Predicting essential components of signal transduction networks

A Boolean model of guard cell signaling

Song Li
Outline

- Introduction (Biological/Mathematical)
- Model construction
- Prediction
- Experimentation
Introduction to Guard Cell
Guard Cell signal transduction

- CO2
- Humidity
- Light
- H2O
ABA induced Stomata Closure

- Anion efflux
- K^+ efflux
- pH increase
- Oscillation
- NO, cADPR, cGMP, S1P, IP3, IP6 etc...
- ABI1(PP2C), ABI2(PP2C), RCN(PP2A), ERA1-2, etc..

ABA → Closure
Guard Cell signal transduction model Hall of Fame

Song et al., unpublished

Schroeder et al.,

Liumin et al.,

Hetherington et al.,

Hetherington et al.,
Problems with graphic model

- What are the timing and duration of each process?
  - What will happen if you perturb several components in the system?
  - Can you reverse engineer the system to produce desired response?
  - Use Mathematical model to understanding the system
Model construction

- From literature to wiring diagram

- Boolean (functional) model for the simplified network
A literature data base of guard cell signal transduction:

<table>
<thead>
<tr>
<th>Index</th>
<th>Species A (effector)</th>
<th>Process B/Species B</th>
<th>Promote/Inhibit</th>
<th>Species Reference</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>SphK</td>
<td>ABA→&gt;Closure</td>
<td>partial promotes</td>
<td>Arabidopsis(Ler)</td>
<td>Nature 423, 651 - 654 (05 June 2003); pharm/DL-threo-DHS or DMS</td>
</tr>
<tr>
<td>18</td>
<td>SphK</td>
<td>ABA→Opening</td>
<td>partial promotes</td>
<td>Arabidopsis(Ler)</td>
<td>Nature 423, 651 - 654 (05 June 2003); pharm/DL-threo-DHS or DMS</td>
</tr>
<tr>
<td>19</td>
<td>SphK</td>
<td>ABA→Potassium in channel</td>
<td>partial promotes</td>
<td>Arabidopsis(Ler)</td>
<td>Nature 423, 651 - 654 (05 June 2003); pharm/DMS</td>
</tr>
<tr>
<td>20</td>
<td>SphK</td>
<td>ABA→&gt;S anion channel</td>
<td>partial promotes</td>
<td>Arabidopsis(Ler)</td>
<td>Nature 423, 651 - 654 (05 June 2003); pharm/DMS</td>
</tr>
</tbody>
</table>
Network motifs to Wiring Diagram

1

A  B  IN  C

A  B  C

2

A  IN  B  C

A  C  B

3

A  B  C

A  IN  B
Wiring Diagram
Model construction

- From literature to wiring diagram
- Boolean (functional) model for the simplified network
Determine Boolean rules for each node

1) $S_{1P_{n+1}} = ABA_n$
   - This is the simplest case where one component’s presence/upregulation is the cause of another component’s upregulation: the S1P production of the next time step is determined by ABA.

2) $KOUT^* = (pH_c \text{ or not } ROS \text{ or not } NO) \text{ and depolar}$
   - Membrane depolarization will drive K+ flow out of the cell, and the activity of outwardly rectifying K+ currents is activated by cytosolic pH increase [24] and inhibited by ROS [116] and nitric oxide [64]
$S1P_{n+1} = ABA_n$

Coursol, S. et al
Nature 2003
$\text{KETA}_n^{n+1} = (\text{pHc}_n \text{ and depolar}_n) \text{ and not ROS}_n$
Boolean network model
Our Improvement

- Synchronous Boolean model assumes all the nodes update simultaneously, which is appropriate for modeling developmental processes.
  - Do all the chemical reactions happen at the same time?
  - Do we know which reaction is faster which is slower?
  - We update the nodes one at a time with randomized order, because we don’t know the exact timing of each reaction.

- We randomize the initial states of all the nodes, because we don’t know most of the states of the components in this network

- We generate 10,000 simulations and average them to obtain a stable output.

- We explore a group of similar wiring diagrams to see if some properties are consistent.
System simulation provide insight into the signal transduction process
Simulation of mutant or inhibitor effects
Testing hypothesis
Model construction

- From literature to wiring diagram ✓
- Boolean model simulation for the simplified network ✓
Results and Prediction

A) Simulation of one component node disruption.

▲ Normal response to ABA stimulus
△ Probability of closure decays in the absence of ABA.
□ Actin and ◇ anion efflux and through the plasma membrane lead to diminished closure probability.
not diminish ABA signaling.
Perturbations in □ S1P ▪ PA
◇ pHc mutants
■ ABI1 recessive mutants show faster than wild type ABA induced closure.
◆ Blocking Ca2+c increase does
Next Step: experimentation

- Our prediction is cytosolic pH and anion channel are the most essential regulators of this network, whereas cytosolic Calcium increase is not crucially required. (Interesting to test).
- Test the effects of inhibiting pH increase and Calcium increase
- Calcium clamping using BAPTA
- pH clamping using Butyrate
Experimental Evidences for pH mutant
Thank you

- Questions?