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1 **Multi-scale modelling to synergise Plant Systems Biology and Crop Science**

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17

18 **Abstract**

19 At the interface of the plant systems biology and crop modelling communities, a recurring
20 theme is the construction of an *in silico* plant that links across many levels of biological
21 organisation. These disciplines are not mutually exclusive; each has some elements of the other
22 and they have an overlapping goal in understanding and assisting crop improvement.
23 Therefore, we believe that synergies can be gained through knowledge exchange between the
24 two. Several modelling frameworks could support this aspiration. Our recent work on a
25 multiscale Arabidopsis Framework Model (FM) combined concepts from both systems biology
26 and crop modelling. We use the FM as a starting point to explore the potential benefits and
27 challenges of applying and extending such cross-disciplinary tools.

28

29 **Keywords:** systems biology; crop modelling; *in silico* plant; multiscale; climate change;
30 breeding

31

32 **1.0 Introduction**

33 The uncertain impact of climate change on crop yield has prompted various efforts to improve
34 the predictive performance of crop models. Recent efforts included systematic comparisons of
35 existing models and quantifying the uncertainty associated with each model, which has brought
36 to fore the variety of model structures, assumptions and the approaches used in developing the
37 models (Asseng et al., 2013; Rosenzweig et al., 2014). Studies have also extended beyond
38 functional-structural plant models (FSPM) and process-based models (PBM), to consider organ
39 level and genetic information that inform yield at the crop level (Chenu et al., 2009; Reymond
40 et al., 2004).

41 The incorporation of genetic information that governs plant traits is not new. Gene actions were
42 represented in earlier studies through linear estimates of effects on parameters to model
43 different cultivars (Hoogenboom et al., 1997; White and Hoogenboom, 1996). More recent
44 work linked crop models to quantitative trait loci (QTL), thus refining the representation to
45 associated genomic regions (Reymond et al., 2003; Yin et al., 2005), though they are restricted
46 to environmentally stable QTL (Chenu et al., 2009). Further refinement to molecular or gene
47 network models has also been proposed (Hammer et al., 2006). The explosion of understanding
48 in plant gene networks offers an opportunity to link the physiology of the plant and crop to
49 mechanisms at the molecular level, and potentially thereafter to genome sequences.

50 Besides improving agricultural management, crop models have been useful in aiding crop
51 breeding efforts (Chapman, 2008). Models can be used as preliminary screening tools to predict
52 the performance of crossing existing cultivars before further tests are conducted, thus reducing
53 the time taken to produce new cultivars. Recently, synthetic biology has been proposed as
54 another alternative to conventional breeding, whereby varieties with desired traits are designed
55 by modifying specific gene(s) through genetic engineering (Baltes and Voytas, 2015).

56 Evaluating alternative engineering strategies will often require quantitative models with
57 explicit representation of the target gene networks, linked to their physiological functions.
58 Moreover, the growth of genome sequences is expected in future to allow the mechanistic
59 understanding of (some fraction of) the causal sequence variation between crop varieties.
60 Again, linking the genomic data to quantitative mechanisms will require models that explicitly
61 represent the functions of the relevant sequences.

62 Many physiological and genetic models have been developed for crops (Bogard et al., 2014;
63 Gu et al., 2012), including a genetic network controlling wheat anthesis (Brown et al., 2013).
64 However, quantitative models with gene networks, regulatory mechanisms and metabolisms
65 are less common than in the model organism *Arabidopsis thaliana* (Lucas et al., 2011). One of
66 the reasons is that crop models generally aim towards parsimony, i.e. capturing only the
67 essential elements of environmental effects on plant performance. The availability of data was
68 also uneven, as genetic tools to decipher molecular mechanisms have been relatively fewer in
69 crop species; crop genomes are larger and more complex; and the timescales and/or facilities
70 required for crop studies can be substantially greater. The majority of the plant gene functions
71 discovered in the last decade have therefore been in *Arabidopsis*, making this the easiest species
72 for mechanistic modelling, despite the considerable distance from crop models.

73 Emblematic examples of crop homologues for these *Arabidopsis* genes were quickly shown to
74 underlie the high yield of crop varieties identified during the first Green Revolution (Ait-ali et
75 al., 2003; Hedden and Kamiya, 1997; Peng et al., 1999; Sasaki et al., 2002). In recent years,
76 many homologues of *Arabidopsis* genes have been found in crops (Chew and Halliday, 2011;
77 Nakamichi, 2014). We are also seeing progressively more application of molecular and systems
78 biology tools in crop studies (Kikuchi et al., 2003; Libault et al., 2010; Schmutz et al., 2010;
79 Schnable et al., 2009). Different approaches have been suggested to make the best use of
80 molecular plant science, systems biology and crop systems modelling in addressing the energy

81 crisis and food security issues (Hammer et al., 2004; Minorsky, 2003; Weckwerth, 2011; Yin
82 and Struik, 2010). A recurring theme is to develop *in silico* or digital plants (Zhu et al., 2015),
83 with integrative representation of gene functions at the molecular level while also linking
84 across all biological levels of organisation, combining existing methods from crop dynamic
85 modelling and the fast-emerging techniques in plant systems biology (Fig. 1).

86 This approach recognises the major opportunity for many more findings of basic plant research
87 to support tangible crop improvement programmes. The considerable, financial and
88 organisational constraints on the process have been reviewed elsewhere (RS, 2009). In this
89 paper, we discuss whether and how multiscale models could provide a new technical avenue
90 for research translation, with benefits for both fundamental and applied research. We propose
91 the bridging of plant systems biology and crop systems modelling at various levels, where the
92 different communities could complement one another (Fig. 1). As a case study, we discuss our
93 recently published multiscale model of Arabidopsis growth (Chew et al., 2014) in relation to
94 crop modelling, and where it stands relative to the *in silico* plant aspiration described above.
95 We also present an example of the circadian clock gene network and its role in photoperiodism,
96 because the molecular mechanisms are relatively well-understood, control important traits and
97 have thus been studied in crops. Our aim here is not to propose this as the network of choice
98 for genetic engineering, but to illustrate how systems biology models with molecular
99 mechanisms may contribute towards crop designs for future breeding, including through
100 synthetic biology. Similar principles could potentially be applied to many molecular processes
101 that control crop traits.

102

103 **2.0 The multiscale Arabidopsis Framework Model**

104 The Arabidopsis Framework Model (FM) was developed using a modular approach by
105 combining published models without modifying them. The FM consists of component models
106 or modules that are characteristic of different research domains, such as molecular systems
107 biology (gene regulatory network), crop science (functional-structural and source-sink
108 relations at the organ level; phenology) and physiology (leaf-level photosynthesis; respiration,
109 metabolism) (Fig. 1). Below, we briefly review each module, its links with crop science and
110 translational potential.

111 **2.1 The biological clock and photoperiodic response mechanisms**

112 The module at the molecular level describes the gene circuit network of the circadian clock in
113 Arabidopsis, which is one of the pervasive molecular networks regulating photosynthesis,
114 metabolism and flowering time (Hotta et al., 2007). The circadian clock enables plants to
115 perceive the duration of sunlight (photoperiod), an important cue for seasonal timing, so that
116 plants can pace their daily biochemical reactions and developmental events to optimise growth
117 and escape unfavourable environmental conditions (Millar, 2016; Simpson and Dean, 2002).
118 The effects of photoperiod on developmental rates have been included in many crop models,
119 even though no molecular basis was discovered until more recently (Nakamichi, 2014; Turner
120 et al., 2005; Yano et al., 2000). Developmental transitions were related to seasonal changes,
121 using a photoperiod-dependent scaling factor to modify the cumulative thermal time required
122 for a developmental switch, measured in the photothermal units of phenology models
123 (Robertson, 1968). For some crop species, photoperiod appears to be an obligatory signal; this
124 is modelled using conditional functions where critical photoperiods must be exceeded before
125 the model can proceed with successive events (Dingkuhn et al., 2008). In the case of the FM
126 (Chew et al., 2014), the photoperiod-dependent scaling factor in the phenology module is a
127 function of the expression level of a flowering gene (*FLOWERING LOCUS T*, *FT*). *FT*
128 expression is linked to the clock gene circuit module, based on the well-characterised

129 photoperiod response network in Arabidopsis (Salazar et al., 2009). Here, gene expression is
130 modelled using a set of ordinary differential equations (ODEs), where the change over time of
131 each molecular component is simulated, along with their multiple responses to the light:dark
132 cycle. This formulation not only provides a direct linkage between individual genes in the
133 clock-photoperiodism pathways, environmental inputs and phenology, but also offers temporal
134 resolution within the day, i.e. the scaling factor for photoperiodic response is continuously
135 tuned to the dynamics of the flowering gene expression (Box 1). One advantage of this is that
136 the changing photoperiod sensitivity within a day-night cycle can be captured, for example to
137 compare the effects of different mutations for plants growing at different latitudes (Box 1).
138 This capability may facilitate the understanding of Genotype x Environment interaction,
139 specifically for crop varieties with genetic variation in the clock/photoperiodism genes (see
140 Section 3.0) (Nakamichi, 2014).

141 **2.2 Carbon metabolism**

142 Metabolism is modelled in the FM in a simplified manner; only sugar (the transported carbon
143 form) and starch (stored carbon) are considered (Gerakis et al., 2006). Sugar is transported
144 from source organs to sink organs for growth and respiration, while part of the assimilated
145 carbon is stored as starch during the day so that it can be converted into sugar at night when
146 there is no photosynthesis. A recent study in Arabidopsis has revealed a circadian-clock control
147 of starch consumption rate, which is paced so that there is enough starch to last the length of
148 the night (Graf et al., 2010). This is currently represented in the FM using a simple division of
149 total starch turnover by night period (Chew et al., 2014). More detailed models linking starch
150 degradation to the clock gene network are also available (Pokhilko et al., 2014; Seaton et al.,
151 2014). These models focus on a subset of the complex metabolic network: their scope could
152 readily be broadened. In recent years, genome-scale metabolic models have been developed
153 for several species, where the fluxes of all metabolites in a plant system are solved by

154 optimising within a set of constraints an objective function, e.g. maximising biomass or
155 minimising total energy costs (Cheung et al., 2014; Grafahrend-Belau et al., 2013; Poolman et
156 al., 2009). Such flux-balance modelling has been useful in identifying redundant or alternative
157 pathways and their relative efficiencies, and can predict the shift in fluxes under different
158 environmental conditions (Cheung et al., 2013; Williams et al., 2010), potentially with tissue
159 resolution (Rolletschek et al., 2015). This level of detail is understandably not included in any
160 crop models, nor is it usually considered in conventional breeding. Nevertheless, metabolic
161 modelling can help identify target enzymes for breeding or genetic manipulation, to achieve
162 desired metabolic outputs thus facilitating metabolic engineering (Schwender, 2008). A major
163 limitation compared to single-cell organisms is that plant systems span a wide range of spatio-
164 temporal scales. Changing a target enzyme may not be sufficient to translate metabolic gains
165 into commensurate benefits at the whole-organism level (Leakey et al., 2012). The second
166 opportunity for modelling is therefore to optimise the effect of modification at the genetic level
167 on events at the whole-plant level and beyond. In this respect, models like the FM can provide
168 a framework for linking metabolic models of increasing breadth to processes at the higher
169 levels, to aid molecular breeding or synthetic biology.

170 **2.3 Plant architecture**

171 The FM also considers plant architecture, specifically shoot structure and its function in light
172 interception for carbon acquisition. This is modelled using a functional-structural module
173 where individual organ growth and leaf orientation are captured. The significance of plant
174 architecture in crop yield has been explored; one good example is the extension of a 3D canopy
175 model of wheat development to include mechanistic details such as organ-level photosynthesis
176 and allocation of assimilate (Evers et al., 2010). Simulating canopy structure is useful in
177 understanding competition for light, both inter-species and intra-species. Thus, crop models
178 that consider plant form and function can be valuable for maximising crop yield per unit area

179 to optimise land use (Egli, 1988; Mao et al., 2014). In the case of Arabidopsis, this plant species
180 has a simple rosette structure during the vegetative phase but upon switching to the
181 reproductive phase, stem elongation and branching occur, forming a more complex
182 inflorescence. The current version of the FM only models the simplest, vegetative phase.
183 Including the developmental phases important for crops will allow future versions of the model
184 to address the resource partitioning issues that are particularly relevant for translational
185 research. An extension to include the functional-structural contribution of the inflorescence
186 until fruit (and thus seed) formation is necessary (Christophe et al., 2008). These models would
187 require comprehensive phenotypic and physiological data, some of which are available
188 (Alonso-Blanco et al., 1999; Bennett et al., 2012; Diggle, 1997). Although the area seems
189 under-explored in Arabidopsis relative to crop species, these studies have already revealed
190 interesting correlations between branching and seed yield, which also depend on the plant
191 varieties, and identified some related QTL regions. Indeed, a recent mechanistic model of
192 sucrose transport in rice also highlighted the effect of grain arrangement on yield (Seki et al.,
193 2015), suggesting that the genetic tools to manipulate carbon partitioning in Arabidopsis will
194 allow future models to contribute further quantitative understanding of this area.

195 In contrast, plant development at the cellular, tissue and organ levels has been intensively
196 studied in Arabidopsis. Many of the molecular mechanisms regulating cell geometry, tissue
197 patterning and organ morphology have been elucidated using mathematical modelling (Roeder
198 et al., 2010; Sauret-Gueto et al., 2013; Torii, 2012), which therefore provide opportunities for
199 linking with the FM. As the FM already has a simple representation at the organ level,
200 incorporating more detailed morphology will be a natural extension. Including geometry at the
201 cellular level will require a major change in the resolution and hence in the modelling methods.
202 Nevertheless, such extensions could provide a platform to further improve yield through altered

203 architecture, as a continuation of what has been achieved during the first Green Revolution
204 (Khush, 2001).

205 **2.4 Phenology**

206 Vegetative development is simulated in the FM by a phenology module (Chew et al., 2012;
207 Wilczek et al., 2009). This module utilises the thermal time concept, which is adapted from
208 crop modelling approaches. Three components contribute: thermal time, photoperiod (see
209 above) and vernalisation. Degree-days are integrated, scaled by the photoperiod and
210 vernalisation factors, until a threshold value is exceeded to indicate the switch from the
211 vegetative to the reproductive phase. Additionally, the FM also simulates the change in
212 phyllochron, which is another phenological event within the vegetative phase, driven by
213 thermal time. To model the whole life cycle, this module will need to include floral initiation,
214 fruit formation, seed development and maturity, and plant senescence after which seeds can be
215 harvested. Seed dormancy has recently been addressed (Springthorpe and Penfield, 2015).

216 Crop modelling techniques that already consider various developmental stages again offer
217 valuable examples. It is worth noting here that ontogeny is actually a continuous process. The
218 ‘discrete ontogeny’ of functional stages allows plant development to be mathematically
219 represented as a sequence of states of finite automata (Komarov et al., 2003). Molecular events
220 that govern plant ontogeny are also continuous, and are often modelled as such in systems
221 biology, though hybrid discrete-continuous models have also been adopted such as for systems
222 exhibiting multiscale dynamics (Lincoln and Tiwari, 2004). Indeed, this is the approach used
223 in the FM, where the continuous gene regulatory module (see above and **Box 1**) was linked to
224 the phenology module. We expect more such hybrid links in the future, especially when
225 combining crop modelling concepts with those in systems biology.

226 The diverse technical approaches, which are natural in models from different research domains,
227 can form a significant barrier to re-using large models. Model exchange standards such as
228 SBML and CellML greatly facilitated progress in some areas of computational systems
229 biology, through model sharing and dissemination (Chew et al., 2014; Le Novere, 2006; Le
230 Novere, 2015). Further tools are required to increase computational efficiency and facilitate
231 model analysis (Qiu et al., 2014), in addition to sharing experimental data (Leonelli et al.,
232 2013). Furthermore, there are also platforms specific for the plant and agricultural research
233 community (reviewed in Adam et al., 2012) like OpenAlea, APSIM and RECORD that support
234 model composition (Bergez et al., 2013; Brown et al., 2014; Pradal et al., 2008). The FM used
235 one such tool, Simile (Muetzelfeldt and Massheder, 2003), to refactor all four modules into a
236 common format. These tools could mean that crop models and contemporary systems biology
237 models can be more conveniently exchanged, reused and combined.

238 **2.5 Photosynthetic engineering**

239 One of the processes central to plant yield is photosynthesis. Crop models like APSIM, Sirius
240 or CERES can effectively simulate growth based on organ demand or plant water status
241 (Hammer et al., 2010; Hoogenboom et al., 1994; Jamieson et al., 1998). In these models, carbon
242 assimilation (or dry mass accumulation) is explicitly modelled but crop growth is driven by
243 phenological development and organ expansion. These approaches also offer the potential to
244 link with systems biology, for as plant water relations (reviewed in (Tardieu et al., 2015);
245 (Parent and Tardieu, 2014)) involve the intensively-studied guard cell signalling network,
246 which was recently modelled in detail (Chen et al., 2012). The FM centres on carbon balancing
247 with a photosynthetic representation using the classical Farquhar model (Farquhar et al., 1980)
248 to simulate photosynthesis. The Farquhar model is commonly used in ecosystem models of
249 carbon cycling, though it has also been adopted in some crop models (e.g. GECROS (Yin and
250 van Laar, 2005)). This model and its later developments consider rate-limiting reactions like

251 carboxylation, electron transport and inorganic phosphate (Pi), using kinetic parameters
252 measured at the leaf level (Farquhar and von Caemmerer, 1982; Sharkey, 1985). More recently,
253 new tools in molecular, physiology, biochemistry and systems biology have facilitated the
254 development of a more detailed model, e-Photosynthesis (Zhu et al., 2013), which has explicit
255 description of individual reactions and major regulatory processes at the molecular level in the
256 photosynthesis network. Models with such details have identified molecular
257 components/pathways for improving photosynthetic capacity, which could serve as a blueprint
258 for the bioengineering of crop species (Wang et al., 2014). The FM's modular approach
259 provides an ideal platform to evaluate alternative modules, such as the coarse-grained Farquhar
260 and fine-grained e-Photosynthesis models. A fine-grained model can explicitly represent the
261 target enzymes and processes for engineering at the molecular level, providing the bridging
262 platform to understand and optimise how candidate manipulations propagate into changes at
263 the whole-plant level.

264

265 **3.0 Classical breeding and directed design**

266 The crops that we consume today have gone through centuries of human cultivation, during
267 which one of the selection aims was to expand the regions where the plants can be grown and
268 produce high yields. The mutations that were selected in the photoperiod pathways include
269 variants in the crop homologues of several Arabidopsis circadian clock genes (see (Nakamichi,
270 2014) for a comprehensive review). Understanding in Arabidopsis has become the reference
271 point for determining the functions of such mutated genes in crop cultivars (Box 1), such that
272 the function of a growing number of genome sequence variants might in future be explained
273 by reference to this system. A multiscale model such as the FM could extend the scope of such
274 understanding, even if the other physiological processes reviewed above remain simply

275 represented in the model. The potential for synergy will grow as further modules gain
276 mechanistic detail, such as the circadian regulation of starch metabolism noted above,
277 especially if mechanisms identified and modelled in model species translate readily to crops.

278 As the demand for food and biofuel increases, the pressure of climate change could also restrict
279 the temporal window for flowering (or other developmental events). A model-assisted breeding
280 strategy, where crop cultivars optimised for specific regions are specially designed and bred or
281 engineered, may open new avenues for local adaptation (Fernandez-Cornejo and Caswell,
282 2006). The mechanistic, molecular models would be a relatively small part of this process.
283 Accurate climate models will be required to provide projected climate inputs (Gleckler et al.,
284 2008; Knutti et al., 2010), though this is also an active research area (Duben et al., 2014;
285 Refsgaard et al., 2014) Latitude-specific ‘maturity groups’ are well established in some crops,
286 such as soybean (Boerma and Specht, 2004), but for other crops this would represent a major
287 change in commercialisation. The *in silico* plant must therefore be considered within a broad
288 research and translation agenda.

289

290 **4.0 Concluding remarks**

291 Our initial work on the Arabidopsis Framework Model is unusual in representing both plant
292 systems biology and elements drawn from crop systems modelling. The FM might be seen as
293 a ‘boundary object’ in sociological terms, at the interface of several research communities,
294 potentially facilitating communication (Star and Griesemer, 1989). While the FM will clearly
295 benefit from extension, it offers a medium to integrate the different types of understanding
296 from fundamental plant research and crop models. Tools of this type also have significant
297 potential to contribute to practical crop improvement, as one of several promising alternatives

298 that might be linked by umbrella structures such as the Joint Programming Initiative on
299 Agriculture, Food Security and Climate Change (FACCE-JPI).

300

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304

305 **Figure 1: *In silico* plant linking across biological levels of organisation.** Plants are complex
306 systems that cross multiple, interactive levels of organisation (column A). Each discipline (C)
307 usually focuses on processes at specific level(s) (B). Shaded boxes indicate processes currently
308 considered in our multiscale Arabidopsis Framework Model (Chew et al., 2014). Different
309 modelling communities (D) could interact and work together at various levels, where synergy
310 might be gained.

311

312 **Box 1. Connecting molecular circuits to flowering phenotypes.** The regulatory mechanisms
313 underlying the sensitivity of flowering time to photoperiod have been characterised at a
314 molecular level. This is illustrated in (A), showing a simplified representation of the regulatory
315 interactions involved in the circadian clock (orange) and the photoperiod pathway (green),
316 culminating in the regulation of *FT*. The dynamics of these networks have previously been
317 described by mathematical models (Pokhilko et al., 2012; Salazar et al., 2009; Song et al.,
318 2012), and were recently combined and updated in a single model (Seaton et al., 2015). This
319 allows simulation of the behaviour of this network in different natural photoperiods at different
320 times of year, for example those occurring in Halle, Germany (B). At different times of year,

321 the model simulates different levels of *FT* at this location (C). Thus, given a date of seedling
322 emergence, the date of flowering can be predicted (D). Flowering times for different genotypes
323 can also be predicted, e.g. in the case of the mutants *prp9;prp7* and *elf3* (knock-out mutants of
324 circadian clock genes with orthologues in crop species (Staiger et al., 2013)). This allows
325 simulation of a population of plants that show a distribution of dates of emergence. As shown
326 in (E), the sensitivity of the wild-type plants to photoperiod means that flowering occurs over
327 a narrower distribution of dates than either the late-flowering (*prp9;prp7*) or early-flowering
328 (*elf3*) circadian clock mutants.

329

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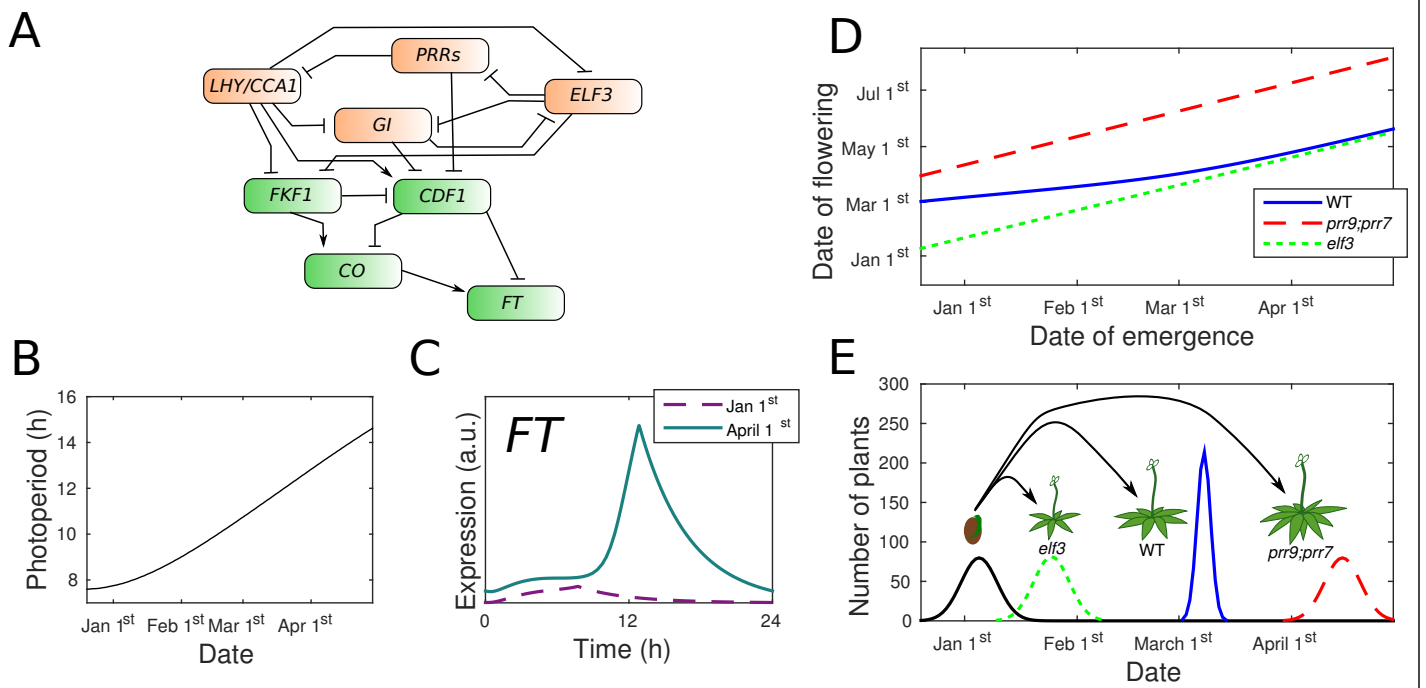
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Box 1. Connecting molecular circuits to flowering phenotypes. The regulatory mechanisms underlying the sensitivity of flowering time to photoperiod have been characterised at a molecular level. This is illustrated in (A), showing a simplified representation of the regulatory interactions involved in the circadian clock (orange) and the photoperiod pathway (green), culminating in the regulation of *FT*. The dynamics of these networks have previously been described by mathematical models (Salazar *et al.*, 2009; Pokhilko *et al.*, 2012; Song *et al.*, 2012), and were recently combined and updated in a single model (Seaton *et al.*, 2015). This allows simulation of the behaviour of this network in different natural photoperiods at different times of year, for example those occurring in Halle, Germany (B). At different times of year, the model simulates different levels of *FT* at this location (C). Thus, given a date of seedling emergence, the date of flowering can be predicted (D). Flowering times for different genotypes can also be predicted, e.g. in the case of the mutants *prr9;prr7* and *elf3* (knock-out mutants of circadian clock genes with orthologs in crop species (Staiger *et al.*, 2013)). This allows simulation of a population of plants that show a distribution of dates of emergence. As shown in (E), the sensitivity of the wild-type plants to photoperiod means that flowering occurs over a narrower distribution of dates than either the late-flowering (*prr9;prr7*) or early-flowering (*elf3*) circadian clock mutants.