Reconstruction Spatiotemporal Gene Expression from Partial Observations

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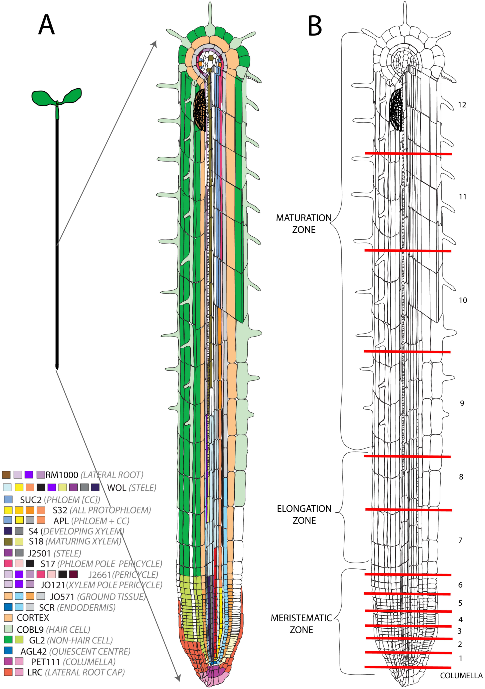
[1] Joint with David Orlando, Siobhan Brady, Bernd Sturmfels, and Philip Benfey. Research supported by the DARPA project Fundamental Laws of Biology

Arabidopsis root



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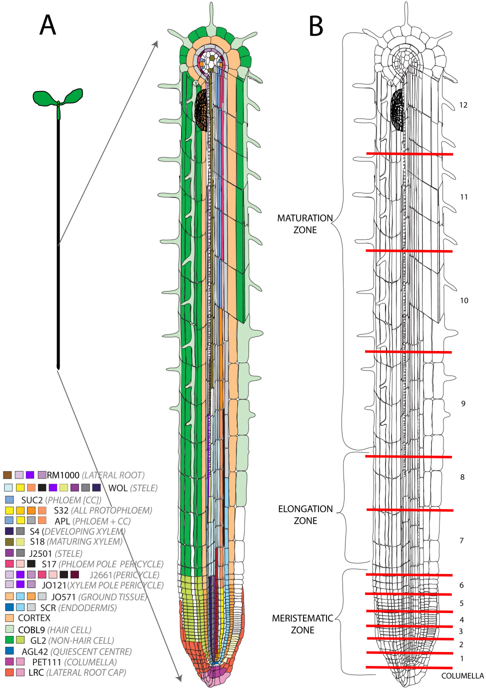

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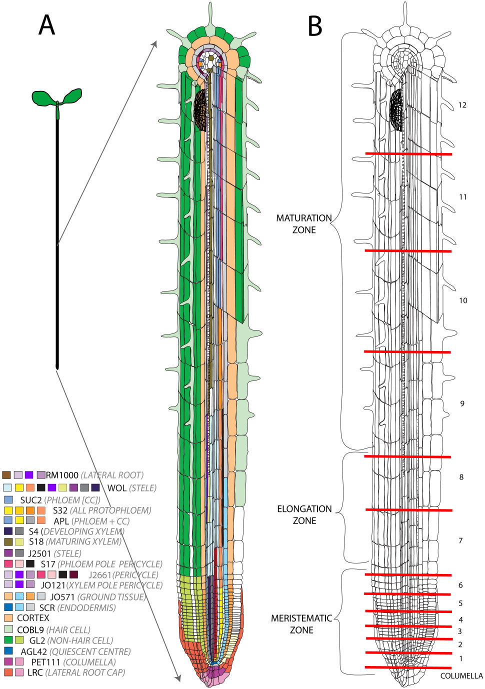

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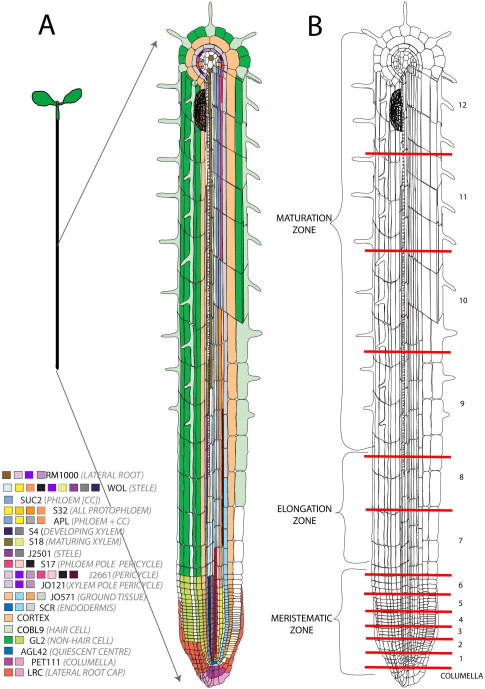
- Chemically, using 18 markers (colors in diagram A)
- Physically, using 13 longitudinal sections (red lines in diagram B)



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Naïve approach would use variation among each set of experiments as proxies for variation along each of the two axes.

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For example, the sample labelled APL consists of mixture of two cell types:

	cell type	
section	phloem	phloem companion cells
12	$\frac{1}{16}$	$\frac{1}{16}$
$\vdots$	$\vdots$	$\vdots$
7	$\frac{1}{16}$	$\frac{1}{16}$
6	$\frac{1}{16}$	0
$\vdots$	$\vdots$	$\vdots$
3	$\frac{1}{16}$	0
2	0	0
1	0	0
columella	0	0

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Conclusion: Need to analyze each transcript across all 31 $(= 13 + 18)$ experiments to model the expression pattern in the whole root.

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Under-constrained system: 31 $(= 13 + 18)$ measurements and 129 expression levels.

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Example

If the expression level is either 0 or 1 (off or on), then our assumption says that it is 1 for the combination of some subset of the sections and some subset of the cell types.

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$$
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x^t A^{(1)} y &= o_1 \\
&\vdots \\
x^t A^{(k)} y &= o_k \\
x_1 + \cdots + x_n &= 1 \quad \text{(normalization)}
\end{aligned}
$$

where

$A^{(1)}, \ldots, A^{(k)}$	$n \times m$ non-negative matrices (cell mixture)
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We want approximate solutions with x and y non-negative vectors of dimensions $n \times 1$ and $m \times 1$ respectively.

Kullback-Leibler divergence

Maximum likelihood estimation: Given a model (function $f : \Theta \to \mathbb{R}^k$) and empirical counts for each of the k events, determine the parameters which maximize the probability of the counts given the model.

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$$D(o \| f(\theta)) := \sum_{\ell=1}^{k} o_\ell \log \left(\frac{o_\ell}{f_\ell(\theta)} \right) - o_\ell + f_\ell(\theta)$$

With two additional terms, the generalized Kullback-Leibler divergence provides a measurement of the difference between any two positive vectors.

Finding maximum likelihood parameters

Two statistical methods for finding maximum likelihood parameters:

- Expectation Maximization: reduce solving mixture model (summation) to solving underlying equations.
- Iterative Proportional Fitting: solving log-linear (monomial) equations.

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Want to solve:

$$\sum_{i,j} A_{ij}^{(\ell)} x_i y_j = o_\ell \text{ for } \ell = 1, \ldots, k \tag{1}$$

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- Estimate contribution of (i,j) term of left side of equation 1 needed to obtain equality:

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Algorithm:

- Adjust $\tilde{x}_i$:

$$\tilde{x}_i \leftarrow \tilde{x}_i \frac{\sum_j e_{ij}}{\sum_j A_{ij} \tilde{x}_i \tilde{y}_j}$$

- Adjust $\tilde{y}_i$:

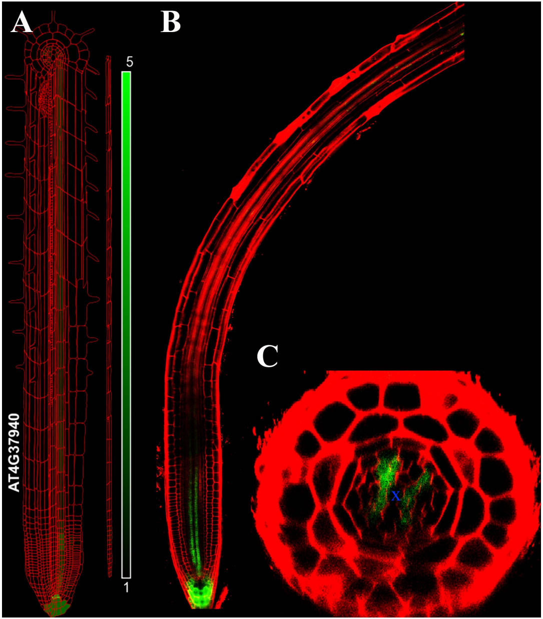
$$\tilde{y}_j \leftarrow \tilde{y}_j \frac{\sum_i e_{ij}}{\sum_i A_{ij} \tilde{x}_i \tilde{y}_j}$$

- Iterate until convergence

Back to Arabidopsis root

Using this algorithm, we estimated the expression profiles of $30,000$ transcripts in several hours.

Validation



A: reconstructed expression levels.
B and C: same transcript visualized using green fluorescent protein (GFP).

Generalization: positive root finding

The EM/IPF-based algorithm can be generalized to find exact or approximate positive solutions to polynomial systems of equations:

$$\sum_{\alpha \in S} a_{\ell\alpha} x^{\alpha} = o_{\ell} \quad \text{for } \ell = 1, \ldots, k,$$

where

- S is a finite set of exponent vectors,
- coefficients $a_{\ell\alpha}$ are all non-negative,
- the o_{ℓ} are positive, and
- a technical condition on the exponents (sufficient to be homogeneous or multi-homogeneous).