De los genes a los patrones florales y su evolución: modelos dinámicos de redes regulatorias
Joint work with:
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Mariana Benítez
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Funding:
UNAM (Institute of Ecology) & CONACYT, México & SFI
How do these modules evolve and how were they assembled into the larger NWs?

What are the topological and dynamical features of different biological GRN that enable function (sensitivity, robustness and evolvability)?
From genes to patterns: INTRODUCTION

• EVOLUTION: origin and change of form & physiology of organisms.

• Neodarwininan Evol Theory: Linear models of Independently evolving genes (whole = Σ parts).

• Challenge: evolutionary models of integrated wholes of interacting genes, cells… (whole > Σ parts).

• General framework: interplay of network structure and function (dynamics) > pattern format
Non-linear relationship between phenotype & genotype: development
Regulatory Networks

GENOME

gene-protein

PROTEOMA

protein-protein
Transcriptional gene regulation
Protocol

- **Define biological study system**: Gene Regulatory Network for floral organ type specification
- **Model input**: Components and states (genes-proteins & level of activation; experimental data)
- **Hypothesis**: Interactions among components & kinetics (discrete [0, 1 and 2] or Boolean; experimental data)
- **Validation**: Capture known behaviour (loss & gain of function mutations)
- **Explore**: Cases not documented before & test parameters and assumptions…L. schismatica??
From genes to patterns

Introduction

- **Gene Regulatory Networks (GRN) and cell-fate determination:** MAIN ASSUMPTIONS & a simple example

- Floral organ specification in Arabidopsis:
  - A discrete single-cell model
  - Spatio-temporal dynamics… *Lacandonia schismatica*??
**Discrete Model**

\[ X_n = (x_1(n), x_2(n),...,x_N(n)), \]

\[ x_i(n) \text{ state of activation of } i\text{-th gene at } n\text{-th iteration.} \]

\[ X_{n+1} = f(X_n), \]

**Activity:** DISCRETE: 0, 1, 2

**Updating:** synchronous
**Boolean Networks**

### Logical rules

- **Z** depends on **Y**
- **X** depends on **Y**
- **Y** depends on **X** & **Z**

**Stationary state = cyclic Circadian rythm**
Boolean Networks

Stationary point = fixed point

“Cell Type”: S. Kauffman, 1969
From genes to patterns

Introducción

- Gene Regulatory Networks (GRN) and cell-fate determination: MAIN ASSUMPTIONS & a simple example

- **Floral organ specification in Arabidopsis:**
  - A discrete single-cell model
  - Spatio-temporal dynamics…
  Lacandonia schismatica??
250,000 flowering plant species

Great diversity, but basic floral plan is conserved:
SEPALS, PETALS, STAMENS, CARPELS
ABC mutants

E. Coen / E. Meyerowitz (1991)
• HOW IS THE COMBINATORIAL SELECTION OF GENE ACTIVITY AND ITS SPATIO-TEMPORAL PATTERN ESTABLISHED?

• PROCESS UNDERLYING ITS ROBUSTNESS: OVERALL ABCs FLORAL PLAN CONSERVATION IN EUDICOTS? WHY?
Logical functions grounded on experimental data

AP3::GUS seedlings

Example

Parcy et al, 1998

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Tables of logical rules summarize data

> 150 papers
### Table of logical rules for AGAMOUS

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Floral organ cell-fate determination gene regulatory network (GRN)

Nodes = genes
Edges = reg
Interactions (+/-)
Dotted = hypoth

Espinosa, Padilla & Alvarez-Buylla
P CELL 2004;
From 139,952 possible initial conditions the GRN converges to 10 steady states.

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 Shoot apical meristem

WUS
WUS + UFO
UFO

Mayer et al. 1998 & Samach et al. 1999
## Size of basins of attraction

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# lug mutant

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Stable cell states | # I.S. leading to each stable state
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4 infl meristem | 7,128
Carpeloid sepals | 50,706
Staminoid petals | 50,706
Stamens | 50,706
Carpels | 50,706
# ap2 mutant

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<td>1</td>
<td>1</td>
<td>Carpels</td>
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<table>
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<th>Stable cell states</th>
<th># I.S. leading to each stable state</th>
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<td>4 infl meristem</td>
<td>4,536</td>
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<tr>
<td>Ectopic carpels</td>
<td>25,110</td>
</tr>
<tr>
<td>Ectopic stamens</td>
<td>25,110</td>
</tr>
<tr>
<td>Estambres</td>
<td>25,110</td>
</tr>
<tr>
<td>Carpelos</td>
<td>25,110</td>
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</table>

*Bowman et al. 1989*
Are steady states **robust** to changes in logical functions?

(bit changes in outputs)

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Z</th>
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</table>

Ran system for all possible initial states and found attractors.
Steady states are robust to quantitative changes in logical functions & certain motifs seem critical for GRN behaviour

- Of 10000 changes tested
- Only < 1 % yielded steady states different to those predicted by original network
- Attractors more sensitive to changes in genes with greatest number of outputs only in network without AG positive feedback loop.
- Boolean NW recovers same 10 attractors…degenerate logical fns? BUT trajectories and basins are different
1. The GRN model incorporates the key components of a developmental “module” (kernel?) of combinatorial gene activity that underlies the ABC model: its output is robust to all input conditions, kinetic parameters & gene duplications. Conserved in all flowering plants (250 mill yrs)...maybe in gymnosperms...(also conserved)...
2. Qualitative models of complex GRN can capture their basic behaviour
Spatio-temporal dynamics of cell types (fixed point attractors)?

1. Deterministic signal

2. Noise
Gene Regulatory Networks (GRN) and cell-fate determination: MAIN ASSUMPTIONS & a simple example

- Floral organ specification in Arabidopsis:
  - A discrete single-cell model
  - Spatio-temporal dynamics... Lacandonia schismatica??
Is the temporal morphogenetic pattern of organ formation a robust emergent consequence of the dynamics of the floral genetic network subject to stochastic fluctuations?

**Linear interpolation:** approximate the discrete single-cell model to a continuous one *(ordinary differential equations)*:

\[
\frac{dX(t)}{dt} = f(X(t))
\]

\[
dX(t) = f(X(t))dt + \varepsilon dW
\]

The probability, \(u(X,t)\) of finding the system at time \(t\) in the state \(X\) satisfies the so-called **Fokker-Planck equation**

\[
\frac{\partial u}{\partial t} + \sum_{i=1}^{N} \frac{\partial}{\partial x_i} (f^i(x)u) = \frac{\varepsilon}{2} \Delta u
\]

**Fokker-Planck equation solution:** given an initial condition, what is the **most likely** temporal sequence of steady states?
PAISAJE EPIGENÉTICO
By solving the Fokker-Planck equation we can obtain, given an initial condition, which steady state for each of the fifteen genes considered in the network will the system most likely end up in at each time point.
Temporal morphogenetic pattern

Probability

Axis1

Axis2

C

A

A+B

B+C

se

pe

st
Novel approach: extends a discrete model grounded on experimental data to a continuous random model. Enables link dynamics of a cell-fate genetic network to spatio-temporal dynamics…recovers CH Waddington’s (1957) idea on “Epigenetic Landscapes”
New predictions & questions:
– noise magnitude that recovers observed morphog. Patterns?
– density or probab peaks = size of primordia or #cells per fate
– heterogeneity in cell-fate within a primordium
– are there key nodes for transition probab & most likely sequence of attractors (applications)
More questions:

– Why this morphogenetic pattern and not other? Lacandonia
– What are other possible dynamic outcomes of interactions between the same set of molecular compo.??
– Random models inspired in the biological structures, alterations of nodes and motifs…
Spatio-temporal dynamics: Turing-type model

We use the continuous interpolated vector field obtained from the discrete model as reactive term in a Turing reaction-diffusion system.

\[
\frac{\partial u}{\partial t} = D_u \Delta u + f(u, v) \\
\frac{\partial v}{\partial t} = D_v \Delta v + g(u, v)
\]
Solution of the Turing system

U "No B"  V "A or C"
The ABC model can be understood in terms of the qualitative behaviour of this solution.
UNIVERSAL LAW IN BIOLOGY: THERE ARE ALWAYS EXCEPTIONS!!

Lacandonia schismatica
DYNAMIC NETWORK MODELS FOR FLORAL ORGAN SPECIFICATION IN ARABIDOPSIS THALIANA

AND

HYPOTHESES FOR LACANDONIA SCHISMATICA UNIQUE FLORAL ARRANGEMENT
“Lacandonia schismatica: one in 1/4 million!!”
“Lacandonia schismatica: Spatio-temporal dynamics of floral organ fate determination?"

Expression of UFO in Arabidopsis

Hypothesis for Lacandonia “UFO”
Thank you!!

Elena R. Alvarez-Buylla
The complexity of GRN ensues that kinetic details of each interaction & activity fn do not need to be modeled in detail: result depend on topology.

R. Thomas et al. 95: both yield = results
Stochastic and Discrete Transcriptional Regulation:

- cell-by-cell analysis >> digital stochastic model of gene expression; the probability of a particular template to be active within a certain time window, rather than the rate of transcription from this template is subject to regulation.

- genes within individual cells have a distinct probability to respond to a given concentration of stimulus of transcription and the gene is either “ON” or “OFF” in a certain time window.
References:

- Ross et al. *Inmunol Cell Biol* 72, 177, 1994
- Hume DA *Blood* 96, 2323, 2000
- Paulsson *Nature* 2004
- Walters et al *PNAS* 92, 7125, 1995
- Fiering et al *Bioessays* 22, 381, 2000
- Ho et al *Nature* 382, 822, 1996

  “Binary response in inducible gene expression: competition of transcription factors with opposing functions (+ and –) for the same target promoter region necessary & sufficient for “ON” “OFF” switch”
Behaviour of AG & WUS

Gómez-Mena et al. 2004

AG:GUS in wild type

35S:AG x AG:GUS
Attractors

Stamen 2

Carpel
\frac{\partial u}{\partial t} + \sum_{i=1}^{N} \frac{\partial}{\partial x_i} (f^i(x)u) = \frac{\varepsilon}{2} \Delta u

Fokker-Planck equation

where $f^i$ stands for the $i$-th component of the vector field

To solve the FP eq in a two dimensional reduction of the system, we assumed that the vector field $f$ is of gradient type: $f(x) = -\text{grad}F(x)$

Then the dynamics of the system is determined by the potential function $F$
In our case:

In this graph of the potential function the minima are at the attractors of the dynamical system and the depth & width of each well around such minima is determined by the size of basins & these were obtained from the discrete syst.
\[ F(x) = \min(F_1(x), F_2(x), \ldots, F_m(x)) \]

where \( m \) is the number of minima (four): one corresponding to the activation states of the genes considered in primordial cells of sepals, petals, stamens and carpels.

Given that the minima lie originally in a 15-dim. space, least squares method were used to obtain the location of the attractors in the 2-dim. plane.
GRN models: organize genetic interactions into mechanistic dynamic explanations for specific developmental processes. Robustness and temporal pattern of floral organ determination are emergent properties of the *Arabidopsis thaliana* GRN. These models can be tested in silico and then in vivo and aid at detecting holes in experimental data.
M. Yanofsky Lab

abc

+A/B/C floral organs?

floral organs?
ABC genes are not sufficient to determine floral organ identity

WT = 35S::ABC

35S::SEP3/AP1/AP3/PI

35S::SEP2/SEP3/AP1/AP3/PI

Current Biology 2001
Effects of gene duplication
Time series for the expression of ABC genes (microarray data)

Level of expression

Time

Schmid et al. Development. 2003