Arabidopsis carpel genetic regulatory network modeling and reconstruction

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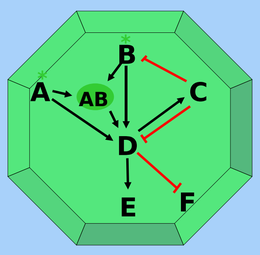
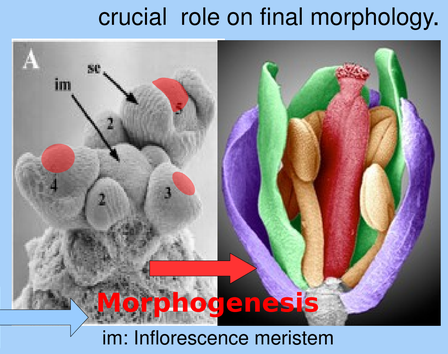
1. Introduction

- Objectives
  - Understand the molecular mechanisms underlying the early carpel development.
- Motivation
  - Carpel gives rise to fruit, major socioeconomic importance.
  - Early stages of development have crucial role on final morphology.



Gene network dynamics + Other factors



im: Inflorescence meristem
1-5: Flower development stages

- To be integrated with cellular model into virtual carpel model

2. Methods

- Methodology.
  - Combination of experimental and modeling approaches.
  - Gathering of transcriptomic data from inflorescences containing mix of early flower development stages, on both wild type and mutant plants affected by carpel development abnormalities (both own and published data).
  - Gathering of knowledge on gene interactions (idem).
  - Identify direct targets of Transcription Factors
  - Data analysis, construction of a raw interaction network.
  - Build of hypothetic scenario and networks.
  - Inference of models.
  - Validation by simulation, comparison with experimental data
  - Iterate until coherent models are found.
- Gene regulatory network (GRN) model

$$q_i(t+1) = H\left(\sum_{j=1}^{n} \alpha_{ij} w_{ij} q_j(t) - \theta_i\right)$$

  - $q_i(t)$: qualitative binary activity for gene i (i =1 .. N)
  - w_{ij} : interaction strength (ratio (induced production)/decay).
  - $\alpha_{i,j}$: Kind of the interaction (inhibition=-1, activation=+1)
  - θ_i : Activation threshold.
  - H : Heavyside function
- Estimation of model parameters
  - Given : i) prior network topology and ii) expression data
  - Find parameters that minimize Hamming distances (D_H) from model steady states to observed gene expression patterns
  - Subject to biological constraints
- Global optimization by mathematical programming

$$\left.\begin{array}{ll} \min_x & f(x) \\ \text{subject to} & g(x) <= 0 \end{array}\right\}$$

x : decision variables, f : objective function, g : constraints

  - Sets: V, A, T, R(genes, interactions, time steps, regions)
  - Variables: $q_{v,r,t} : V \times R \times T \to \{0,1\}$, $w : A \to \mathbb{R}^+$, $\theta : A \to \mathbb{R}$
    $y_{r,t} : R \times T \to \{0,1\}$ (=1 if fixed point condition)
  - Parameters: $\alpha : A \to \{-1,+1\}$, bounds: $\theta^L, \theta^U, \theta^L, \theta^U, w^L, w^U$
    $q^o_{v,r}, q^i_{v,r}$ (observed gene expression and initial cond.)
  - Objective function: $\sum_{r \in R_s} \sum_{t \in R_s} y_{r,t} \sum_{v \in V_s} \left| q_{v,r,t} - q^o_{v,r} \right| + \ldots$
  - Evolution rule and fixed point condition as constraints

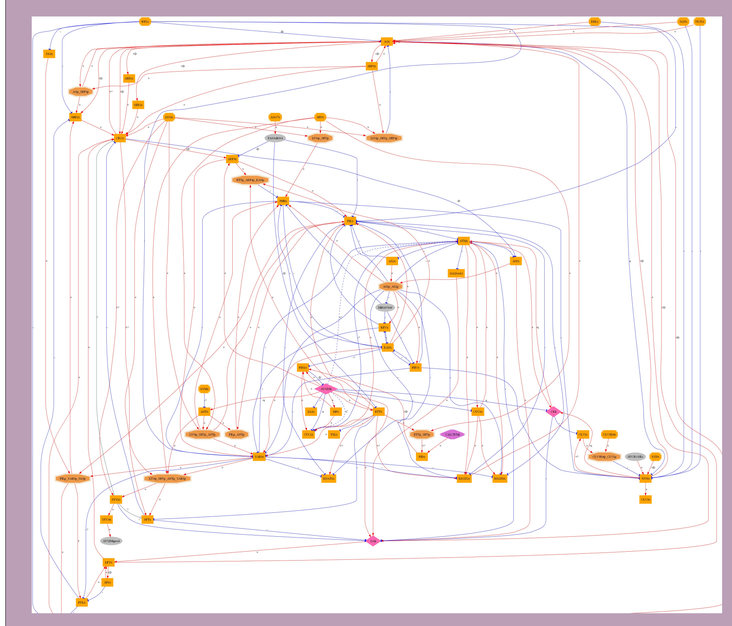
$$\sum_{uinV:(u,v)inA} \alpha_{u,v} w_{u,v} q_{u,r,t-1} >= \theta_{u,r} q_{v,r,t} - \|V\| (1 - q_{v,r,t})$$

$$\sum_{uinV:(u,v)inA} \alpha_{u,v} w_{u,v} q_{u,r,t-1} <= \theta_{u,r} (1 - q_{v,rt}) - \|V\| q_{v,r,t}$$

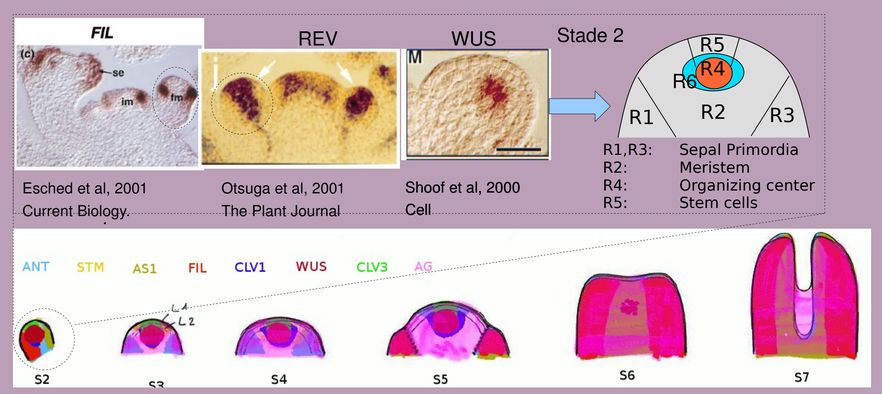
  - Subject to constraints on variable bounds and initial cond.
  - Reformulation and use of solvers (CPLEX, MINLP, etc)

3. Results

- Recensed interactions

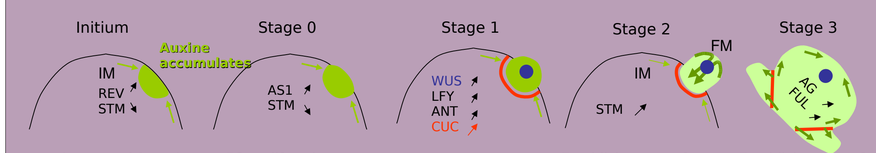


- Gene expression patterns



- Superposition of expression patterns reveals regions.
- Most of the data is difficult to analyze, multiple interpretations are possible.
- Tentative subdivisions in homogeneous regions are proposed.

- Scenario of flower development

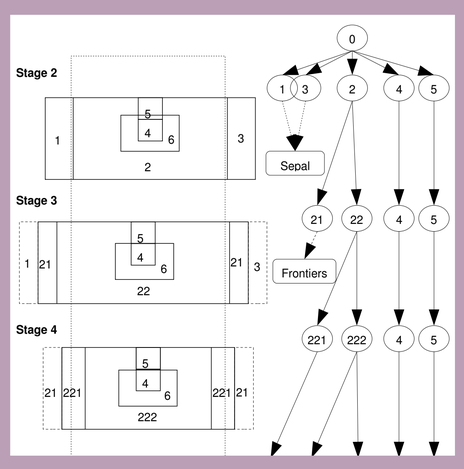


Recruitment of founder cells from the flanks of the IM.

FC proliferation, outgrowth begins.

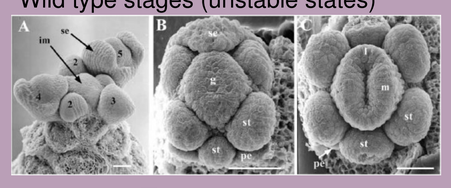
Establishement of Floral Meristem (FM). Sepal Primordia appears.

Establishement of carpel identity.



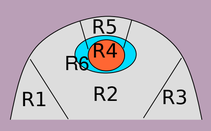
- Problem decomposition in stable subnetworks

Wild type stages (unstable states)



Flower: wild type stable states

Unstable states stage 2 ~ (ag, pi) mutant stable states

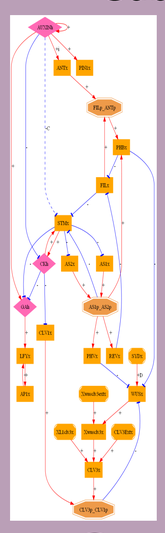


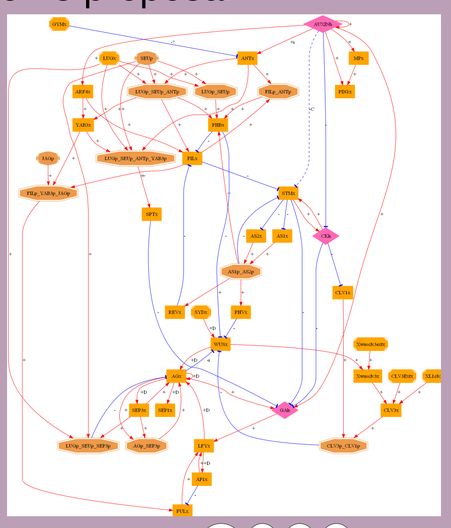
(Pelaz, 2000)

Number of stable states = number of final tissues (organs)

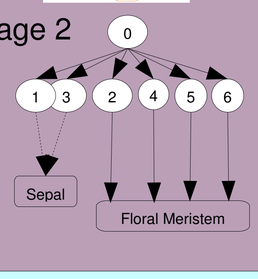
stage 2 = at least 4 stable states (sepals (1) + meristem (3))

- Subnetworks proposal

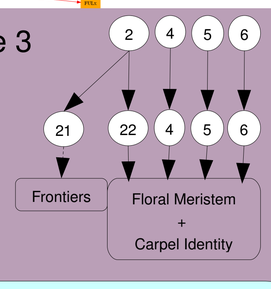




Stage 2

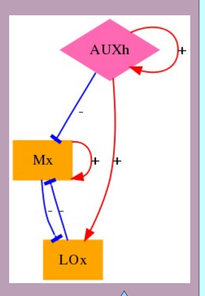


Stage 3



- Validation of identified model by simulation
  - Stability test

Stage-Region	S2–R2			S2–R1						S2–R3							
t	0	1	2	0	1	2	3	4	5	0	1	2	3	4	5	6	7
AP1x	1	**1**	**1**	1	1	1	1	**1**	**1**	1	1	1	1	1	1	**1**	**1**
LFYx	1	**1**	**1**	1	1	1	1	**1**	**1**	1	1	1	1	1	1	**1**	**1**
AS1x	0	**0**	**0**	1	1	1	1	**1**	**1**	1	1	1	1	1	1	**1**	**1**
PHBx	1	**1**	**1**	0	1	1	1	**1**	**1**	0	0	0	1	1	1	**1**	**1**
STMx	1	**1**	**1**	0	0	0	0	**0**	**0**	0	0	0	0	0	0	**0**	**0**
AUXINh	0	**0**	**0**	1	1	1	1	**1**	**1**	1	1	1	1	1	1	**1**	**1**
ANTx	1	**0**	**0**	1	1	1	1	**1**	**1**	1	1	1	1	1	1	**1**	**1**
ETTx	0	**0**	**0**	1	1	1	1	**1**	**1**	1	1	1	1	1	1	**1**	**1**
CKh	1	**1**	**1**	0	0	0	0	**0**	**0**	0	0	0	0	0	0	**0**	**0**
GAh	0	**0**	**0**	1	1	1	1	**1**	**1**	1	1	1	1	1	1	**1**	**1**
FILx	0	**0**	**0**	1	1	1	0	**0**	**0**	0	1	1	1	1	0	**0**	**0**
ETTp_KANp	0	**0**	**0**	1	1	1	0	**0**	**0**	1	1	1	1	1	0	**0**	**0**
FILp_ANTp	0	**0**	**0**	1	1	1	1	**0**	**0**	0	0	1	1	1	1	**0**	**0**
KANx	0	**0**	**0**	1	1	0	0	**0**	**0**	1	1	1	1	0	0	**0**	**0**
DH		1						5								3	



  - Analysis
    - Consistent for (Meristem – Lateral Organ)
      - Simplified (Meristem – Lateral Organ) Network
    - Unconsistent for lateral organ polarity
    - Return to data and propose network modification

4. Summary

- First time a molecular regulatory network for carpel development is constructed.
  - Current network for stage 2 supports meristematic and lateral organ identity stable states as expected but still not organ polarity.
- Complexity of genetic and molecular data on interactions
  - Large number of genes and interactions.
  - Very uncertain and contradictory data.
- Modeling
  - First approach with bivalued qualitative model
    - Adapted to the complexity of the network.
    - Convenient for qualitative stable state analysis.
    - Drawback: Not adapted to study transient phenomena.
  - Decomposition in subnetworks facilitates analysis.
  - Mathematical programming methods have been applied successfully on small gene networks for parameter estimation.

5. Perspectives

- Current work
  - Study next stages: 3 to 5 (carpel formation).
  - Test prediction of mutant phenotypes.
- Model
  - Extension to multivalued model is probably needed.
  - Addition of constraints based on more detailed biological information on interactions.
  - Comparison of mathematical programming model methods with simulation approaches for bigger networks.
- Future
  - Availability of expression data at cell resolution.
  - Integration of the network into cellular model

    (currently constructed by partner team in Montpellier).