. A strong diversity in sugar composition exists among fruit species but also within different accessions of a same species. Knowledge of the mechanisms involved in sugar metabolism is essential for the creation of fruit varieties that can meet consumer expectations.

In collaboration with Bénedicte Quilot-Turion (INRAE, GAFL, Avignon) we tried to decipher the molecular mechanisms underlying differences in sugar composition observed in a large peach progeny, obtained by backcross between a wild and a commercial variety. Within the large phenotypic diversity displayed by our population, 77 out of the 106 individuals under study exhibited a 'standard'

fructose-to-glucose ratio *i.e.* an equivalent concentration of glucose and fructose at maturity, whereas the remaining ones presented a 'low fructose' phenotype. We started by performing an exhaustive phenotyping of the underlying sugar metabolic network by assaying four metabolites and twelve enzymatic capacities at different stages of fruit development, using high-throughput methods (PhD thesis of E. Desnoues). Our results revealed a remarkable robustness of enzymatic capacities across genotypes and years despite strong variations in the sugar composition, discarding the hypothesis of a straightforward enzymatic control of sugar concentration in the fruit [11].

To better understand the origin of the observed phenotypic differences, we thus decided to build

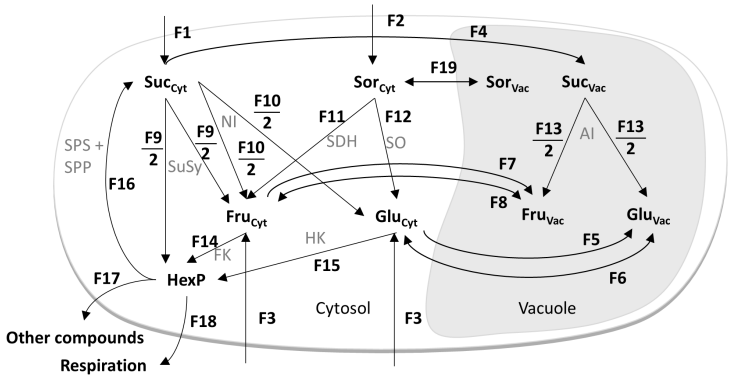


Figure 1.3: Schematic network of the peach fruit sugar accumulation model [20]. Arrows represent carbon flows. Abbreviations: AI, acid invertase; cyt, cytosol; FK, fructokinase; Fru, fructose; Glu, glucose; HexP, hexose-phosphate; HK, hexokinase; NI, neutral invertase; SDH, sorbitol dehydrogenase; SO, sorbitol oxidase; Sor, sorbitol; SPP, sucrose-phosphate phosphatase; SPS, sucrose phosphate synthase; Suc, sucrose; SuSy, sucrose synthase; Vac, vacuole.

a kinetic model of sugar metabolism in peach fruit [18, 20]. The model described carbon pathways through different metabolites and cell compartments during fruit development (Figure 1.3), as a set of ordinary differential equations. Cell compartmentalization (cytosol and vacuole) was described explicitly. Measured fruit mass growth (dry and fresh components) and enzyme activities were used to parametrize equations, leading to a system of equation of the form:

$$\frac{dx}{dt} = f(x(t), I(t), v(t), p), \qquad x(t_0) = x_0 \tag{1.5}$$

where $x \in R_+^{10}$ is the concentration vector of metabolites in the corresponding intra-cellular compartment, $I \in R_+$ is the time-dependent input of carbon from the plant and $v \in R_+^7$ is the vector of time-dependent measured enzymatic activities; $p = (p_1, \ldots, p_{23})$ is the vector of parameters defining the reaction rates. Dilution due to fruit expansion was accounted for, via its impact on metabolite concentrations and on the dynamical patterns of enzymes activities [12]. The model was calibrated on ten contrasted genotypes (five having a standard fructose-to-glucose ratio and five having a low-fructose phenotype) using literature information and numerical estimation of 14 parameters. The model correctly accounted for the observed annual and genotypic variations in sugar concentrations and provided important information on the mechanisms underlying the specification of phenotypic differences. In particular, the model supported the hypothesis that a difference in fructokinase affinity could be responsible for the low fructose phenotype, observed in the studied population. By modifying the value for the fructokinase affinity parameter (Kfk), indeed, fruits having a standard fructose content could be virtually transformed into low-fructose fruits, and conversely (Figure 1.4).

In order to validate this hypothesis and get further insights into the genetic control of sugar metabolism, it was necessary to calibrate the model over the whole progeny of 106 genotypes and to perform a QTL-analysis over the estimated parameters values [28]. Unfortunately, the size of the parameter space and the non-linearity of the reaction rates made the calibration of the original model difficult and extremely time-consuming. To overcome this problem, in collaboration with JL Gouzé

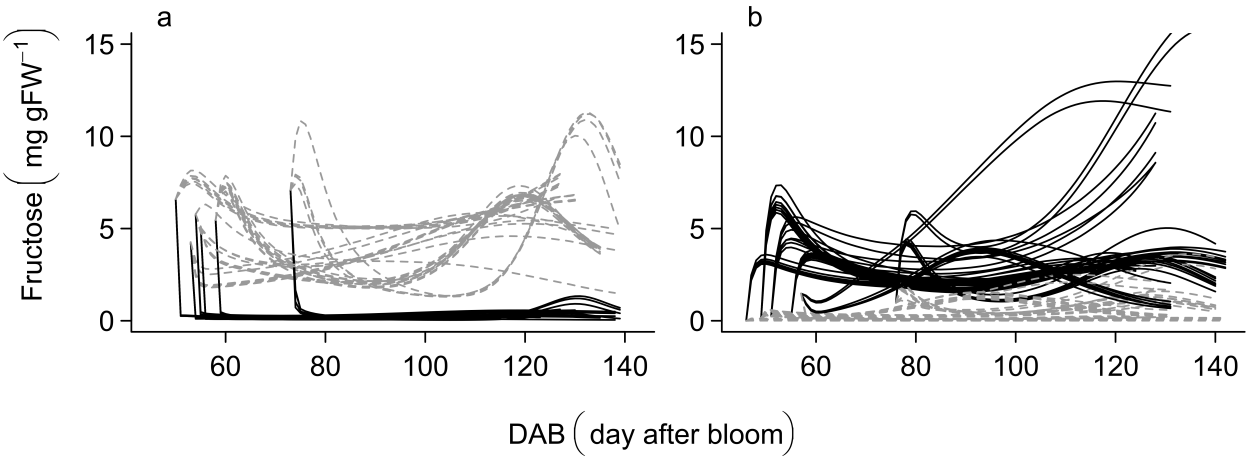


Figure 1.4: Simulated dynamics of fructose concentration during peach fruit development. (a) Black lines correspond to simulations of five genotypes with 'standard fructose-to-glucose ratio' phenotypes using average values of Kfk parameter estimated from genotypes with 'low fructose-to-glucose ratio' phenotype; (b) simulations of the five genotypes with 'low fructose-to-glucose ratio' phenotype with average values of Kfk parameters estimated from genotypes with 'standard fructose-to-glucose ratio' phenotype. Grey dotted lines correspond with original fructose concentration simulations.

et O. Bernard (Inria, BIOCORE, Sophia-Antipolis), the PhD thesis of H. Kanso (2017-2021) aimed at developing a reduction method that was adapted to the specificity of our objectives in that: i) it yielded a unique reduced model for whole population ii) it maintained network structure and variable identity, in order to facilitate the biological interpretation of the subsequent genetic analysis [24]. The retained reduction strategy was based on the systematic test of different methods in several parallel steps that, if retained, were combined together into a final reduced model. Three main criteria were used to asses the interest of each reduction method: i) the AIC value, evaluating the relative gain between model simplification and loss of accuracy over an experimental dataset, ii) the calibration time, as a measure of model efficiency, iii) the expected error between the original and the reduced model over a population of virtual genotypes, as a measure of the reliability of the simplification scheme over a large genetic diversity. Applied to the model of sugar metabolism by Desnoues et al.(2018), this procedure yielded a reduced model having linear reaction rates, a reduced size and only 9 unknown parameters (out of 14 in the original model). The model was shown to correctly reproduced data on the original ten genotypes with a gain in calibration time over 40%.
The reduced model was then calibrated on the whole inter-specific peach progeny of 106 genotypes. Two strategies for parameter estimation were tested, namely the estimation of each genotype independently and the estimation of all genotypes simultaneously, by means of non-linear mixed effect models [Baey *et al.*, 2018]. The two methods were compared based on goodness-of-fit criteria as well as on the robustness of the estimated parameters values, following multiple repetitions of the calibration algorithms. In spite of a satisfactory agreement between predictions and data, results showed that the genotype-by-genotype strategy suffered from a lack of reproducibility, with several parameters sets giving an equivalent agreement with data. The simultaneous estimation of all genotypes instead provided robust and accurate parameter estimates, thanks to the joint analysis of multiple datasets that further constrained the estimation process. Estimations obtained using a population-based scheme ultimately allowed for the analysis the genetic architecture of fruit sugar metabolism, and the identification of several genomic regions (Quantitative-Trait Locus, QTL) of interest. Two articles are currently in preparation on these topics. At term, the integration of genetic control into the model, using a QTL-based approach [28], will permit the design of new plant cultivars ('ideotypes') expressing an optimal

phenotype, adapted to a particular biophysical environment, crop management, and end-use.

Collaborations:

- B. Quilot-Turion, GAFL, INRAE, Avignon
- Y. Gibon, INRAE, Bordeaux
- M. Génard, PSH, INRAE, Avignon
- M.M. Memah,PSH, INRAE, Avignon
- O. Bernard, Biocore, Inria, Sophia-Antipolis
- J.L. Gouzé, Biocore, Inria, Sophia-Antipolis
- C. Baey, University of Lille

Students:

- E. Desnoues, PhD 2011-2015
- H. Kanso, PhD 2017-2021

Fruit sugar metabolism : inter-specific variability

In the works on peach fruit, we showed how phenotypic differences can arise within a same fruit species, following differences at the molecular level. In the case of different species, variations can be even stronger: fruit species can differ in the mechanisms of sugar import, in the accumulated metabolites as well as in the structure and regulation of the underlying metabolic network. Despite theses divergences, soluble sugar (S) accumulation in fruits can be resumed to three main processes: sugar import (u), sugar metabolism (m), and water dilution (d), due to fruit volume increase. Using a coarse-grained model of the form

$$\frac{dS}{dt} = u(t) + m(t) - d(t) \tag{1.6}$$

is thus possible to identify the relative contribution of each individual processes all along fruit development, across different species. This can help to understand whether the main control levers of soluble sugar concentration are species-specific or follow a species-overarching manner.
In a first work, in collaboration with Zhanwu Dai (INRAE, Bordeaux, now at the Chinese Academy of Sciences), the accumulation of soluble sugars in the fruit has been compared among 3 fruit species: peach, tomato and grape [17]. Developmental profiles of fruit flesh fresh weight, dry weight, and soluble sugar concentration were collected from both published and unpublished data, including different genotypes and growing conditions. Data were used to estimate the dynamics of the three considered processes and to compare their relative contribution to soluble sugar concentration, along fruit development. Our analysis showed the existence of different patterns for the control of soluble sugar concentration, either import-based, dilution-based, or import-dilution coupled. On the other hand, a conserved metabolic rate was observed among the three fruit species for the synthesis of cellular compounds other than sugars (*e.g.* starch, organic acids, structural carbohydrates, and proteins). The different modes of control appeared to be quite species-specific, but the intensity of the effect could significantly vary depending on the genotype and management practices.

Given the strong differences observed among species concerning their starch content, the thesis of C.B. Cakpo (2015-2019) aimed at extending the work of Dai et al. (2016) to a larger panel of species and to account for the role of starch metabolism and recycling in the dynamics of sugar accumulation. For this aim, we proposed a dynamical model explicitly describing the variation in sugar and starch

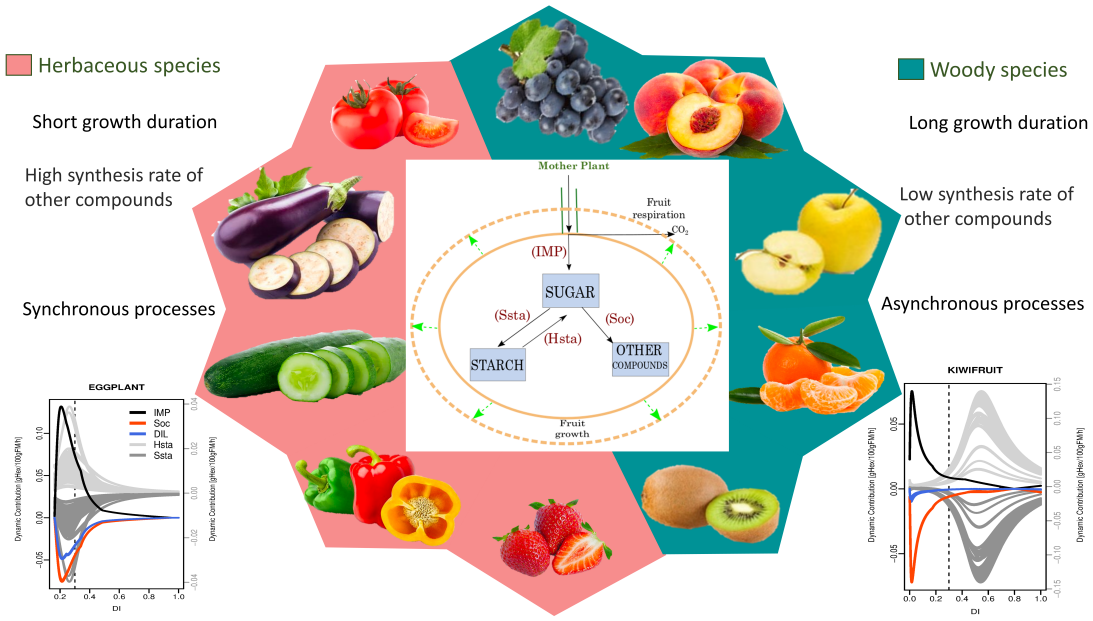


Figure 1.5: Schematic representation of the results obtained during the PhD thesis the C.B. Cakpo [25] on the comparison of sugar metabolism across 10 fruit species. A diagram of the model is reported at the center of the figure. Herbaceous species were characterized by a high synthesis rate of compounds other than sugar and starch (eg organic acids, structural compounds..), compared to woody species, and by a remarkable synchronization of sugar uptake, metabolism and dilution processes. In woody species starch metabolism was temporally separated from other processes.

concentrations during fruit development, based on generic reaction rates (Figure 1.5) [25]. The model was successfully calibrated on 10 contrasting species of fleshy fruits, including both starch-free and starch-rich species, and used to investigate the coordination and contribution of the different process (sugar import, sugar and starch metabolism, water dilution) to the accumulation of soluble sugars during fruit development. Results showed that species could be separated into six groups accordingly to the rate of synthesis of compounds other than sugar and starch (eg organic acids, structural compounds..). In particular, herbaceous species (cucumber, tomato, eggplant, pepper and strawberry) were characterized by a higher synthesis rate than woody species (apple, nectarine, clementine, grape and kiwi). Inspection of the dynamics of the processes involved in sugar accumulation revealed that net sugar importation, metabolism and dilution processes were remarkable synchronous in most herbaceous plants, whereas in kiwifruit, apple and nectarine, processes related to starch metabolism were temporally separated from other processes (Fig. 1.5).

Collaborations:

- Z. Dai, INRAE, Bordeaux
- Y. Gibon, INRAE, Bordeaux
- M. Génard, PSH, INRAE, Avignon
- G. Vercambre, PSH, INRAE, Avignon

Students:

- C.B. Cakpo, PhD 2015-2019

Associated projects:

- INRA CaKi project
- ANR FRIMOUSS project

1.2.2 The control of fruit growth

Fruit growth results from the interplay of several processes, of different nature, implying metabolic, biophysical, genetic and environmental factors. Nutrients and water needed for organ growth are assimilated at the plant scale, depending on environmental conditions, and then distributed through a network of specific vessels to the different organs. A panel of transport mechanisms allow for the unloading of assimilates into the developing organ, where they are metabolized into structural and soluble compounds, following a complex genetic and hormonal regulation. At last, cell expansion is the result of the interplay between cell mechanical properties and the turgor pressure, generated by the accumulation of water and solutes inside the cells.

In the following I will try to illustrate my contribution to this topic on the basis of the factors and the scale of interest that the models accounted for. Of course, this classification is motivated by presentation purposes, but in reality all scales contribute to the resulting phenotype, with many interactions and feedback loops between different organisational levels.

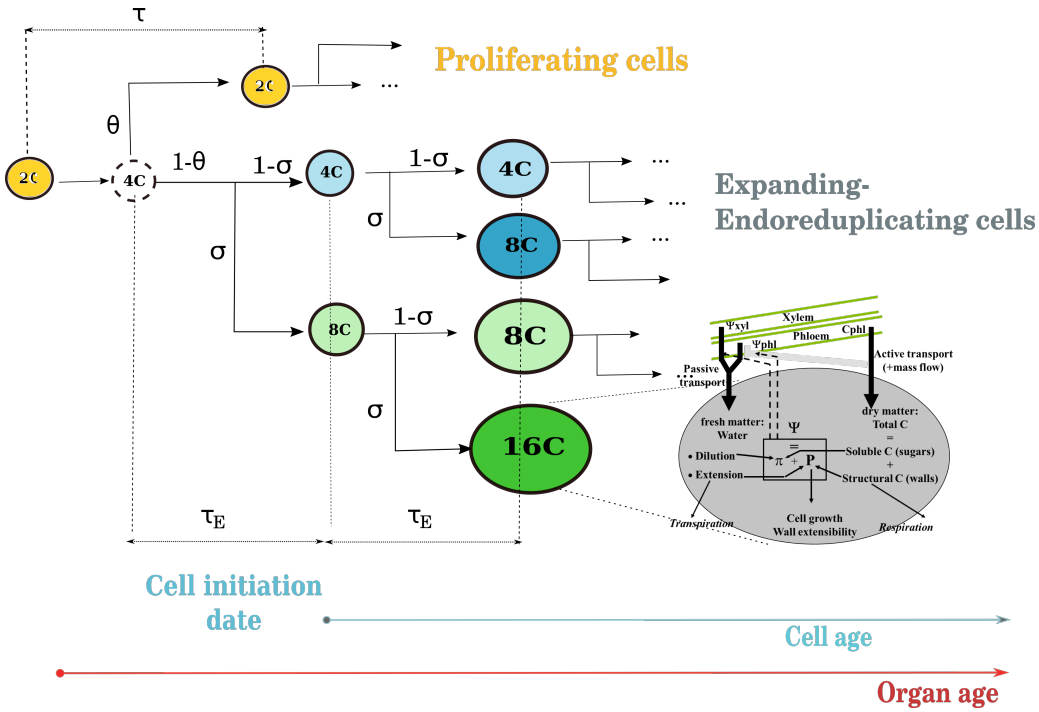


Figure 1.6: Structure of the integrated model of fruit development. The fruit is described as a collection of cell populations, each one having a specific age, ploidy and volume. Cell populations are indicated with different colors. Proliferating cells are lumped in a single population and assumed to have a constant volume, ploidy (2C) and age. Expanding cells grow according to a biophysical model describing the main processes involved in carbon and water accumulation. Two timescales are recognizable in the model: the organ age *i.e.* the time since the beginning of the simulation, and the cell age *i.e.* the time since the cell left the mitotic cycle and entered the expansion-endoreduplication phase.

Cell scale: process interactions in the early phase of fruit development

The development of a fruit, from its early stages, is the result of coordinated events of *cell division*, setting the total number of cells, *cell expansion*, setting the final cell sizes, and *endoreduplication i.e.*

Model Variant	ORGAN CONTROL	ENDO EFFECT		
	Symplastic transport	Active C uptake	Carbon allocation	Wall plasticity
M0				
M1	✔			
M2	✔	✔		
M3	✔		✔	
M4	✔			✔
M5		✔		
M6			✔	
M7				✔
M23	✔	✔	✔	
M24	✔	✔		✔

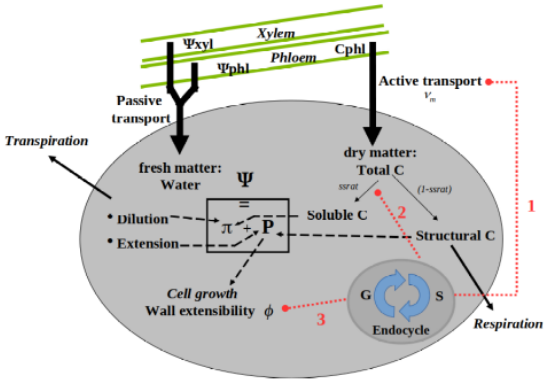


Figure 1.7: Left: Experimental design showing the characteristics of the 10 model versions tested in Baldazzi et al. (2019). Right: Schematic representation of the three hypothetical mechanisms of interaction between cell ploidy and cell expansion: 1. cell ploidy may affect the carbon uptake rate, 2. ploidy may increase the fraction of soluble components in the cell, thus increasing cell osmotic pressure, 3. ploidy may affect cell wall extensibility.

a modified cell cycle without mitosis, resulting into an increase of DNA copies per cell. The way these processes interact and coordinate at the organ scale remains elusive.The current view is that, although cells are the units of plant morphology, their behavior (division, expansion) is not autonomous, but coordinated at the organ level by cell-to-cell communication mechanisms [Van Norman *et al.*, 2011, Sablowski & Carnier Dornelas, 2014]. Moreover, a significant correlation between cell ploidy (*i.e.* number of DNA copies) and cell size has been observed in different species, suggesting a potential role of endoreduplication into the control of organ growth [Breuer *et al.*, 2010, Chevalier *et al.*, 2011, Lang & Schnittger, 2020].

In order to answer some of these questions, I built an integrated model of tomato fruit development coupling cell division, expansion and endoreduplication, based on previous works. Briefly, the fruit was described as a collection of cell populations, each one having a specific age, ploidy and volume, which evolve and grow over time during fruit development (Fig. 1.6). A cell division-endoreduplication module [Bertin *et al.*, 2007] governed the evolution of the number of cells in each population, their age (initiation date) and ploidy level, based on genotype-specific parameters. Cell expansion was described by means of a biophysical model [Fishman & Génard, 1998, Liu *et al.*, 2007] and depended on both cell's characteristics (age, ploidy) and on available resources from the mother plant. Moreover, a number of time-dependent functions accounted for developmental regulations of cell metabolism and physical properties. Depending on the definition of the reference time-scale (individual cell age vs organ age), different cellular processes could be put under cell-autonomous or non-cell autonomous control.

The model was used to investigate different hypotheses concerning the regulation and the interaction among cellular processes, with special attention to 1) the importance of a non cell-autonomous (organ-level) regulation of cell growth and 2) the potential effect of endoreduplication on cell expansion. For this aim, different control schemes (either cell-autonomous or organ-controlled, with or without ploidy effect on cell expansion) were tested in silico by means of specific model variants (see Fig 1.7). The model showed that a pure cell-autonomous control could not reproduce the experimental cell size distribution in tomato fruit, and organ-wide and ploidy-dependent controls were required in order to get realistic cell sizes. In particular, our simulation suggested that a direct effect of endoreduplication on cell expansion was needed in order to obtain a significant correlation between size and ploidy, as observed in real data [23].

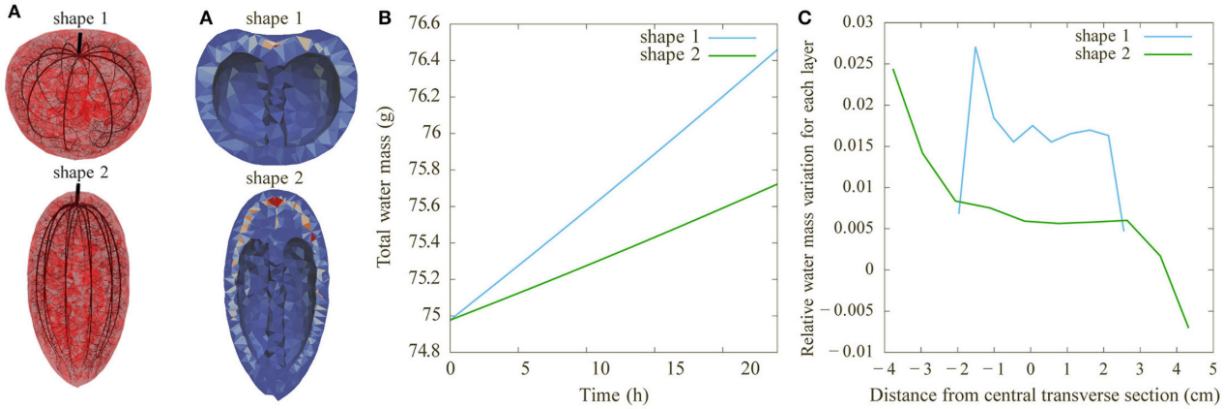


Figure 1.8: Comparison of the effects of fruit shape on water distribution as predicted by [14]. A: Fruit vasculature and relative water mass variation in 24-hours. B: Total water mass as a function of time. C: Mean value of the relative mass variation per layer along the pedicel to blossom end.

Fruit scale: resources transport and metabolism

Vascular structure and spatial heterogeneities. The architectural properties of a fruit, such as its size, shape, internal structure (number of carpels, pericarp thickness, etc.) and pattern of vasculature can be remarkably diverse. These architectural traits may have a significant impact on the distribution of water and carbohydrates inside the fruit, and thus, ultimately, on its quality. In collaboration with the team of C. Godin (Inria, Montpellier), we developed a generic 3D functional-structural model of the fruit that combined selected biophysical functions with an accurate description of fruit shape, tissue compartmentalization, and vascular networks [14]. The model was used to examine the impact of fruit structure on water and dry matter distribution in two species: tomato, as representative of berries, and nectarine, representative of drupes. The key difference was that tomato fruit had a heterogeneous internal structure with regular skin, whereas nectarine fruit had a homogeneous interior with microcracking on its skin. Moreover, tomato had a much lower fruit conductance to water and thus it had a lower transpiration rate compared to nectarine.

We showed that fruit shape affected vascular patterns and induced, independently of size, an important and contrasted gradient of water supply from the pedicel to the blossom end of the fruit. In particular, the model predicted lower water supply to the tip end of elongated fruits, which is consistent with the sensitivity of elongated tomatoes to blossom-end-rot disorder. We also demonstrated how skin morphology related to microcracking distribution affected the distribution of water and sugars inside nectarine fruit.

Inter-specific variability. As a natural follow-up of the PhD thesis of C.B. Cakpo, we continued our inter-species comparison by looking at the processes involved in fruit expansion. To this aim, the biophysical growth model originally developed by Fishman and Génard [Fishman & Génard, 1998] was improved and coupled to the model of sugar metabolism [25] in order to simulate the development of our ten fruit species, from the flowering stage until the maturity. The resulting model is able to account for three mechanisms that are reported to vary considerably among species: (1) the dynamics of water import to the fruit, via the variation of the xylem hydraulic conductivity, (2) the dynamics of carbon unloading, via the balance between apoplastic and symplastic transport mechanisms and (3) the differences in carbon allocation to non-soluble carbon components, like starch and structural tissues, that do not contribute to the internal turgor pressure.

Preliminary results confirmed a separation between herbaceous and woody species. Herbaceous, short-growing species were characterized by high hydraulic conductivities during the early phase of fruit development, resulting in a high turgor pressure and a low sugar content in the fruit. Woody species, instead, were associated with a strong plasticity of the tissues, which compensated for the lower turgor pressure, and with a more regular, apoplastic, sugar unloading over time.

Notice that these differences do not only affect the final fruit quality but can directly impact the ability of the fruit to develop under limiting environmental conditions. A previous work on a panel of tomato varieties [15] showed indeed that hydraulic conductivities and apoplasmic unloading mechanisms were important determinants of the fruit sensitivity to water deficit. It would be interesting to extend this work to different environmental conditions, in order to identify those traits and mechanisms that may most limit fruit growth, and to a panel of different genotypes, in order to decipher possible correlations among traits due to their genetic architecture.

Plant scale: Spatial and environmental control

Plant architecture plays an important role in organ development as it affects both resources acquisition (light interception for photosynthesis, soil exploration and hydraulics for water and mineral uptake) and transport. As a consequence, the position of the organ is strongly related to its final size and may have an effect on its ability to respond to environmental stresses.

In a first work, the variability of organ growth was investigated *in silico* by connecting our fruit division-expansion model to an architectural model of tomato plant [10]. Plant architecture was used to estimate resource acquisition (carbon) and water transpiration distribution under different environments. The resulting fruit growth, in both dry and fresh mass, was then evaluated as a function of fruit position, developmental stage and nutrient availability.
Results showed that, independently of the environment, fruits on the the 1st trusses were always smaller compared to later in the season because the leaf area was not totally developed, inducing a shortage in carbon supply. The application of a stress had a considerable impact on the relation between fruit growth and truss rank, with different outcomes depending on the affected resource (carbon vs water stress), the timing and the duration of the stress. Moreover, within a single truss, fruits in the early expansion phase were the most affected by stress, due to the mechanical and hydraulic properties of young cells.

In [10], cell division was assumed to be independent from environment, so that differences in fruit sizes were only due to cell expansion. In reality, cell cycle progression may be modified by environmental and develpmental signals [Komaki & Sugimoto, 2012], adding a further degree of freedom to organ plasticity. In order to quantify these effects, we performed a comprehensive phenotyping of the main cellular processes (cell division, endoreduplication and expansion) in both tomato leaves and fruits, as a function of their position on the plant and for different water regimes (PhD thesis of G. Koch). On leaves, data showed that leaf area, leaflet area and cell number increased with leaf rank until reaching a plateau [21]. The application of a water deficit leaded to similar cellular responses in both vegetative and reproductive organs: cell number and division rate were reduced but the duration of the cell division phase increased [22]. Cell expansion rate was also lowered by stress, earlier in the leaf than in the fruit, resulting in a overall reduction of organ and cell sizes, whereas endoreduplication was only slightly affected. In perspective, these results could be integrated into the model of fruit development (section "Cell scale") in order to refine our prediction of fruit growth (including its cellular phenotype) under different environmental conditions.

Collaborations:

- N. Bertin, PSH, INRAE, Avignon
- M. Génard, PSH, INRAE, Avignon
- G. Vercambre, PSH, INRAE, Avignon
- C. Granier, AGAP, INRAE, Montpellier
- C. Godin, Inria, Lyon
- M. Cieslask, post-doc 2011-2012

- I. Cheddadi, post-doc 2013-2014

Students:

- G. Koch, PhD student 2015-18
- D. Constantinescu, internship & CDD 2015-2016
- C.B. Cakpo, PhD student 2015-2019

Associated projects:

- EU project, FRIM
- Agropolis Foundation, MecaFruit3D
- Agropolis Foundation, Integrated Model of Plant and Organ Growth
- EU project, Carbon-LED

CHAPTER 2

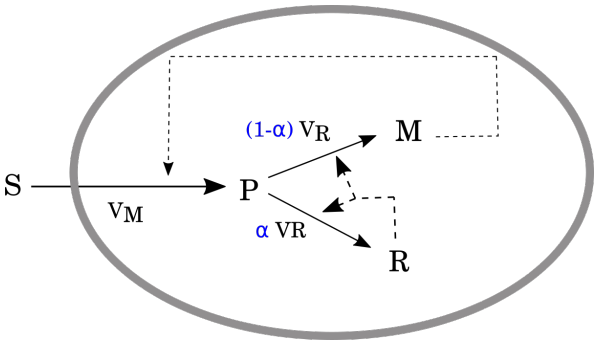
On-going work and Scientific perspectives

My move to the Sophia Agrobiotech Institut (ISA) in March 2016 and the collaboration with the Inria Biocore team brought about the appearance of new research themes and methods. My current work and my scientific perspectives reflect this new environment.
On a one side, I would like to pursue the study of the mechanisms underlying cell growth using a more theoretical approach based on coarse-grained models of cell functioning.This should allow a more comprehensive analysis of possible growth patterns, as a function of the environment and the phenotypic differences among cell types. On the other side, my integration to ISA introduced a novel ecological perspective to some pre-existing themes related to plant growth and yield. In addition to abiotic factors, indeed, plant are subjected to interaction with other organisms, with which they share available nutrients. The question of resource allocation therefore scales from the cell to the whole plant, with important consequences on the dynamics of the coupled plant-biome system.

2.1 Cell economy and control of cell growth

The most fundamental feature of living systems is self-replication. Whenever the organisms and cell type, cells have to sustain their own growth and functions by continuously absorbing available external substrates and transforming them into useful compounds. This includes the synthesis of different classes of macromolecules that ensure (proteins) most cellular functions, including signalling, regulatory and catalytic functions, as well as the storage of essential genetic information (nucleic acids as DNA and RNAs). Proteins in particular are necessary for the uptake and metabolism of external substrates (enzymes) as well as for the synthesis of proteins themselves via the action of ribosomes.
Given the intrinsic cost of maintaining such a internal machinery, cells are constantly obliged to modulate their functions to better fit their current needs. In response to changing environmental conditions, in particular, the cell modifies the expression of specific genes allowing for a re-allocation of available resources to different biological processes. Notice that proteome allocation defines the demand of the cell but also the attainable growth rate, in turn affecting the concentration of proteins and metabolites within the cell. This gives rise to a highly non-linear system in which proteome and biomass composition both determine and depend on the growth rate [de Groot *et al.*, 2020].

In the last few years, coarse-grained models of the cell (also called self-replicator models) have been developed specifically focusing on the auto-catalytic nature of cell growth. Instead of accounting for individual molecular reactions, cell components are lumped together into a few classes, with macro-reactions describing their conversion rates. In its simplest form, a self-replicator model can include only two macroreactions (Figure 2.1), describing the conversion of external substrate into metabolic precursors (V_M) and their subsequent consumption for the synthesis of ribosomes and enzymes via the macroreaction V_R [Giordano *et al.*, 2016]. By defining cell biomass in terms



$$\dot{p} = v_M(m, s) - \mu\, p$$
$$\dot{r} = \alpha\, v_R(r, p) - \mu\, r$$
$$\dot{m} = (1 - \alpha)\, v_R(r, p) - \mu\, m$$

Growth rate :
$$\mu = f(v_M, v_R)$$

Figure 2.1: Exemple of self-replicator model, based on the work by de Jong and coworkers [Giordano *et al.*, 2016]. The model includes two macroreactions, describing the conversion (V_M) of external substrate S into metabolic precursors P and their subsequent consumption for protein synthesis, via macroreaction V_R. Proteins are subdivided into two classes, enzymes (M), needed for substrate uptake and metabolism, and ribosomes (R) responsible for the production of M and R itself, according to the allocation parameter α. (p, m, r) design the concentrations of P,M and R, respectively.

of cellular components, cell growth rate μ can be explicitly calculated as a function of cellular fluxes, making the intrinsic non-linearity of the system apparent. Starting from this basic picture, more complex models can be constructed by considering additional proteome classes for specific cellular functions, including transport, energy metabolism or house-keeping cellular processes [Molenaar *et al.*, 2009, Scott *et al.*, 2014, Weiße *et al.*, 2015].

2.1.1 Energy constraints in microbial growth

Bacterial growth involves the conversion of nutrients to biomass (proteins and other macromolecules) and to small energy-carrier molecules (ATP, NADP, NADPH, ...) driving the synthesis of biomass. Coarse-grained models have provided insights in the resource allocation principles underlying microbial growth. In unicellular systems, indeed, partitioning between ribosome and protein synthesis has been shown to control cell growth rate as a function of carbon availability [Scott *et al.*, 2014, Giordano *et al.*, 2016]. Moreover, models have shown how protein synthesis costs clarify the role of alternative ATP-production pathways [Molenaar *et al.*, 2009, Basan *et al.*, 2015].

In collaboration with H. de Jong (Inria, Grenoble), we developed a coarse-grained dynamical model of coupled energy and mass fluxes in microorganisms, based on minimal assumptions, and calibrated the model using data for *E. coli*. The model is based on the partition of the proteome into different functional classes, each one catalysing a specific macro-reaction. In particular, a class of energy proteins works to transfer the energy contained in carbohydrate substrates to small energy-carrying metabolites, like ATP, whereas biomass synthesis consume that energy. A perfect balance between these two processes is needed to ensure a fast cell growth, but possibly at the expense of growth efficiency. Calling B the total cell biomass [gDW], we define the growth rate of the cell μ $[h^{-1}]$ as the relative biomass increase over time, as

$$\mu = \frac{1}{B}\frac{dB}{dt}. \tag{2.1}$$

The growth yield Y, defined as the fraction of biomass produced per unit of carbon uptake (v_{upk}), measures the efficiency growth and is given by

$$Y = \frac{1}{\beta}\frac{\mu}{v_{upk}} \tag{2.2}$$

where β is the biomass carbon content [gDW/Cmmol], assumed constant. According to the above definition, yields are dimensionless and vary between 0 and 1, which allows for a direct comparison of different resource allocation strategies.

By sampling the whole space of possible protein allocation schemes, the intrinsic connection between

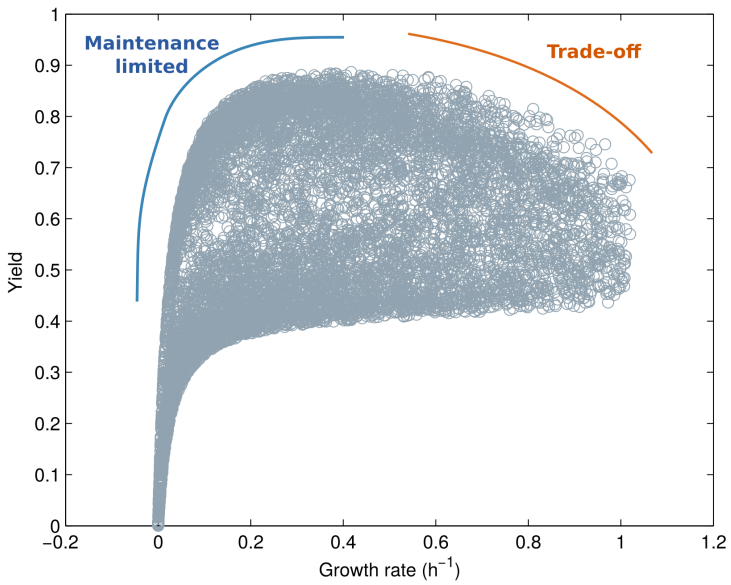


Figure 2.2: Predicted combinations of steady-state growth rate and growth yield for batch growth of *E. coli* in minimal medium with glucose.

growth and yield can be brought to light. Preliminary simulations showed indeed that the model is able to capture the expected relationship between growth rate and yield (Fig. 2.2): for low growth rates, the maximum growth yield increases with the rate, whereas it decreases for high growth rates [Lipson, 2015]. The initial yield increase can be attributed to the proportionally lower burden of the non-growth-associated maintenance costs when the growth rate increases. The subsequent decrease of the maximum yield with a further increase of the growth rate reflects a rate-yield tradeoff experimentally observed in unicellular systems [Beardmore *et al.*, 2011]. Analysis of the model revealed that the trade-off at the level of rate and yield translated to different trade-offs on the level of fluxes and enzyme and metabolite concentrations, following a hierarchy of internal constraints. Interestingly, the model even predicted that the availability of two alternative ATP production pathways is not necessary for occurrence of rate-yield trade-off, suggesting that, within the context of the core dependencies between resource allocation parameters modelled here, the choice between fermentation and respiration is secondary. Further work is needed in order to verify the robustness of the above conclusions to more realistic model assumptions. Recent works on large genome scale metabolic models are encouraging though, showing similar shapes for the rate-yield solution space over different datasets [Cheng *et al.*, 2019].
On the longer term, perspectives of this work include the transition from the steady-state to a dynamical perspective. Given its ode formalism, the developed model can be used to investigate the adaptation of cell allocation scheme following a change in environmental conditions. With respect to previous work in which a single allocation choice was considered [Giordano *et al.*, 2016], the task is harder here as multiple allocation parameters are concerned, each one related to a different cellular process. Moreover, when looking at single strain, the space of admissible allocation solutions could be reduced with respect to Fig. 2.2 due to the specificity of its own regulatory network. Interactions among cellular processes may in fact create dependencies among allocation parameters, acting as inherent constraints to cell admissible control strategies, that have to be accounted for.

At term, the analysis of allocation-derived constraints could have important implications for the correct prediction of cell growth and metabolic fluxes, both for fundamental research and biotechnological applications [Hartline *et al.*, 2021]. From an ecological perspective, the growth-yield properties of microbial cells are also important for communities assembly [Beardmore *et al.*, 2011, Lipson, 2015] and may play a role in the the functioning of both artificial and natural ecosystems.

Collaborations:

- H. de Jong, Inria, Grenoble
- D. Ropers, Inria, Grenoble
- T. Gedeon, Montana State University, USA
- J.L. Gouzé, Inria, Sophia-Antipolis

Students:

- A. Fraisse, internship 2019-2020

Associated projects:

- Maximic, ANR project

2.1.2 Biophysical constraints in plant cell growth

In plant cells, growth is the result of two distinct but intertwined processes: a cytoplasmic growth, driven by macromolecular synthesis, and an expansive growth resulting in vacuole enlargement and water uptake. In most plant cell models, only the expansive growth is described, usually by means of the Lockhart equation, as resulting from the balance between the mechanical properties of the cell wall and the internal turgor pressure, generated by the accumulation of water and solutes inside the cell [Lockhart, 1965]. The role of macromolecular synthesis and proteome allocation has been rarely account for.
Based on the experience gained with the *E.coli* model, my long-term project is to combine models of protein allocation, originally developed for unicellular systems to a biophysical model of cell expansion, based on the Lockhart equation. In a first internship on this topic (L. Guitou 2018-2019), the choice between ribosome (R) and enzyme synthesis has been investigated assuming that enzymes acted on the uptake and synthesis of soluble compounds, whereas ribosomes assured the synthesis of proteins, including enzymes and ribosome themselves (see [Giordano *et al.*, 2016]). Contrary to classical microbial models, cell growth rate was described in term of volume instead than biomass and depended on solute concentration, via the osmotic pressure. Analysis of the model showed that the viscoelastic properties of the cell naturally translated into an allocation constraint, resulting in a minimal proportion of enzymes (and thus a minimal concentration of solutes) in order to sustain growth.

A number of improvements are needed to correctly account for the complexity of plant cell growth. First, plant cells have a large vacuole that allows for an increased storage of soluble osmolites and water, independently from protein synthesis. This could partially release the above-mentioned allocation constraints, allowing for a further decoupling of macromolecular and volume growth. Second, cell mechanical properties are not static but tightly controlled by the expression of specific proteins that regulate the both the synthesis and the dynamics of wall compounds. To address this point, enzymes could be subdivided into two distinct pools: primary metabolic enzymes (E_S), driving central metabolism and cell osmotic pressure, and cell wall enzymes (E_W), controlling the deposition of wall materials and the resulting wall stiffness (Figure 2.3). Last but not least, mechanosensing can feed back on gene expression, dynamically regulating the allocation scheme of the cell depending on the environment or on developmental signals. In a full integrated model, the allocation parameters *i.e.* the fraction of proteome allocated to different proteins classes, would be dynamically adjusted by specific feedback control functions [Giordano *et al.*, 2016]).
The model will be initially used to analyse the mechanisms controlling plant cell growth, in both biomass and volume, over a range of possible parameterisation (mechanical-hydraulic balance, surface-to-volume ratio) and (fixed) allocation schemes, and progressively adding further layers of complexity.

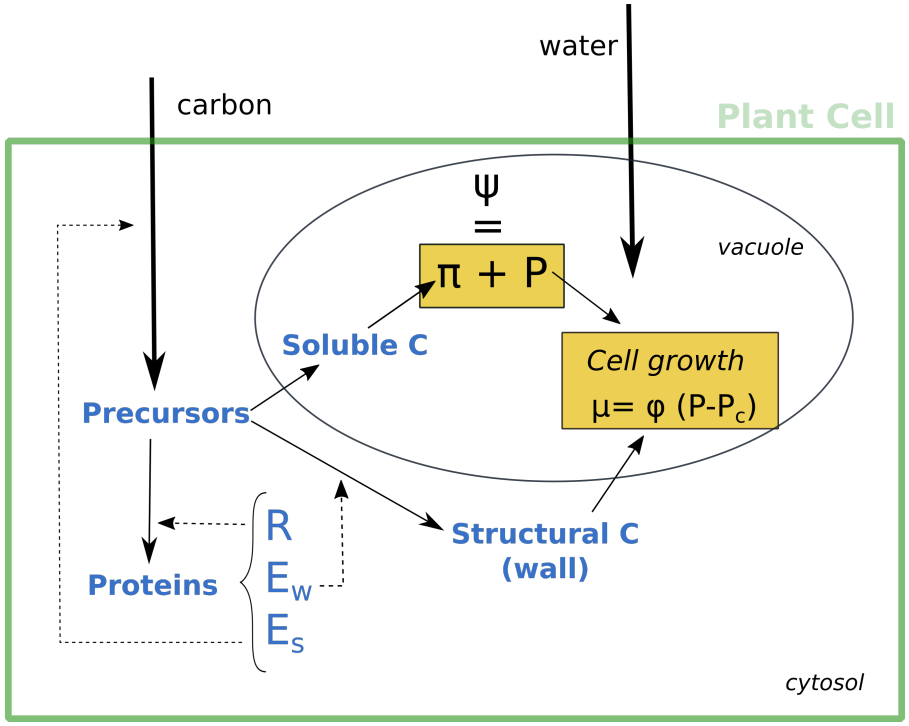


Figure 2.3: Schematic view of a possible biophysical-allocation model of plant cell growth. Enzymes E_S convert external carbon substrates into precursors for the synthesis of proteins, via the action of ribosomes (R), and structural compounds, via the action of enzymes E_W. Soluble metabolites can be transported into the vacuole, where they accumulate and generate an osmotic pressure π, inducing a water inflow towards the interior of the cell. Cell growth is described by means of the Lockhart equation, $\mu = \phi(P - Y)$, and depends on the hydrostatic pressure P and on the mechanical properties of the cell wall, via the extensibility ϕ and the critical turgor threshold P_c.

On a longer perspective, the addition of these mechanisms to multicellular models [Cheddadi *et al.*, 2019] could provide new insights into the complex control of tissue growth by mechanical, hydraulic and osmotic processes. Possible founding may be provided by Inria through their "Action exploratoire" program or by INRAE DIGIT-BIO program.

Collaborations:

- I. Cheddadi, University Grenoble-Alpes
- J.L. Gouzé, Inria, Sophia-Antipolis
- A. Singh, University of Delaware, USA

Students:

- L. Guitou, internship 2018-2019

2.2 Eco-physiological modelling of plant-biome interactions

During their life, plants experience a wide range of biotic interactions. Some are beneficial to plant health, as in the case of pollinators or symbiotic organisms, whereas others are negative, as in the case of pathogens or herbivores. The dynamics and outcome of these interactions depend on the ecological conditions, including the phenotypes of the interacting species, their physiology and the abiotic environment in which the interaction takes place. Phenotypic differences and plant plasticity *i.e.* the capacity of the plant to modify specific functional or phenotypic traits in response to environmental conditions, can shape the dynamics of the plant-biome system and is important to understand observed trade-offs between complex traits, like growth and defence.
In this context, my long-term project builds on the ecophysiological knowledge acquired during my past work and aims to better analyse the (eco)physiology of the plant, with respect to resources partitioning between the plant and its biotic partners and between growth and defence-related metabolism.

2.2.1 Plant-Root-knot nematodes and role of root system architecture

Root-knot nematodes (RKN) are microscopic worms that cause considerable yield losses in many crop plants [Jones *et al.*, 2013]. The reaction of a plant to parasitism by RKN depends on the plant species and cultivar. Typical symptoms include stunted growth, wilting and deformation of the roots, but strong differences in the extent of damages are observed both intra- and inter-species. For instance, cucurbits generally show high nematode infections in comparison to Solanaceous crops but they are able to preserve a good fruit production. In spite of their economic importance, nematode infestation has been rarely modelled and their consequences on plant's physiology were not accounted for. In collaboration with some ISA colleagues, we aim at developing an integrated model of the plant-nematode system, explicitly coupling the description of plant eco-physiology to a dynamic model of nematode population. In a previous internship on the topic (T. Brenière, 2017-2018), a first model of plant growth has been developed based on the works of Thornley [Thornley, 1998] and Dewar [Dewar, 1993]. Accordingly, the plant was divided into shoots, source of carbon for the plant, and roots, source of water. Carbon uptake and transport between shoots and roots was described explicitly, so that any diversion of substrate induced by the pest could be modelled and the feedback on plant physiology taken into account. Based on literature information, nematodes were supposed to induce a) a decrease in plant's hydraulic conductivity, and b) the appearance of an additional carbon sink at the roots level. Current step includes the coupling of the plant growth model to a demographic model describing the changes of pest population over time (internship C. Bourgade). Specificity of the nematode life-cycle are included at this stage, as well as the effect plant physiological status on pest multiplication and survival.

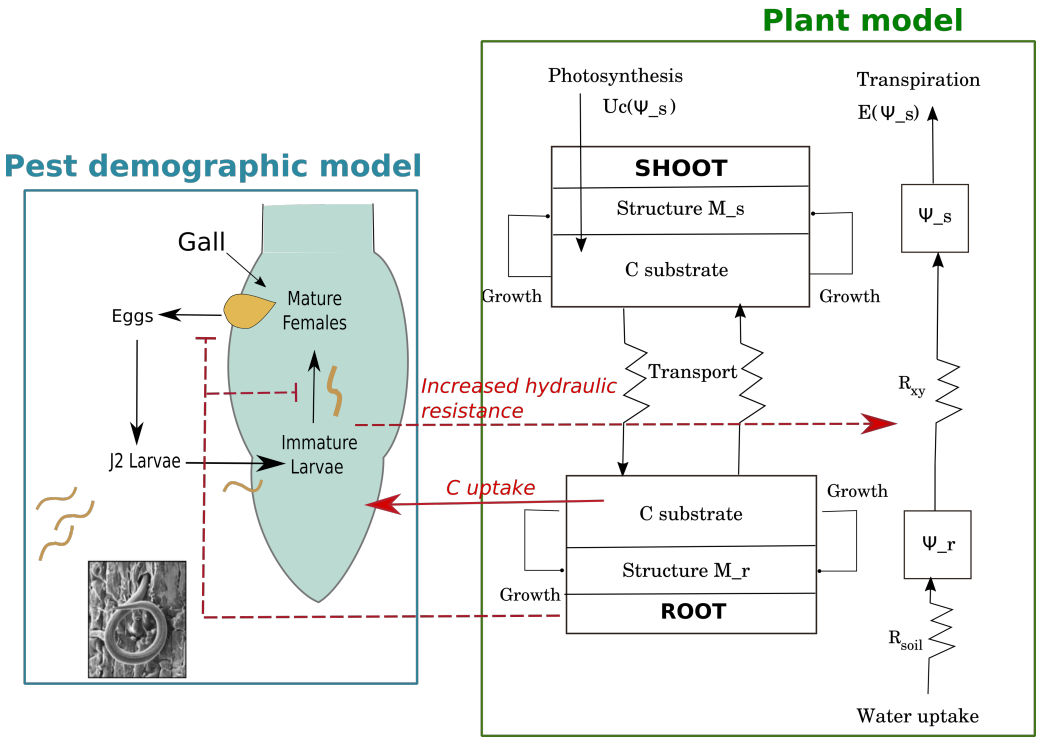


Figure 2.4: Schematic representation of the integrated plant-nematode model, explicitly connecting an ecophysiological plant model to a demographic model of the pest. Red arrows indicate interactions between plant and nematode models. Nematode J2 larvae infect plant roots and establish their feeding site, inducing the appearance of a gall. Developing nematodes feed on carbon diverted from plant roots but plant status can affect their life cycle. The presence of galls impairs plant water uptake, inducing an increase in plant hydraulic resistance.

At term, the integrated plant-pest model will allow to simulate the effect of nematodes over the plant but also the effect of the plant over the pest. In addition, a particular attention will be devoted to the role of root system architecture (RSA) both from a plant's functional point of view and from an epidemiological perspective, as an important modulator of the probability of infection by nematodes. In collaboration with L. Pagès and C. Daussan (INRAE, Avignon), dedicated experiments are currently conducted to assess the architecture (branching, root diameters) and hydraulic properties of the root system on the three contrasted species, in both infected and healthy plants. Collected data will be used to parameterize existing root architectural models [Pagès *et al.*, 2014, Doussan *et al.*, 1998] in order to investigate i) the evolution of root hydraulic conductance during plant development, over et large variety of RSA, ii) the impact of nematodes on hydraulic properties of the root system and iii) the probability of encounters between roots and nematodes (supposed static and uniformly distributed in the soil), as a function of RSA. In addition, architectural models will be used to establish simple relations between the observable descriptors (number of galls, number of infested root roots, etc.) of infestation and the global root system conductance, which directly influences the hydraulic functioning of the whole plant. These relations will be then included into the integrated plant-pest model in order to investigate the effect of RSA on the dynamics of nematode population as well as on the expected damage at the plant scale. Potential trade-off between physiological vs epidemiological consequences of the architecture of root systems could be pointed out at this stage. At term, the model could be used to define optimal root architectures with respect to a specific agronomic target (*e.g.* maximum yield), under different infection and environmental scenarii.
In the near future, in collaboration with the collegues of the inria project-team Biocore, a reduced version of the plant-nematode model could be proposed, based on the work by Lebon et al. (2014) [Lebon *et al.*, 2014], in which relevant properties identified on the complete model will be included. The mathematical analysis of its properties will indicate conditions for the different outcomes of the infestation over the year: death of the plant, tolerance with over-compensation, nematodes exclusion,... These conditions will then be used to determine which control actions can ensure limited yield loss. This same model could also be put in a hybrid seasonal framework, where the hybrid component will represent the overwintering of the nematodes in absence of its host in order to analyse the scale of the epidemic, and whether and how it develops in the longer term.
In the objective of control, this work could also be extended to resistant plants, as a part of promising agroecological strategies [Nilusmas *et al.*, 2020, Clin *et al.*, 2020]. This project has received the support of Idex UCA JEDI via the founding of T. Brenière's internship and of INRAE AgroEcoSyst Department via the founding of the ArchiNem project (2020-2021). Applications for a PhD founding are currently under submission to the EUR LIFE of the University Côte d'Azur and to the Inria-INRAE fellowship program. The possibility of a CIFRE PhD thesis is also under discussion with Limagrain.

In perspective, the model could be used to investigate more complex situations, as a tripartite interaction including two pests or plant-symbiote partnership.
Most of modelling works on pathosystems refer to one crop and its main pest, possibly including the main antagonist of the pest. However real crops are subject to **multiple pest** attacks. Following a biotic interaction, systemic changes in plant traits, like architecture, nutritional status or induced defence compounds can considerably modify the dynamics and outcome of plant response to further attacks. It is therefore evident that separately considering the consequences of different pests might not be adequate to describe real crop systems. In collaboration with D. Bevacqua (INRAE, Avignon), we plan to couple the plant-nematode model to an existing model of aphid infestation [Zaffaroni *et al.*, 2020]. This will allow to evaluate the importance of plant-mediated interactions between below-ground and above-ground pest, and their modulation by plant architectural features and cultural practices [Kaplan *et al.*, 2008, Kutyniok *et al.*, 2014].

Plant fitness and growth can also be affected by the interaction with **symbiotic partners**. Evidences show that symbiosis can shape plant response to both abiotic and biotic stresses [Kumar & Verma, 2018].

The modelling framework already developed for the plant-pest system could be adapted to describe resources sharing between plant and symbiote, based on similar models and literature information [Umbanhowar & McCann, 2005, Thornley & Parsons, 2014]. Assuming the existence of an established symbiotic relation, my objective will be then to investigate and quantify the effect of the symbiosis on the dynamics of plant-pest interactions, with particular attention to strength symbiotic link (resource payback among symbiotic partners) and with regard to environmental conditions (resource availability, abiotic stress..) and plant phenotype. Two possible applications are foreseeable at this stage: i) the effect of mycorrhiza fungi on plant-root-knot nematodes interactions [Schouteden *et al.*, 2015], in the framework of our ongoing collaboration with the ISA-IPN team, ii) the study of the rhizobia bacteria-legume-aphids system in collaboration with the ISA-Symbiosis team, for which preliminary data have already been acquired [Pandharikar *et al.*, 2020]. Possible sources of funding for these topics include INRAE Departments SPE and AgroEcoSystems, and the National Research Agency (ANR).

Collaborations:

- C. Caporalino, ISA, INRAE, Sophia-Antipolis
- S. Touzeau, ISA, INRAE, Sophia-Antipolis
- L. Mailleret, ISA, INRAE, Sophia-Antipolis
- L. Pagès, PSH, INRAE, Avignon
- D. Bevacqua, PSH, INRAE, Avignon
- C. Daussan, EMMAH, INRAE, Avignon
- F. Grognard, Inria, Sophia-Antipolis

Students:

- T. Brenière, internship 2017-2018
- N. Jauzion-Graverolle, internship 2019-20, 2020-21
- C. Bourgade, internship 2020-2021

Associated projects:

- ArchiNem, INRAE project

CHAPTER 3

Conclusions and acknowledgments

Trained as a physicist, my approach to biology has been gradual. I started from the behaviour of a single molecule and I progressively discovered the complexity of living systems, through the many research themes I had the luck to participate to. My career indeed has been marked by multiple shifts in research topics as well as in the biological systems under study. This thematic "mobility" also affects my future research project, in which applied and fundamental research questions, at different scales, coexist. I am fully aware of the potential risk of dispersion that this choice implies as well as the difficulty of constantly moving from one topic to another. In spite of this, I find the combination of fundamental and applied topics, on multiple biological systems, both inspiring and healthy. On one side, it allows to step back from the system-specific mechanisms, get a wider view of biological processes, promoting connections between different domains. On the other side, applied research topics are essential to stay grounded on biological reality, restraining dangerous generalizations. They help recognizing that biological systems are indeed different and that sometimes the kinetics of a few interactions can be important.

Since my PhD, I had the luck to work with people of great human values and endowed with a undeniable passion for science. Among them, I owe a special gratitude to Hidde de Jong who, by his own example and his advices, really learnt me what being a good researcher means. I would also like to thank Michel Genard who introduced me to the biology of plants and with whom I shared a number of interesting discussion on the right way to model them.

It now comes my turn to guide students to become young mindful researchers. When building a model many criteria come into play, including the the purpose of the model (either for understanding, prediction or control), the available information, technical and computational costs but also intuition and personal preferences concerning the mathematical formalisms to be adopted. As supervisor, I feel that my role is mostly to transmit and support good research practices and only secondly to provide tools and methods to solve problems. I feel crucial to keep trace of the motivations and hypotheses that led us to build a particular mathematical model. The choice of a mathematical formalism, in particular, is always accompanied by some underlying hypotheses that can have important consequences on the dynamical behaviours we can observe. In this perspective, I try to learn students to always keep a critical regard on their results and not be afraid to verify scripts, find errors or come back their original hypotheses. I learnt by experience the importance of fully understanding model results and carefully verifying whenever a small doubt appears in the behaviour of numerical simulations. Methods exist indeed to test numerical scripts, evaluate the importance of selected parameters values, or to compare alternative model formulations. Based on my personal experience, combining approaches at different levels of description on a same biological system, is also very instructive. It offers the possibility to change perspective, explore different facets of the same problem and, in the case of simpler small-size model, give access to mathematical tools that are unavailable when dealing with large numerical

models. In this perspective, I encourage students to be curious, discuss together and with other colleagues and to read about models and approaches developed for other systems. Whenever possible, the participation to local seminars or international congress is always a source of inspiration. Last but not least, I will try to educate students to the importance of well presenting their ideas and projects, both in oral and written forms. With the generalization of project-based research, telling a good story indeed has become an essential skill not only for result dissemination but also for founding and career progress. Precisely defining the research question, its motivation and the reasoning that lies behind the work can make a difference for an effective communication.

Bibliography

2006

[1] Baldazzi, V., Cocco, S., Marinari, E., Monasson, R. (2006). Inference of DNA sequences from mechanical unzipping: an ideal-case study. Phys Rev Lett, 96(12), 128102.

[2] Baldazzi, V., Castiglione, F., Bernaschi, M. (2006). An enhanced agent based model of the immune system response. Cell Immunol, 244(2), 77–79.

2007

[3] Baldazzi, V., Bradde, S., Cocco, S., Marinari, E., Monasson, R. (2007). Inferring DNA sequences from mechanical unzipping data: the large-bandwidth case. Phys Rev E, 75(1), 11904.

2009

[4] Baldazzi, V., Paci, P., Bernaschi, M., Castiglione, F. (2009). Modeling lymphocyte homing and encounters in lymph nodes. BMC Bioinformatics, 10, 387.

2010

[5] Baldazzi, V., Ropers, D., Markowicz, Y., Kahn, D., Geiselmann, J., de Jong, H. (2010). The Carbon Assimilation Network in Escherichia coli Is Densely Connected and Largely Sign-Determined by Directions of Metabolic Fluxes. PLoS Computational Biology, 6(6), e1000812.

2011

[6] Ropers, D., Baldazzi, V., de Jong, H. (2011). Model reduction using piecewise-linear approximations preserves dynamic properties of the carbon starvation response in Escherichia coli. IEEE/ACM Trans Comput Biol Bioinform, 8, 166–181.

2012

[7] Baldazzi, V., Ropers, D., Geiselmann, J., Kahn, D., de Jong, H. (2012). Importance of metabolic coupling for the dynamics of gene expression following a diauxic shift in Escherichia coli. Journal of Theoretical Biology, 295(0), 100–115.

[8] Baldazzi, V., Bertin, N., de Jong, H., Génard, M. (2012). Towards multiscale plant models: integrating cellular networks. Trends in Plant Science, 17(12), 728–736.

[9] Baldazzi, V., Bertin, N., Génard, M. (2012). A model of fruit growth integrating cell division ans expansion processes. Acta Horticulturae, 957, 191–196.

2013

[10] Baldazzi, V., Pinet, A., Vercambre, G., Bénard, C., Biais, B., Génard, M. (2013). In-silico analysis of water and carbon relations under stress conditions. A multi-scale perspective centered on fruit. Frontiers in Plant Science, 4, 495.

2014

[11] Desnoues, E., Gibon, Y., Baldazzi, V., Signoret, V., Génard, M., Quilot-Turion, B. (2014). Profiling sugar metabolism during fruit development in a peach progeny with different fructose-to-glucose ratios. BMC Plant Biology, 14(1), 336.

[12] Génard, M., Baldazzi, V., Gibon, Y. (2014). Metabolic studies in plant organs: don't forget dilution by growth. Frontiers in Plant Science, 5, 85.

2015

[13] Desnoues, E., Signoret, V., Quilot-Turion, B., Baldazzi, V., Génard, M., Gibon, Y. (2015). High or low fructose?Consequences for sugar metabolism in peach fruit. Acta Horticulturae, 1084, 599–604.

2016

[14] Cieslak, M., Cheddadi, I., Boudon, F., Baldazzi, V., Génard, M., Godin, C., Bertin, N. (2016). Integrating Physiology and Architecture in Models of Fruit Expansion. Frontiers in Plant Science, 7(November), 1–19.

[15] Constantinescu, D., Memmah, M.-M., Vercambre, G., Génard, M., Baldazzi, V., Causse, M., Albert, E., Brunel, B., Valsesia, P., Bertin, N. (2016). Model-Assisted Estimation of the Genetic Variability in Physiological Parameters Related to Tomato Fruit Growth under Contrasted Water Conditions. Frontiers in Plant Science, 7(December), 1–17.

[16] Desnoues, E., Baldazzi, V., Génard, M., Mauroux, J.-B., Lambert, P., Confolent, C., Quilot-Turion, B. (2016). Dynamic QTLs for sugars and enzyme activities provide an overview of genetic control of sugar metabolism during peach fruit development. Journal of Experimental Botany, 67(11), 3419–3431.

[17] Dai, Z. W., Wu, H., Baldazzi, V., van Leeuwen, C., Bertin, N., Gautier, H., Wu, B., Duchêne, E., Gomès, E., Delrot, S., Lescourret, F., Génard, M. (2016). Inter-Species Comparative Analysis of Components of Soluble Sugar Concentration in Fleshy Fruits. Frontiers in Plant Science, 7.

2017

[18] Desnoues, E., Génard, M., Quilot-Turion, B., Baldazzi, V. (2017). A kinetic model of sugar metabolism in peach fruit allows the exploration of genetic variability. Acta Horticulturae, 1182, 169–176.

[19] Baldazzi, V., Génard, M., Bertin, N. (2017). Cell division, endoreduplication and expansion processes: setting the cell and organ control into an integrated model of tomato fruit development. Acta Horticulturae, 1182.

2018

[20] Desnoues, E., Génard, M., Quilot-Turion, B., Baldazzi, V. (2018). A kinetic model of sugar metabolism in peach fruit reveals a functional hypothesis of a markedly low fructose-to-glucose ratio phenotype. The Plant Journal, 94(4), 685–698.

[21] Koch, G., Rolland, G., Dauzat, M., Bédiée, A., Baldazzi, V., Bertin, N., Guédon, Y., Granier, C. (2018). Are compound leaves more complex than simple ones? A multi-scale analysis. Annals of Botany, 122(7), 1173–1185.

2019

[22] Koch, G., Rolland, G., Dauzat, M., Bédiée, A., Baldazzi, V., Bertin, N., Guédon, Y., Granier, C. (2019). Leaf Production and Expansion: A Generalized Response to Drought Stresses from Cells to Whole Leaf Biomass—A Case Study in the Tomato Compound Leaf. Plants, 8(10), 409.

[23] Baldazzi, V., Valsesia, P., Génard, M., Bertin, N. (2019). Organ-wide and ploidy-dependent regulation both contribute to cell-size determination: evidence from a computational model of tomato fruit. Journal of Experimental Botany, 70(21), 6215-6228.

2020

[24] Kanso, H., Quilot-Turion, B., Memah, M. M., Bernard, O., Gouzé, J. L., Baldazzi, V. (2020). Reducing a model of sugar metabolism in peach to catch different patterns among genotypes. Mathematical Biosciences, 321, 108321.

[25] Cakpo, C.B., Vercambre G., Baldazzi V., Roch L., Dai, Z., Valsesia P., Memah M.M., Colombié S.,Moing A, Gibon Y., Génard M. (2020). Model-assisted comparison of sugar accumulation patterns in ten fleshy fruits highlights differences between herbaceous and woody species. Annals of Botany, 126(3), 455-470

Book chapters

[26] Baldazzi, V., Monteiro, P. T., Page, M., Ropers, D., Geiselmann, J., de Jong, H. (2011). Qualitative analysis of genetic regulatory networks in bacteria. In Understanding the Dynamics of Biological Systems. Springer.

[27] Baldazzi, V., Bertin, N., Gautier, H., Génard, M. (2014). Ecophysiological process-based model to simulate carbon fluxes in plants. In Methods in molecular biology (Clifton, N.J.) (Vol. 1090, pp. 347–361).

[28] Baldazzi, V., Bertin, N., Génard, M., Gautier, H., Desnoues, E., Quilot-Turion, B. (2016). Challenges in integrating genetic control in plant and crop models. In X. Yin and P. C. Struik (Eds.), Crop Systems Biology. Narrowing the gaps between crop modelling and genetics (pp. 1–31). Springer.

[29] Génard, M., Memmah, M.-M., Quilot-Turion, B., Vercambre, G., Baldazzi, V., Le Bot, J., Bertin, N., Gautier, H., Lescourret, F., Pagès, L. (2016). Process-based simulation models are essential tools for virtual profiling and design of ideotypes: Example of fruit and root. In X. Yin and P. C. Struik (Eds.), Crop systems biology - narrowing the gaps between crop modelling and genetics (pp. 83–104). Springer.

Literature cited

[Baey *et al.*, 2018] Baey, Charlotte, Mathieu, Amélie, Jullien, Alexandra, Trevezas, Samis, & Cournède, Paul Henry. 2018. Mixed-Effects Estimation in Dynamic Models of Plant Growth for the Assessment of Inter-individual Variability. *Journal of Agricultural, Biological, and Environmental Statistics*, **23**(2), 208–232.

[Basan *et al.*, 2015] Basan, Markus, Hui, Sheng, Okano, Hiroyuki, Zhang, Zhongge, Shen, Yang, Williamson, James R., & Hwa, Terence. 2015. Overflow metabolism in Escherichia coli results from efficient proteome allocation. *Nature*, **528**(7580), 99–104.

[Beardmore *et al.*, 2011] Beardmore, Robert E., Gudelj, Ivana, Lipson, David A., & Hurst, Laurence D. 2011. Metabolic trade-offs and the maintenance of the fittest and the flattest. *Nature*, **472**(7343), 342–346.

[Benes *et al.*, 2020] Benes, Bedrich, Guan, Kaiyu, Lang, Meagan, Long, Stephen P., Lynch, Jonathan P., Marshall-Colón, Amy, Peng, Bin, Schnable, James, Sweetlove, Lee J., & Turk, Matthew J. 2020. Multiscale computational models can guide experimentation and targeted measurements for crop improvement. *The Plant Journal*, **103**(1), 21–31.

[Bertin *et al.*, 2007] Bertin, Nadia, Lecomte, Alain, Brunel, Béatrice, Fishman, Svetlana, & Génard, Michel. 2007. A model describing cell polyploidization in tissues of growing fruit as related to cessation of cell proliferation. *Journal of Experimental Botany*, **58**(7), 1903–1913.

[Bockelmann *et al.*, 1998] Bockelmann, U., Essevaz-Roulet, B., & Heslot, F. 1998. DNA strand separation studied by single molecule force measurements. *Physical Review E*, **58**(2), 2386–2394.

[Bockelmann *et al.*, 2002] Bockelmann, U., Thomen, Ph, Essevaz-Roulet, B., Viasnoff, V., & Heslot, F. 2002. Unzipping DNA with optical tweezers: High sequence sensitivity and force flips. *Biophysical Journal*, **82**(3), 1537–1553.

[Brazhnik *et al.*, 2002] Brazhnik, P., de la Fuente, A., & Mendes, P. 2002. Gene networks: How to put the function in genomics. *Trends Biotechnology*, **20**(11), 467–472.

[Breuer *et al.*, 2010] Breuer, Christian, Ishida, Takashi, & Sugimoto, Keiko. 2010. Developmental control of endocycles and cell growth in plants. *Current Opinion in Plant Biology*, **13**(6), 654–60.

[Cheddadi *et al.*, 2019] Cheddadi, Ibrahim, Génard, Michel, Bertin, Nadia, & Godin, Christophe. 2019. Coupling water fluxes with cell wall mechanics in a multicellular model of plant development. *PLoS Computational Biology*, **15**(6).

[Cheng *et al.*, 2019] Cheng, Chuankai, O'Brien, Edward J., McCloskey, Douglas, Utrilla, Jose, Olson, Connor, LaCroix, Ryan A., Sandberg, Troy E., Feist, Adam M., Palsson, Bernhard O., & King,

Zachary A. 2019. Laboratory evolution reveals a two-dimensional rate-yield tradeoff in microbial metabolism. *PLOS Computational Biology*, **15**(6), e1007066.

[Chevalier *et al.*, 2011] Chevalier, Christian, Nafati, Mehdi, Mathieu-Rivet, Elodie, Bourdon, Matthieu, Frangne, Nathalie, Cheniclet, Catherine, Renaudin, Jean-Pierre, Gévaudant, Frédéric, & Hernould, Michel. 2011. Elucidating the functional role of endoreduplication in tomato fruit development. *Annals of Botany*, **107**(7), 1159–69.

[Clin *et al.*, 2020] Clin, Pauline, Grognard, Frederic, Mailleret, Ludovic, Val, Florence, Andrivon, Didier, & Hamelin, Frédéric. 2020. Taking advantage of pathogen diversity and immune priming to minimize disease prevalence in host mixtures: a model. *Phytopathology®*, dec, PHYTO–09–20–0429–R.

[Coen *et al.*, 2004] Coen, Enrico, Rolland-Lagan, Anne Gaëlle, Matthews, Mark, Bangham, J. Andrew, & Prusinkiewicz, Przemyslaw. 2004. The genetics of geometry. *Proceedings of the National Academy of Sciences of the United States of America*, **101**(14), 4728–4735.

[Danilowicz *et al.*, 2003] Danilowicz, Claudia, Coljee, Vincent W., Bouzigues, Cedric, Lubensky, David K., Nelson, David R., & Prentiss, Mara. 2003. DNA unzipped under a constant force exhibits multiple metastable intermediates. *Proceedings of the National Academy of Sciences of the United States of America*, **100**(4), 1694–1699.

[de Groot *et al.*, 2020] de Groot, Daan H., Lischke, Julia, Muolo, Riccardo, Planqué, Robert, Bruggeman, Frank J., & Teusink, Bas. 2020. The common message of constraint-based optimization approaches: overflow metabolism is caused by two growth-limiting constraints. *Cellular and Molecular Life Sciences*, **77**(3), 441–453.

[de Jong *et al.*, 2017] de Jong, Hidde, Casagranda, Stefano, Giordano, Nils, Cinquemani, Eugenio, Ropers, Delphine, Geiselmann, Johannes, & Gouzé, Jean-Luc. 2017. Mathematical modelling of microbes: metabolism, gene expression and growth. *Journal of The Royal Society Interface*, **14**(136), 20170502.

[Dewar, 1993] Dewar, R C. 1993. A Root-Shoot Partitioning Model Based on Carbon-Nitrogen-Water Interactions and Munch Phloem Flow. *Functional Ecology*, **7**(3), 356–368.

[Doussan *et al.*, 1998] Doussan, Claude, Pagès, Loïc, & Vercambre, Gilles. 1998. Modelling of the Hydraulic Architecture of Root Systems An Integrated Approach to Water Absorption - Model Description. *Annals of Botany*, 213–223.

[Fishman & Génard, 1998] Fishman, Svetlana, & Génard, M. 1998. A biophysical model of fruit growth: simulation of seasonal and diurnal dynamics of mass. *Plant Cell Environ*, **21**(8), 739–752.

[Giordano *et al.*, 2016] Giordano, Nils, Mairet, Francis, Gouzé, Jean-Luc, Geiselmann, Johannes, & de Jong, Hidde. 2016. Dynamical Allocation of Cellular Resources as an Optimal Control Problem: Novel Insights into Microbial Growth Strategies. *PLOS Computational Biology*, **12**(3), e1004802.

[Hartline *et al.*, 2021] Hartline, Christopher J., Schmitz, Alexander C., Han, Yichao, & Zhang, Fuzhong. 2021 (jan). *Dynamic control in metabolic engineering: Theories, tools, and applications.*

[Heil, 2010] Heil, Martin. 2010. Plastic defence expression in plants. *Evolutionary Ecology*, **24**(3), 555–569.

[Jones *et al.*, 2013] Jones, John T., Haegeman, Annelies, Danchin, Etienne G. J., Gaur, Hari S., Helder, Johannes, Jones, Michael G. K., Kikuchi, Taisei, Manzanilla-López, Rosa, Palomares-Rius, Juan E., Wesemael, Wim M. L., & Perry, Roland N. 2013. Top 10 plant-parasitic nematodes in molecular plant pathology. *Molecular Plant Pathology*, **14**(9), 946–961.

[Kaplan *et al.*, 2008] Kaplan, Ian, Halitschke, Rayko, Kessler, André, Sardanelli, Sandra, & Denno, Robert F. 2008. Effects of Plant Vascular Architecture on Aboveground–Belowground-Induced Responses to Foliar and Root Herbivores on Nicotiana tabacum. *Journal of Chemical Ecology*, **34**(10), 1349–1359.

[Komaki & Sugimoto, 2012] Komaki, Shinichiro, & Sugimoto, Keiko. 2012. Control of the plant cell cycle by developmental and environmental cues. *Plant and Cell Physiology*, **53**(6), 953–64.

[Kumar & Verma, 2018] Kumar, Akhilesh, & Verma, Jay Prakash. 2018. Does plant—Microbe interaction confer stress tolerance in plants: A review? *Microbiological Research*, **207**(mar), 41–52.

[Kutyniok *et al.*, 2014] Kutyniok, Magdalene, Persicke, Marcus, & Müller, Caroline. 2014. Effects of Root Herbivory by Nematodes on the Performance and Preference of a Leaf-Infesting Generalist Aphid Depend on Nitrate Fertilization. *Journal of Chemical Ecology*, **40**(2), 118–127.

[Lang & Schnittger, 2020] Lang, Lucas, & Schnittger, Arp. 2020. Endoreplication — a means to an end in cell growth and stress response. *Current Opinion in Plant Biology*, **54**(apr), 85–92.

[Lebon *et al.*, 2014] Lebon, A., Mailleret, L., Dumont, Y., & Grognard, F. 2014. Direct and apparent compensation in plant-herbivore interactions. *Ecological Modelling*, **290**(C), 192–203.

[Lipson, 2015] Lipson, David A. 2015. The complex relationship between microbial growth rate and yield and its implications for ecosystem processes. *Frontiers in Microbiology*, **6**(jun), 615.

[Liu *et al.*, 2007] Liu, Huai-Feng F Huai-Feng, Génard, Michel, Guichard, Soraya, & Bertin, Nadia. 2007. Model-assisted analysis of tomato fruit growth in relation to carbon and water fluxes. *Journal of Experimental Botany*, **58**(13), 3567–3580.

[Lockhart, 1965] Lockhart, James A. 1965. An analysis of irreversible plant cell elongation. *Journal of Theoretical Biology*, **8**(2), 264–275.

[Lucas *et al.*, 2013] Lucas, William J., Groover, Andrew, Lichtenberger, Raffael, Furuta, Kaori, Yadav, Shri-Ram, Helariutta, Ykä, He, Xin-Qiang, Fukuda, Hiroo, Kang, Julie, Brady, Siobhan M., Patrick, John W., Sperry, John, Yoshida, Akiko, López-Millán, Ana-Flor, Grusak, Michael A., & Kachroo, Pradeep. 2013. The Plant Vascular System: Evolution, Development and Functions F. *Journal of Integrative Plant Biology*, **55**(4), 294–388.

[Marshall-Colon *et al.*, 2017] Marshall-Colon, Amy, Long, Stephen P., Allen, Douglas K., Allen, Gabrielle, Beard, Daniel A., Benes, Bedrich, von Caemmerer, Susanne, Christensen, A. J., Cox, Donna J., Hart, John C., Hirst, Peter M., Kannan, Kavya, Katz, Daniel S., Lynch, Jonathan P., Millar, Andrew J., Panneerselvam, Balaji, Price, Nathan D., Prusinkiewicz, Przemyslaw, Raila, David, Shekar, Rachel G., Shrivastava, Stuti, Shukla, Diwakar, Srinivasan, Venkatraman, Stitt, Mark, Turk, Matthew J., Voit, Eberhard O., Wang, Yu, Yin, Xinyou, & Zhu, Xin-Guang. 2017. Crops In Silico: Generating Virtual Crops Using an Integrative and Multi-scale Modeling Platform. *Frontiers in Plant Science*, **8**(may), 786.

[Molenaar *et al.*, 2009] Molenaar, Douwe, van Berlo, Rogier, de Ridder, Dick, & Teusink, Bas. 2009. Shifts in growth strategies reflect tradeoffs in cellular economics. *Molecular systems biology*, **5**(323), 323.

[Nicotra *et al.*, 2010] Nicotra, A.B., Atkin, O.K., Bonser, S.P., Davidson, A.M., Finnegan, E.J., Mathesius, U., Poot, P., Purugganan, M.D., Richards, C.L., Valladares, F., & van Kleunen, M. 2010. Plant phenotypic plasticity in a changing climate. *Trends in Plant Science*, **15**(12), 684–692.

[Nilusmas *et al.*, 2020] Nilusmas, Samuel, Mercat, Mathilde, Perrot, Thomas, Djian-Caporalino, Caroline, Castagnone-Sereno, Philippe, Touzeau, Suzanne, Calcagno, Vincent, & Mailleret, Ludovic. 2020. Multiseasonal modelling of plant-nematode interactions reveals efficient plant resistance deployment strategies. *Evolutionary Applications*, 1–16.

[Pagès *et al.*, 2014] Pagès, Loïc, Bécel, Carole, Boukcim, Hassan, Moreau, Delphine, Nguyen, Christophe, & Voisin, Anne Sophie. 2014. Calibration and evaluation of ArchiSimple, a simple model of root system architecture. *Ecological Modelling*, **290**(C), 76–84.

[Pandharikar *et al.*, 2020] Pandharikar, Gaurav, Gatti, Jean-Luc, Simon, Jean-Christophe, Frendo, Pierre, & Poirié, Marylène. 2020. Aphid infestation differently affects the defences of nitrate-fed and nitrogen-fixing Medicago truncatula and alters symbiotic nitrogen fixation. *Proceedings of the Royal Society B: Biological Sciences*, **287**(1934), 20201493.

[Peng *et al.*, 2020] Peng, Bin, Guan, Kaiyu, Tang, Jinyun, Ainsworth, Elizabeth A., Asseng, Senthold, Bernacchi, Carl J., Cooper, Mark, Delucia, Evan H., Elliott, Joshua W., Ewert, Frank, Grant, Robert F., Gustafson, David I., Hammer, Graeme L., Jin, Zhenong, Jones, James W., Kimm, Hyungsuk, Lawrence, David M., Li, Yan, Lombardozzi, Danica L., Marshall-Colon, Amy, Messina, Carlos D., Ort, Donald R., Schnable, James C., Vallejos, C. Eduardo, Wu, Alex, Yin, Xinyou, & Zhou, Wang. 2020. Towards a multiscale crop modelling framework for climate change adaptation assessment. *Nature Plants*, **6**(4), 338–348.

[Peters *et al.*, 2000] Peters, Winfried S., Hagemann, Wolfgang, & Deri Tomos, A. 2000. What makes plants different? Principles of extracellular matrix function in 'soft' plant tissues. *Comparative Biochemistry and Physiology - A Molecular and Integrative Physiology*, **125**(2), 151–167.

[Rojas & Huang, 2018] Rojas, Enrique R., & Huang, Kerwyn Casey. 2018. Regulation of microbial growth by turgor pressure. *Current Opinion in Microbiology*, **42**(apr), 62–70.

[Sablowski & Carnier Dornelas, 2014] Sablowski, Robert, & Carnier Dornelas, Marcelo. 2014. Interplay between cell growth and cell cycle in plants. *Journal of Experimental Botany*, **65**(10), 2703–2714.

[Schouteden *et al.*, 2015] Schouteden, Nele, De Waele, Dirk, Panis, Bart, & Vos, Christine M. 2015. Arbuscular Mycorrhizal Fungi for the Biocontrol of Plant-Parasitic Nematodes: A Review of the Mechanisms Involved. *Frontiers in Microbiology*, **6**(nov), 1280.

[Scott *et al.*, 2014] Scott, Matthew, Klumpp, Stefan, Mateescu, Eduard M, & Hwa, Terence. 2014. Emergence of robust growth laws from optimal regulation of ribosome synthesis. *Molecular Systems Biology*, **10**(8), 1–15.

[Snowden *et al.*, 2017] Snowden, Thomas J., van der Graaf, Piet H., & Tindall, Marcus J. 2017. Methods of Model Reduction for Large-Scale Biological Systems: A Survey of Current Methods and Trends. *Bulletin of Mathematical Biology*, **79**(7), 1449–1486.

[Southern *et al.*, 2008] Southern, James, Pitt-Francis, Joe, Whiteley, Jonathan, Stokeley, Daniel, Kobashi, Hiromichi, Nobes, Ross, Kadooka, Yoshimasa, & Gavaghan, David. 2008. Multi-scale computational modelling in biology and physiology. *Progress in Biophysics and Molecular Biology*, **96**(1), 60–89. Cardiovascular Physiome.

[Szallasi *et al.*, 2006] Szallasi, Z, Stelling, Jörg, & Periwal, Vipul (eds). 2006. *System Modeling in Cellular Biology*. MIT Press.

[Thornley, 1998] Thornley, John H.M. 1998. Modelling shoot: Root relations: The only way forward? *Annals of Botany*, **81**(2), 165–171.

[Thornley & Parsons, 2014] Thornley, John H.M., & Parsons, Anthony J. 2014. Allocation of new growth between shoot, root and mycorrhiza in relation to carbon, nitrogen and phosphate supply: Teleonomy with maximum growth rate. *Journal of Theoretical Biology*, **342**(feb), 1–14.

[Umbanhowar & McCann, 2005] Umbanhowar, James, & McCann, Kevin. 2005. Simple rules for the coexistence and competitive dominance of plants mediated by mycorrhizal fungi. *Ecology Letters*, **8**(3), 247–252.

[Van Norman *et al.*, 2011] Van Norman, Jaimie M, Breakfield, Natalie W, & Benfey, Philip N. 2011. Intercellular communication during plant development. *The Plant cell*, **23**(3), 855–64.

[Viterbi, 1967] Viterbi, Andrew J. 1967. Error Bounds for Convolutional Codes and an Asymptotically Optimum Decoding Algorithm. *IEEE Transactions on Information Theory*, **13**(2), 260–269.

[Weiße *et al.*, 2015] Weiße, Andrea Y., Oyarzún, Diego a., Danos, Vincent, & Swain, Peter S. 2015. Mechanistic links between cellular trade-offs, gene expression, and growth. *Proceedings of the National Academy of Sciences*, **112**(9), E1038–E1047.

[Zaffaroni *et al.*, 2020] Zaffaroni, Marta, Cunniffe, Nik J., & Bevacqua, Daniele. 2020. An ecophysiological model of plant-pest interactions: the role of nutrient and water availability. *Journal of the Royal Society, Interface*, **17**(172), 20200356.

Appendix: Curriculum Vitae

Contact details

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l'Agriculture et l'Environnement (INRAE)
Institut Sophia Agrobiotech
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Employment

2016- present	Researcher (CRCN), Institut Sophia Agrobiotech, INRAE, Sophia-Antipolis, France and Biocore project-team, Inria, Sophia-Antipolis, France
2010-2016	Researcher (CR2), Unité Plantes et Systèmes de cultures Horticoles (PSH), INRA, Avignon, France
2007-2009	Post-doc, Ibis project-team, Inria, Grenoble, France
2006-2007	Post-doc, Instituto Applicazioni del Calcolo (IAC), Italian National Research Council (CNR), Rome, Italy

Education & Training

2002-2005	PhD in Physics, University of Rome "Tor Vergata" and University of Strasbourg "Louis Pasteur". Tutor: prof. L. Biferale, Advisor: dr. S.Cocco, co-advisor: dr. E. Marinari. Degree awarded on March 2006. Thesis title: " Statistical mechanics of unzipping: bayesian inference of DNA sequence "
1998-2002	M.S. in Physics, University of Rome "La Sapienza"

Involvement in research projects

2007-2009 MetaGenoReg: Understanding the interaction between metabolic and genetic regulations: case of *E.coli* carbon metabolism
Sponsor: ANR

2007-2009 EC-MOAN: Scalable modeling and analysis techniques to study emergent cell behavior: Understanding the *E. coli* stress response
Sponsor: EU

2010-2013 FRIM:Fruit Integrative Modelling
Sponsor: EU-ERASysBio

2012-2015 CAQ-40: Climate change and Quality of fruit, grain and seeds in the next 40 years: adaptation to high temperature and water stresses at the end of crop cycle
Sponsor: INRA

2012-2013 CaKi: Kinetic modeling for multispecies comparative analysis of sugar metabolism in fleshy fruits
Sponsor: INRA, EA department

2013-2015 MecaFruit3D: Combined (eco)-physiological and 3D-modelling approach to understand and analyse the role of cuticle in growth and quality of fleshy fruits
Sponsor: Agropolis Foundation

2015-2018 Integrated Model of Plant and Organ Growth
Sponsor: Agropolis Foundation

2015-2018 CARBON-LED: Carbon footprint reduction via LED based production systems
Sponsor: EU-Climate-KIC

2015-2020 FRIMOUSS: FRuit Integrative MOdelling for a Unified Selection System
Sponsor: ANR

2018-2022 MAXIMIC: Optimal control of microbial cells by natural and synthetic strategies
Sponsor: ANR

2020-2021 ArchiNem: ecophysiological modeling of plant-nematodes interactions. Importance of root architecture
Sponsor: INRA, EA department

Supervising, Advising and Teaching

Post-doc fellows

2013-2014 *Ibrahim Cheddadi* (co-advisor) "Combined (eco)-physiological and 3D-modelling approach to understand and analyse the role of cuticle in growth and quality of fleshy fruits"

2013-2015 *Fernando Alvarez-Vasquez* (co-advisor) "Climate changes and virtual grain/seed modeling"

PhD students

2011-2015 *Elsa Desnoues* (co-advisor) "Du gène au phénotype : contrôle génétique et modélisation du métabolisme des sucres chez la pêche", PhD in Agronomic Sciences, University of Avignon

2015-2018 *Garance Koch* (co-advisor) "Effet du stress hydrique sur la croissance de la tomate: une étude multi-échelle, de la cellule à la plante entière pour une meilleure compréhension des interactions entre les échelles", PhD in Biology, University of Avignon

2015-2019 *Coffi Belmys Cakpo* (co-advisor),"Analyse multi-espèces de la croissance et du métabolisme des sucres en lien avec la qualité des fruits: approche par modélisation écophysiologique", PhD in Agronomic sciences, University of Avignon

2017-2021 *Hussein Kanso* (co-advisor) "Reduction de modèle, estimation des paramètres pour une population de génotypes et analyse du contrôle génétique. Cas du métabolisme des sucres dans la pêche", PhD in Biostatistics, University of Avignon

Master students

February-July 2012 *Sébastien Beauquis* (co-Advisor) "Conception et développement d'un logiciel de simulation de fruit en Java ", M2-internship in Bioinformatics, University of Bordeaux.

May-June 2015 *Stéphane Leveau* (advisor) "Modélisation de l'effet de la température dans un modèle fruit", L3-internship in Agrosciences, University of Avignon

July-August 2016 *Rozenn Pineau* (co-advisor) "Effects of simulated photovoltaic panels shading on tomato plant growth", L3-internship in Applied Mathematics and Biology, University Pierre and Marie Curie, Roscoff

May-August 2018 *Thomas Brenière* (advisor) "Physiologie de la plante attaqué par les nematodes: modélisation et expérimentation", M1-internship in Bioinformatics and Modeling, INSA Lyon

May-August 2019 *Lena Guitou* (advisor) "Modelling cell growth: coupling resources allocation with biophysical growth model", M1-internship in Applied Mathematics and Modeling, Polytech Nice-Sophia Antipolis

March-June 2020 *Nathan Jauzion-Graverolle* (co-advisor) "Role of the root system architecture in the progression of infestation with root-knot nematodes", M1-internship in Biocontrol Solution for Plant Health (BOOST), University Côte d'Azur

Avril-July 2020 *Achille Fraisse* (co-advisor) "Modeling energetic constraints in cellular resources allocation", M2-internship in Biosciences, ENS Lyon

February-July 2021 *Nathan Jauzion-Graverolle* (co-advisor) "Role of the root system architecture in the progression of infestation with root-knot nematodes", M2-internship in Biocontrol Solution for Plant Health (BOOST), University Côte d'Azur

February-July 2021 *Clément Bourgade* (advisor) "Development and calibration of an integrated model of the plant-nematode system. Effect of plant phenotypic variations.", M2-internship in ecological modeling (MODE), University of Rennes 1

Teaching

2016	Temporary teacher in Data Analysis (18 ETD), Cursus M1 "Genie Biologique", Polytech Nice, University of Nice-Sophia-Antipolis, France
2006-2007	Temporary teacher in basic mathematics ($\approx$ 40 ETD), Geology department, University of Rome 3, Italy

International Conferences

Items with my name in bold font are the ones I presented myself. * if oral presentation, poster otherwise

* **V. Baldazzi,** D. Ropers, H. Geiselmann, H. de Jong. Qualitative simulation of carbon starvation response in *E.coli*. European conference in Mathematical and Theoretical Biology (ECMTB),29 June-4 July 2008, Edinburgh (Scotland)

* **V. Baldazzi,** D. Ropers, D. Kahn, H. Geiselmann, Y. Markowicz, H. de Jong. The carbon assimilation network in E. coli is densely connected and largely sign-determined. European Conference on Complex Systems (ECCS), 21-25 September 2009, Warwick (England)

*Baldazzi,V. Ropers,D, Markowicz,Y, Kahn,D., Geiselmann,J, de Jong, H. " The carbon assimilation network in Escherichia coli is densely connected and largely sign-determined by directions of metabolic fluxes", JOBIM , 7-9 September 2010, Montpellier (France)

*Baldazzi,V., Ropers D, Geiselmann J., Kahn D, de Jong H. Importance of Metabolic Coupling for the Dynamics of Gene Expression Following a Diauxic Shift in E. coli. IFAC World Congress, 28 August- 2 Sept 2011, Milan (Italy)

* **V. Baldazzi,** D. Ropers, D. Kahn, H. Geiselmann, Y. Markowicz, H. de Jong. The carbon assimilation network in E. coli is densely connected and largely sign-determined by directions of metabolic fluxes. Biochemical Society Conference, 21-25 March 2010, York (England)

V.Baldazzi, G. Vercambre, M. Génard, Mark Poolman , D. Fell. Bringing the gap between ecophysiology and molecular system biology: The « Fruit Integrative Modeling » project, Physics and Biology Meeting, 14-17 June 2011 , Paris (France)

*Baldazzi, V., Bertin, N., and Génard, M.. A Model of Fruit Growth Integrating Cell Division and Expansion Processes, HORTIMODEL 2012, 4-8 November 2012, Nanjing (China)

*Gautier, H., Bertin, N., Baldazzi, V., Brunel, B., L'hôtel, J.-C., Génard, M., Orlando, P., Pradier, M., Serra, V., Vercambre, G., Biais, B., Gibon, Y. (2012). Impact of the tomato fruit temperature on its growth and composition. Presented at 2. Symposium on Horticulture in Europe , 1-5 July 2012, Angers (France)

Desnoues, E., Gibon, Y., Baldazzi, V., Signoret, V., Génard, M., Quilot-Turion, B. (2012). High or low fructose? Consequences for sugar metabolism in peach fruit. Presented at 6. Rosaceous Genomics Conference , 30 Sept - 4 October 2012, San Michele all'Adige (Italy)

* Desnoues, E., Gibon, Y., Baldazzi, V., Signoret, V., Génard, M., Quilot-Turion, B. (2013). High or low fructose? Consequences for sugar metabolism in peach fruit. Presented at 8. ISHS International Peach Symposium, 17-20 July 2013, Matera (Italy)

Bertin, N., Baldazzi, V.,Génard, M. Experimental and modelling approaches to understand interactions among cell division, cell expansion and endoreduplication in the control of tomato fruit growth. Presented at the 'Plant Organ Growth Symposium', 10-12 March 2015, Ghent (Belgium)

* **Baldazzi, V**., Génard, M., Bertin, N. Cell division, endoreduplication and expansion processes: setting the cell and organ control into an integrated model of tomato fruit development. Acta Horticulturae. Presented at HortiModel 2016: 5. International Symposium on Models for Plant Growth, Environment Control and Farming Management in Protected Cultivation., 19-22 September 2016, Avignon (France)

* **Baldazzi, V.**, Génard M, Bertin, N. Unravelling the contribution of cell cycle and cell expansion in an integrated model of tomato fruit development. Presented at 11. European Conference on Mathematical and Theoretical Biology (ECMTB), 23-37 July 2018, Lisbon, (Portugal)

Kanso, H., Quilot-Turion, B., Memah, M. M., Bernard, O., Gouzé, J. L., Baldazzi, V. A reduction strategy to simplify a model of sugar metabolism for application to a large panel of genotypes, IFAC Conference on Foundations of Systems Biology in Engineering (FOSBE19), 15-18 October 2019, Valencia (Spain)

* Kanso, H., Quilot-Turion, B., Memah, M. M., Bernard, O., Gouzé, J. L., Baldazzi, V. (2020). Reducing a model of sugar metabolism in peach to catch different patterns among genotypes, International Crop Modelling Symposium (ICROPM), 3-5 February 2020, Montpellier (France)

National Conferences

* **V. Baldazzi**, D. Ropers, D. Kahn, H. Geiselmann, Y. Markowicz, H. de Jong. The carbon assimilation network in E. coli is densely connected and largely sign-determined. XXIX Séminaire de la Societé Francophone de Biologie Théorique, June 2009, Saint Flour (France)

Academic services

Since my post-doc, I have acted as reviewer for a number of journals and international conferences, including *New Phythologist*, *Frontiers in Plant Science*, *PloS One*, *Agronomy*, *Agriculture*, *Post-harvest Biology*, ...
I was co-convener of the International ISHS congress 'Hortimodel 2016' that took place in Avignon from 19-22 September 2016 and that hosted 63 participants coming from 20 countries. Oral and poster communications covered topics related to greenhouses climate control, irrigation management, plant response to abiotic and biotic stresses, integrated approaches for phenotypic trait dissection as well as more methodological issues related to parameter uncertainty and genotypic differentiation in plant models.
Since 2019, I am an elected member of the ISA council.

Bibliography

[1] V. Baldazzi, S. Cocco, E. Marinari, and R. Monasson, "Inference of DNA sequences from mechanical unzipping: an ideal-case study.," *Phys Rev Lett*, vol. 96, p. 128102, mar 2006.

[2] V. Baldazzi, F. Castiglione, and M. Bernaschi, "An enhanced agent based model of the immune system response.," *Cell Immunol*, vol. 244, no. 2, pp. 77–79, 2006.

[3] V. Baldazzi, S. Bradde, S. Cocco, E. Marinari, and R. Monasson, "Inferring DNA sequences from mechanical unzipping data: the large-bandwidth case.," *Phys Review E*, vol. 75, p. 11904, jan 2007.

[4] V. Baldazzi, P. Paci, M. Bernaschi, and F. Castiglione, "Modeling lymphocyte homing and encounters in lymph nodes.," *BMC Bioinformatics*, vol. 10, p. 387, 2009.

[5] V. Baldazzi, D. Ropers, Y. Markowicz, D. Kahn, J. Geiselmann, and H. de Jong, "The Carbon Assimilation Network in Escherichia coli Is Densely Connected and Largely Sign-Determined by Directions of Metabolic Fluxes," *PLoS Computational Biology*, vol. 6, p. e1000812, jun 2010.

[6] D. Ropers, V. Baldazzi, and H. de Jong, "Model reduction using piecewise-linear approximations preserves dynamic properties of the carbon starvation response in Escherichia coli," *IEEE/ACM Trans Comput Biol Bioinform*, vol. 8, pp. 166–181, 2011.

[7] V. Baldazzi, D. Ropers, J. Geiselmann, D. Kahn, and H. de Jong, "Importance of metabolic coupling for the dynamics of gene expression following a diauxic shift in Escherichia coli," *Journal of Theoretical Biology*, vol. 295, no. 0, pp. 100–115, 2012.

[8] V. Baldazzi, N. Bertin, H. de Jong, and M. Génard, "Towards multiscale plant models: integrating cellular networks.," *Trends in Plant Science*, vol. 17, pp. 728–736, jul 2012.

[9] V. Baldazzi, N. Bertin, and M. Génard, "A model of fruit growth integrating cell division ans expansion processes," *Acta Horticulturae*, vol. 957, pp. 191–196, 2012.

[10] V. Baldazzi, A. Pinet, G. Vercambre, C. Bénard, B. Biais, and M. Génard, "In-silico analysis of water and carbon relations under stress conditions. A multi-scale perspective centered on fruit.," *Frontiers in Plant Science*, vol. 4, p. 495, jan 2013.

[11] E. Desnoues, Y. Gibon, V. Baldazzi, V. Signoret, M. Génard, and B. Quilot-Turion, "Profiling sugar metabolism during fruit development in a peach progeny with different fructose-to-glucose ratios.," *BMC Plant Biology*, vol. 14, p. 336, nov 2014.

[12] M. Génard, V. Baldazzi, and Y. Gibon, "Metabolic studies in plant organs: don't forget dilution by growth.," *Frontiers in plant science*, vol. 5, p. 85, jan 2014.

[13] E. Desnoues, V. Signoret, B. Quilot-Turion, V. Baldazzi, M. Génard, and Y. Gibon, "High or low fructose?Consequences for sugar metabolism in peach fruit," *Acta Horticulturae*, vol. 1084, pp. 599–604, 2015.

[14] M. Cieslak, I. Cheddadi, F. Boudon, V. Baldazzi, M. Génard, C. Godin, and N. Bertin, "Integrating Physiology and Architecture in Models of Fruit Expansion," *Frontiers in Plant Science*, vol. 7, pp. 1–19, nov 2016.

[15] D. Constantinescu, M.-M. Memmah, G. Vercambre, M. Génard, V. Baldazzi, M. Causse, E. Albert, B. Brunel, P. Valsesia, and N. Bertin, "Model-Assisted Estimation of the Genetic Variability in Physiological Parameters Related to Tomato Fruit Growth under Contrasted Water Conditions," *Frontiers in Plant Science*, vol. 7, pp. 1–17, dec 2016.

[16] E. Desnoues, V. Baldazzi, M. Génard, J.-B. Mauroux, P. Lambert, C. Confolent, and B. Quilot-Turion, "Dynamic QTLs for sugars and enzyme activities provide an overview of genetic control of sugar metabolism during peach fruit development.," *Journal of experimental botany*, vol. 67, pp. 3419–31, may 2016.

[17] Z. W. Dai, H. Wu, V. Baldazzi, C. van Leeuwen, N. Bertin, H. Gautier, B. Wu, E. Duchêne, E. Gomès, S. Delrot, F. Lescourret, and M. Génard, "Inter-Species Comparative Analysis of Components of Soluble Sugar Concentration in Fleshy Fruits," *Frontiers in Plant Science*, vol. 7, may 2016.

[18] E. Desnoues, M. Génard, B. Quilot-Turion, and V. Baldazzi, "A kinetic model of sugar metabolism in peach fruit allows the exploration of genetic variability," *Acta Horticulturae*, vol. 1182, pp. 169–176, 2017.

[19] V. Baldazzi, M. Génard, and N. Bertin, "Cell division, endoreduplication and expansion processes: setting the cell and organ control into an integrated model of tomato fruit development," *Acta Horticulturae*, vol. 1182, 2017.

[20] E. Desnoues, M. Génard, B. Quilot-Turion, and V. Baldazzi, "A kinetic model of sugar metabolism in peach fruit reveals a functional hypothesis of a markedly low fructose-to-glucose ratio phenotype," *The Plant Journal*, vol. 94, pp. 685–698, may 2018.

[21] G. Koch, G. Rolland, M. Dauzat, A. Bédiée, V. Baldazzi, N. Bertin, Y. Guédon, and C. Granier, "Are compound leaves more complex than simple ones? A multi-scale analysis," *Annals of Botany*, vol. 122, pp. 1173–1185, dec 2018.

[22] G. Koch, G. Rolland, M. Dauzat, A. Bédiée, V. Baldazzi, N. Bertin, Y. Guédon, and C. Granier, "Leaf Production and Expansion: A Generalized Response to Drought Stresses from Cells to Whole Leaf Biomass—A Case Study in the Tomato Compound Leaf," *Plants*, vol. 8, p. 409, oct 2019.

[23] V. Baldazzi, P. Valsesia, M. Génard, and N. Bertin, "Organ-wide and ploidy-dependent regulation both contribute to cell-size determination: evidence from a computational model of tomato fruit," *Journal of Experimental Botany*, p. erz398, aug 2019.

[24] H. Kanso, B. Quilot-Turion, M. M. Memah, O. Bernard, J. L. Gouzé, and V. Baldazzi, "Reducing a model of sugar metabolism in peach to catch different patterns among genotypes," *Mathematical Biosciences*, vol. 321, p. 108321, mar 2020.

[25] C. B. Cakpo, G. Vercambre, V. Baldazzi, L. Roch, Z. Dai, P. Valsesia, M.-M. Memah, S. Colombié, A. Moing, Y. Gibon, and M. Génard, "Model-assisted comparison of sugar accumulation patterns in ten fleshy fruits highlights differences between herbaceous and woody species," *Annals of Botany*, vol. 126, pp. 455–470, aug 2020.

[26] V. Baldazzi, P. T. Monteiro, M. Page, D. Ropers, J. Geiselmann, and H. de Jong, "Qualitative analysis of genetic regulatory networks in bacteria," in *Understanding the Dynamics of Biological Systems*, Springer, 2011.

[27] V. Baldazzi, N. Bertin, H. Gautier, and M. Génard, "Ecophysiological process-based model to simulate carbon fluxes in plants.," in *Methods in molecular biology (Clifton, N.J.)*, vol. 1090, pp. 347–61, Springer, jan 2014.

[28] V. Baldazzi, N. Bertin, M. Génard, H. Gautier, E. Desnoues, and B. Quilot-Turion, "Challenges in integrating genetic control in plant and crop models," in *Crop Systems Biology. Narrowing the gaps between crop modelling and genetics* (X. Yin and P. C. Struik, eds.), pp. 1–31, Springer, 2016.

[29] M. Génard, M.-M. Memmah, B. Quilot-Turion, G. Vercambre, V. Baldazzi, J. Le Bot, N. Bertin, H. Gautier, F. Lescourret, and L. Pagès, "Process-based simulation models are essential tools for virtual profiling and design of ideotypes: Example of fruit and root," in *Crop systems biology - narrowing the gaps between crop modelling and genetics* (X. Yin and P. C. Struik, eds.), pp. 83–104, Springer, 2016.