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## Review

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**Abstract**

Quantitative approaches in plant biology have a long history that have led to several ground-breaking discoveries and given rise to new principles, new paradigms and new methodologies. We take a short historical trip into the past to explore some of the many great scientists and influences that have led to the development of quantitative plant biology. We have not been constrained by historical fact, although we have tried not to deviate too much. We end with a forward look, expressing our hopes and ambitions for this exciting interdisciplinary field.

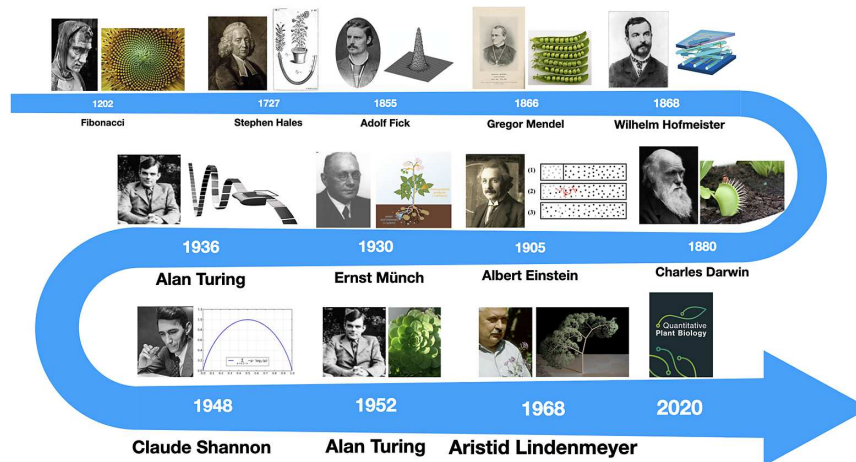
## 1. Introduction

Quantitative approaches in plant biology have a long history. Many such developments have exceeded their original remit and proven to be important discoveries beyond plant biology, including general biological principles, statistical methodologies, unexpected physical phenomena and new computational frameworks. In this short perspective, we start with a historic overview of some selected scientific developments that have shaped the field of quantitative plant biology (Figure 1), and then discuss the contributions of a few key figures in a little more detail before leaping into the future. History is not what is used to be and our historical overview is of course biased by our fields of expertise and preferences, and many alternative historical paths leading up to (some aspect of) quantitative plant biology can be imagined. To mention but a few, historical developments could be delineated from optics via microscopy, the discovery of cells and plant cell physics to quantitative plant biology; but also from counting, via number theory, algorithms to computing, computational biology and then quantitative plant biology; as well as from alchemy via the periodic table of elements, organic chemistry, metabolism, to metabolic engineering and quantitative plant biology. Indeed, we invite readers to find their own favourite route back through history. We end with some thoughts that we hope capture our excitement for this field, for the new journal *Quantitative Plant Biology*, and for the wealth of stimulating scientific challenges we can start addressing.

## 2. Figures from the past

In biology, particularly quantitative biology, but also many other areas of science, interdisciplinarity is considered a key innovation of the last few decades. However, it is important to realize that in the earlier days of science, interdisciplinarity was the rule rather than the exception. Driven by scientific curiosity and unconstrained by concerns that moving between disciplines is not the most effective way of maximising your h-index, scholars of the past, think for example of Descartes, Pascal or Newton, made significant contributions in diverse areas, crossing disciplinary boundaries that were not yet established.

With regards to the interdisciplinary field of quantitative plant biology, it could be argued to have started around 1860 when an Augustinian friar thought it may be a good idea to start counting peas (Figure 1) (Mendel, 1865). Casual as that may sound and perhaps giving the impression of short citizen science project, this endeavour was a carefully planned, long-term, interdisciplinary, strategic programme. The outcome of this work was the first mathematical theory of genetics, laying the foundation for the field of quantitative genetics and evolution.



**Fig. 1.** A biased, nonlinear timeline of some scientific breakthroughs in the areas of measurement, quantification, mathematics, computer science, plant biology and their combination. Photograph of Prof. A. Lindenmayer courtesy of Prof. Przemyslaw Prusinkiewicz. All other pictures were taken from Wikimedia Commons ([commons.wikimedia.org](https://commons.wikimedia.org)) and the Free Image Library ([www.freeimages.com](http://www.freeimages.com)) and are under CC BY-SA 4.0 <https://creativecommons.org/licenses/by-sa/4.0> or GFDL 1.2 or <http://www.gnu.org/licenses/old-licenses/fdl-1.2.html>.

Johann Mendel was born in Heinzendorf, Austria, in 1822. His academic aptitude was recognised early on by a local priest who convinced Johann's parents to send him away to boarding school where he graduated with honours. After this, he enrolled in philosophy at the University of Olmütz (University Olomouc, the oldest university in Moravia, now Czech Republic), where he demonstrated a talent for mathematics and physics (he later studied at the University of Vienna under Christian Doppler).

In 1843, Mendel joined the Augustinian Monastery in Brunn. The monastery gave Johann access to excellent research facilities, including the library and experimental field stations. Furthermore, many of the friars were active in their own research pursuits as well as in local education. It is here that Johann became Gregor.

A change in regulations meant that Mendel needed a certificate to teach, so in 1851 the monastery paid for Mendel to go to the University of Vienna to continue his studies and gain his teaching certificate. Mendel took several courses, including mathematics and biochemistry, but focussed on botany and physics. Upon completion of his studies in Vienna in 1853, Mendel returned to the monastery and took up a teaching position in a secondary school in Brunn.

Shortly thereafter, Mendel started his now game-changing experiments on heritable traits. Hybridisation had been worked on previously in the monastery and Mendel could convince the Abbot to support him with scientific resources (field experimentation facilities) and research assistants (fellow friars).

Using his knowledge of botany, Mendel was able to choose a suitable model system with clear reproducible phenotypes, ease of crossing and short generation times. Building on his education in physics, Mendel carried out careful experimental design, involving thousands of plants grown over several generations, and perhaps making this one of the first high-throughput phenotyping experiments. Using his skills in mathematics, in particular combinatorics and probability theory, Mendel was able to formulate hypotheses as testable mathematical statements. What emerged were the laws of inheritance and a mathematical theory of heritable traits, now considered one of the pillars of biology. Unable (and most likely also unwilling given his reported timid and modest nature) to tweet about his findings, Mendel's work lay dormant for decades. Mendel died in 1884 with his astonishing breakthroughs yet to be rediscovered. Today, Mendel is considered the father of genetics.

Based on dubious assumptions concerning randomization that have been allowed to propagate in the field of statistics, questions have been raised about the plausibility of some of Mendel's experimental data, but that is another story. It may have helped if Mendel had had the opportunity to place all his original data and data processing methods on github so that others could readily reproduce his results. But we are happy to report that Mendel's scientific integrity has recently been restored (Ellis et al., 2019).

Much less well known, even inside plant biology, is Mendel's contemporary Wilhelm Hofmeister. Intriguingly and impressively, despite not having received any academic training, Hofmeister was such a great observer and talented experimenter that the insights he obtained on plant reproduction and movement inspired both Mendel and Darwin. Although society in those days may have been more hierarchical, academia was perhaps more tolerant in that respect than today and the quality of his work earned Hofmeister an academic position despite his lack of formal training. In other aspects, academia was less diverse and both authors felt deep frustration with what may appear to be a gender-biased selection of contributors from the past.

Later in his life, Hofmeister made important contributions to plant tissue mechanics, quantifying tissue strength, bending and deformations and relating this to his observations on plant cell wall architecture, cell expansion and division. As such, Hofmeister can be considered the grandfather of modern quantitative plant biophysics, with his then highly debated ideas on tissue tension theory recently gaining considerable support.

There have been many impressive examples of interdisciplinary success stories in plant biology since Mendel and Hofmeister. Arguably one of the most influential figures was Ronald Fisher whose work gave rise to many of statistical foundations that are in use today. We mention here two other figures whose legacy continues to dominate.

We start with Alan Turing, outside biology famous for his contributions to breaking the Enigma code during World War II as well as his major contributions to the fields of computer science and artificial intelligence. Although perhaps less well known than his work on the foundations of computer science, Turing also had a keen interest in biological pattern formation, particularly the type of intricate, iterative patterns seen in sunflower phyllotaxis previously quantified by Fibonacci. Turing's article "The chemical basis

of morphogenesis, inspired by the vision of D'Arcy Thompson for a mathematical approach to biology (Thompson, 1917), has been highly influential in the field of biological pattern formation and the so-called Turing patterning is nowadays thought to explain phenomena ranging from asymmetric cell divisions, plant phyllotaxis, patterning of animal skin, bone, scale and feather patterns as well as ecosystem vegetation patterns (Turing, 1952). For plants, this range of processes has recently been further expanded to encompass plant vasculature cell wall patterning, pigment patterning of plant flowers and leaf trichome patterning (Nagashima et al., 2018; Jacobs et al., 2020, Ding et al., 2020, Okamoto et al., 2020).

Turing's proposed theory has proven extremely powerful in explaining a wide range of different patterning processes and has received substantial experimental support, yet the theory has not always been that popular (Green & Sharpe, 2015). While admittedly some may have pushed for it too far to explain phenomena for which the experimental evidence was pointing elsewhere (Drosophila body axis segmentation), acceptance of Turing's theory suffered from the unsuccessful search for morphogens of significantly different diffusivities. While biologically active, diffusing molecules with different transport rates may be unlikely to exist, others have shown that divergent diffusion rates are not essential for Turing patterns to form, and also the often heard critique of absent scaling behaviour has meanwhile been countered [see e.g., (Gierer & Meinhardt, 1972; Ishihara & Kaneko, 2006)]. Still perhaps most importantly, experimental support for Turing's mechanism took so long to accumulate because his model predictions were simply taken too literally. One should always keep in mind that models are a simplification, particularly the broad, generalist type models to which Turing's model belongs.

Once scientists moved away from the idea of Turing patterns necessarily requiring diffusing chemicals, but instead arising from, for instance, motile cells (fish skin patterning), different modes of cell-cell communication (direct receptor-ligand vs. long range signalling), or physical processes (buckling) support for the mechanism has mounted in many areas. This is perhaps a lesson to keep in mind when asking modellers to support their new theory with experimental data in order for it to be published. While of course validation of models is key to determine their merit in explaining biological phenomena, experimental support is not always feasible within the same lab or with existing techniques, and would thus substantially delay progress in terms of conceptual development. Indeed, in physics, the value of ideas and theory in the absence of data that may take decades to obtain is much more widely accepted. We hope to set similar traditions here.

Another key computational concept not unrelated to Turing's fascination with sunflower patterns, namely iteration, came from the Hungarian biologist Aristid Lindenmayer. His focus was on the algorithms on life.

Science in the post-genomic era has revealed that while genome data are immensely valuable, they fall short of providing an organism's blue-print—at least in terms of understanding how things work, that is, their algorithms. Instead, mechanistic answers for how genotypes lead to phenotypes are to be sought in the architecture and dynamics of complex regulatory, signalling and metabolic networks and their interplay with the physics of biological matter. But how much does one lead to the other?

The idea that the genotype encodes a complex, iterative algorithm and that it is this algorithm that dictates the unfolding of phenotype is not new.

In 1968, Lindenmayer invented a formal rewriting grammar called L-systems to model the modular, iterative, development

of algae and cyanobacteria over time (Lindenmayer, 1968). The perhaps more well-known critters or biomorphs Richard Dawkins proposed in his book 'The Blind Watchmaker' largely follow the same iterative, algorithmic principles (Dawkins, 1986). Indeed, modularity and re-usage are thought to play key roles in the evolution of complex organisms (evo-devo field).

L-systems have since been expanded to describe shoot and root branching patterns of a wide range of plant species, and adapted to enable incorporation of physiologically and developmentally relevant parameters. With this, a powerful approach for modelling environmentally sensitive plant development and intra-plant feedbacks, as well as evolutionary transitions in plant architecture, has emerged. The challenge now lies in integrating into these models the underlying genomics through developmental networks and processes to provide a truly mechanistic basis for the iterative formation of new and branching of old modules (for a nice recent example, see Azpeita et al., 2021). Although, while some may feel that a *in silico* plant encompassing all known details should be sought for, most modellers will hopefully realize this is neither possible nor even desirable. Fundamental questions in modelling are how to truly bridge the divide from genes to organism and eventually population, and how effective course graining at lower levels, possibly derived from dedicated models there, can be achieved.

What unites the above figures was their drive to explain natural phenomena through the distillation of simple principles that can be captured in a mathematical framework. As mathematics has developed through history, it has become more abstract and today much of mathematics focuses on structure (entities and the relationship between these entities) but without actually needing to define what the individual entities are. This has given rise to structures such as rings, groups and fields. Disparate mathematical objects obey the same basic rules within these structures, allowing results to be transferred and applied to several seemingly different problems.

Physics has very much adopted such frameworks for the description of natural phenomena, allowing for more general principles to be formulated and tested. Such principles can be used to explain large sets of empirical observations, thus effectively carrying out highly efficient data compression. The value of a theory is related to this data compression ability. This of course need not be mathematical or computational, although by virtue they often are. Classic examples of theories with great data compression capacities (in the sense of explaining a lot from very little) are Euclid's elements, Newton's laws of gravitation, Mendeleev's Periodic Table of Elements, Darwin's theory of evolution or Shannon's Theory of Communication. The above-mentioned examples from Mendel, Hofmeister, Turing and Lindenmayer include theories and rules of similar impact that have found application in areas well beyond the original puzzles they sought to solve.

### 3. A perspective

So what are our hopes and dreams for future quantitative plant biology? We hope that this new journal will contribute to the integration and mutual strengthening of different approaches in quantitative plant science. While in the times of Mendel and Darwin participation in the scientific endeavour by people outside of academia was fairly common, since then science has been largely restricted to professionals called academics who tend to hang out in universities. Only in recent years this has started to change again. With the rise of online means to share, analyse and store data, and public interest in science and the natural environment rising,

citizen science is now here to stay. Citizen science holds the promise of massive, yet potentially heterogeneous and biased datasets that offer new challenges and opportunities for academia in developing the proper statistical and modelling tools to maximally and effectively extract insights from these data.

Another area for improved integration high on the authors' wish list is that between the massive, quantitative and high-dimensional data generated by current state-of-the-art imaging and 'omics techniques and the typically lower-dimensional models aimed at providing mechanistic explanations. On the data side, the big data approach can be seen as unbiased, but also as hypothesis free. The correlations it detects do not necessarily reflect causation, and may not all be biologically meaningful. To make inferences, assumptions need to be made (MacKay, 2002), in particular for the inference of causal relationships (Pearl, 2009). On the modelling side, the mechanistic approach that necessarily focuses at key players is hypothesis-driven yet by therefore also biased. Biased by the knowledge and imagination of the modeller as well as the intractability of exploring model space. While this approach is powerful in determining the factors and interactions necessary and sufficient to explain a particular biological process, it may easily fail in identifying all players relevant for the process' robustness, particularly if these become relevant under highly different conditions.

Currently, there does not seem to be much interaction between the big data community and the modelling community. Yet, both communities are trying to do essentially the same, namely reduce observations to simpler rules or patterns. Ideally, these communities and approaches should become more integrated, with modelling driving the detection of causality in big data correlations, and large-scale data filling in the gaps and blind spots in models. Again, this further integration will require the development and application of new techniques, and an important role for machine learning is expected. We are excited about the possibility of these two approaches working synergistically to shed new light on complex challenges in plant biology.

#### 4. Figures from the future

So what could this improved integration and mutual reinforcement of different aspects of quantitative plant sciences offer? For that, let us consider a thought experiment about some great plant science happening in the not too distant future. Let us imagine that a renowned future leader in quantitative plant biology, Johanna Mendel, wishes to repeat some of the classical pea experiments of her famous family member.

Johanna has at her disposal state-of-the-art genome sequencing, single-cell expression, methylation analysis, proteomics, metabolomics, high-resolution imaging and high-throughput phenotyping experimental techniques. In addition to being a gifted quantitative plant biologist, Johanna is passionate about science outreach, particularly to young children. Via her vlog, she reaches out to thousands of school children worldwide, asking them to take part in her experiments and proving them with support for doing their own pea experiments in their school gardens. Each school has been provided with a set of different genotypes. They all have been shipped mobile sequencing machines to allow them to reconstruct the full genome rearrangements in every generation. Additionally, they are asked to take photographs of their pea plants at regular intervals, and measure plant height, leaf and flower numbers. All these data are sent straight to the cloud for more detailed analysis by Johanna and her team of statistical data analysts. Additionally,

a selection of the seeds is grown in Johanna's lab, and are analysed in more detail using gene expression, methylation, proteomics and metabolomics measurements as well as an automated phenotyping platform to measure plant geometry, petal shape and colour gradients,

So with all these tools, techniques and data available, what will Johanna discover, how much time will it take, and what will she need for this? First and foremost, in addition to the young citizen scientists, Johanna will need to collaborate with many more people from different disciplines and backgrounds. Only through collaboration of people with complementary expertise, will progress of a breakthrough nature will be achieved that provide a fuller and deeper understanding. Yet for such collaborations to succeed, quantitative plant biologists of the future will need an understanding of experimental design, imaging, bioinformatics as well as modelling. Through offering a joint platform for these different areas of expertise, this new journal aims to contribute to the interdisciplinary education of future plant scientists.

Importantly, setting up interdisciplinary collaborations and turning them into a success takes time. Time is needed to learn to speak each other's language, but also to iterate between experiments, analysis and modelling, particularly if new protocols and approaches need to be invented. Indeed, it may seem that publications, although less comprehensive, come easier when not taking this collaborative, interdisciplinary approach. It is thus important that journals like ours support the interdisciplinary approach by also welcoming intermediate products of such projects such as data or methods papers.

So indeed, first Johanna published her new web-based open access tools for data collection.

But when analysing her data, she is confronted with puzzling results. While for most genotypes and schools, the Mendelian laws of genetics seem to hold up, this is not the case for all genotypes and schools. To solve these riddles, she decides to contact three other quantitative plant biologists, Wilhelmina Hofmeister, a leading cell biophysicist, Alanis Turing, a rising star in the application of machine learning to plant biology, and Astrid Lindenmayer, a renowned computational plant biologist. Alanis' expertise helps detect that some apparent deviations from standard Mendelian genetics were correlated to highly subtle changes in intracellular pH. This helped the team reveal that these deviations only arose in school gardens with a low pH soil, and that soil-acidification has a pronounced effect on pea flower colour. Additionally, development of new machine learning approaches helped reveal how an interesting variation in chromosome organization affecting cross-over frequency in an African pea variety would subtly perturb inheritance ratios.

Still, some riddles remained, particularly with regards to the inheritance of flower shape. Because of the complex biophysical nature of flower shape development, Astrid Lindenmayer decided to construct a new computational model incorporating the gene regulation, hormonal signalling and mechanics of flower formation guided by the physical theories suggested by Wilhelmina. Making this model turned out to be highly non-trivial, which of the many relevant genes and interactions was she to include? Here, Johanna, Wilhelmina, Alanis and Astrid joined forces. With Johanna using her knowledge to pinpoint key players, machine learning techniques were developed to extract additional players based on their correlations with known key players as well as their strength of impact on flower phenotype. These were inserted into the model to investigate whether they are necessary and sufficient to explain the data. After several iterations between data, machine learning and



modelling, the new model was complete and revealed a highly non-linear genotype-phenotype mapping arising from the interplay between mechanics and patterning that explained the final counter-intuitive results.

Together, Johanna, Wilhelmina, Alanis and Astrid publish their findings, as well as additional papers on phenotyping and genomics analysis, new machine learning techniques, plant biophysics and computational models in the renowned journal of *Quantitative Plant Biology*. All the data, the meta data, the scripts and software are deposited as supporting materials so that anyone anywhere can freely gain access to their study and reproduce all the steps they made.

## 5. Final thoughts

The work of Mendel, Hofmeister, Turing, Lindenmayer and others clearly demonstrates that both quantitative and modelling approaches in plant biology have a long and successful history. The continuous technical developments in omics approaches, bioinformatic data analysis, high-resolution microscopy, image segmentation, live-tracking of samples, automated phenotyping and genome editing of the last few decades have given a tremendous boost to quantitative thinking in biology. Additionally, by revealing the complex, multi-factorial, multi-scale and multi-feedback nature of biological processes, these techniques have been instrumental in a shift from reductionist to systems thinking in mainstream biology. This shift towards quantitative, systems thinking has significantly contributed to the integration between experimental and model-based plant biology, and in many of the best studies in our field mechanistic models and dedicated, quantitative measurements now go hand in hand.

Biology is the science of this century, and the relevance of quantification, and mechanistic modelling has become crystal clear during this current corona pandemic. We hope and aim for quantitative plant biology to provide for equally important contributions to the challenges in food supply and climate crisis we are currently facing. Therefore, it is about time that this great field of ours is now rewarded with its own dedicated journal. We hope that you agree with us that this is a great and exciting time to be a quantitative plant biologist and hope you will all join us on this journey.

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