Asymmetric Centrosome Maturation in the Early *C. elegans* Embryo Revealed by Multi-scale Microscopy and Mathematical Modeling

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INTRODUCTION

The process by which cells position their centrosomes is critically important for proper cell divisions[1,2]. Centrosomes are the main microtubule organizing centers of the cell and abnormal positioning during cell division is one potential cause leading to cancer metastasis[3].

Microtubule (MT) Array Asymmetry in *C. elegans*

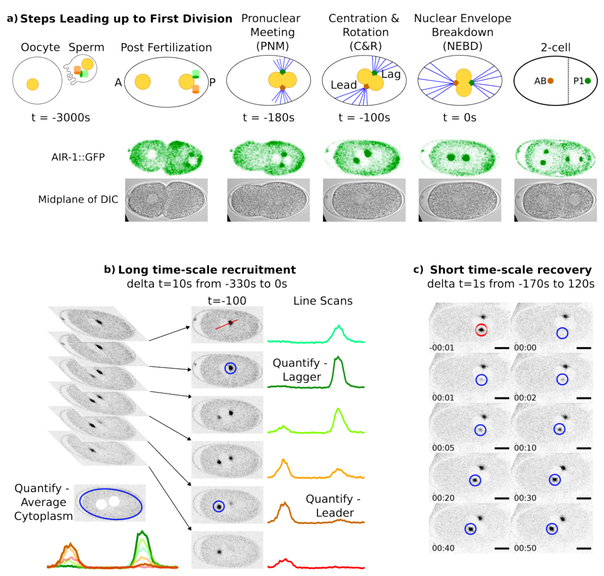
We use *C. elegans* as a model for asymmetric cell division and centrosome placement because the steps leading up to the first asymmetric cell division are tightly regulated[4] (Fig. 1a).

Our lab previously reported an asymmetry in the size and density of the MT arrays from the two centrosomes during the first cellular division of the *C. elegans* embryo[5]. The source of this asymmetry is currently unknown.

We analyze the fluorescence intensity of a GFP tagged AIR-1, a factor found in the centrosome that is required for microtubule nucleation in both centrosomes.

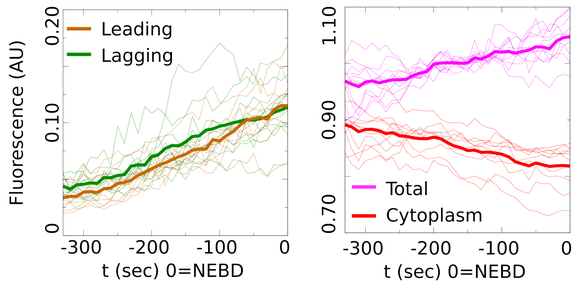
- **Leading** centrosome found in the anterior (larger) cell.
- **Lagging** centrosome found in the posterior (smaller) cell.

Figure 1. Imaging Fluorescent Centrosomes Leading up to the First Division of *C. elegans*

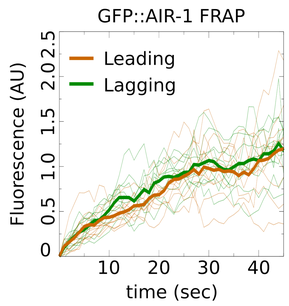


RESULTS

Figure 2. Asymmetric Centrosome Recruitment & Recovery Revealed by Precise Quantification



Normalized Lagging Intensity Higher Than Leading



Normalized Curves Were Not Significantly Different

Statistical Analysis Shows Asymmetries

Our recently published Gromov-Wasserstein based distance metric was used to identify any potential differences between the shapes of the calculated recruitment and recovery curves[7].

The recruitment did not show a difference between leading and lagging centrosomes indicating that their dynamics were overall similar. However, the recruitment in the lagging centrosomes is greater than the leading centrosome until ~-50s which would not be captured by this analysis (Fig. 2).

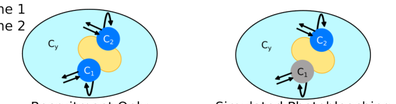
The FRAP curve analysis identified distinct recovery dynamics between the two centrosomes even though the curves recovered to the same final amount (Fig. 2).

MATHEMATICAL MODELING

A 3-compartment model representing the two centrosomes as well as the cytoplasm was constructed to simulate a maturation factor's recruitment and recovery in a one-cell embryo (Fig. 3).

Figure 3. 3-Compartment Model of Centrosome Recruitment & Recovery After Photobleaching

C_y - Cytoplasm
C_1 - Centrosome 1
C_2 - Centrosome 2



Basal Gain Carrying Capacity Cooperativity Basal Loss

$$\frac{dC_{1b}}{dt} = C_0^{n1}\left(1-\frac{C_{1b}B+C_{1f}F}{\alpha_4}\right)C_{yb}(C_{1b}B+C_{1f}F)^{n_1} - \alpha_1 C_{1b}$$

$$\frac{dC_{1f}}{dt} = C_0^{n1}\left(1-\frac{C_{1b}B+C_{1f}F}{\alpha_4}\right)C_{yf}(C_{1b}B+C_{1f}F)^{n_1} - \alpha_1 C_{1f}$$

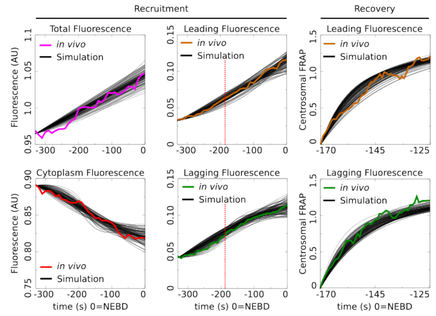
$$\frac{dC_{2b}}{dt} = \alpha_3 C_0^{n2}\left(1-\frac{C_{2b}B+C_{2f}F}{\alpha_5}\right)C_{yb}(C_{2b}B+C_{2f}F)^{n_2} - \alpha_2 C_{2b}$$

$$\frac{dC_{2f}}{dt} = \alpha_3 C_0^{n2}\left(1-\frac{C_{2b}B+C_{2f}F}{\alpha_5}\right)C_{yf}(C_{2b}B+C_{2f}F)^{n_2} - \alpha_2 C_{2f}$$

$$\frac{dC_{yb}}{dt} = -\alpha_7 C_{yb} - \frac{dC_{1b}}{dt} - \frac{dC_{2b}}{dt}$$

$$\frac{dC_{yf}}{dt} = \frac{\alpha_6}{C_0 F} - \alpha_7 C_{yf} - \frac{dC_{1f}}{dt} - \frac{dC_{2f}}{dt}$$

Figure 4. 112 Parameter Sets that Recapitulate *in vivo* Recruitment & Recovery Data



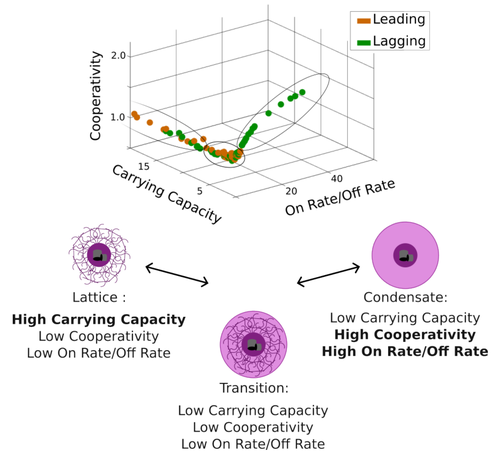
Using a parameter search based on our MCMC method[8] we were found 112 parameter sets that fit the model's maturation factor to the observed AIR-1::GFP data.

Parameter Space of the Model Reveals Structural Features of the Centrosomes

Three features define the structural dynamics of the centrosome compartments in the model. The cooperativity, carrying capacity, and the ratio of the on rate to the off rate.

Plotting all 112 parameter sets on a 3D plot with these features as the axis and differentiating the leading from the lagging centrosome revealed a high level of restriction to the location of possible parameters (Fig. 5).

Figure 5. Parameter Space Shows Asymmetry in Centrosome Structural Composition



DISCUSSION

Early embryo *C. elegans* Centrosomes are asymmetric.

Combining a precise quantification of a factor required for MT nucleation and mathematical modeling we found that the leading and the lagging centrosomes have different dynamics.

Emergent Centrosome Structural Asymmetry

The two extremes of the parameter space coincide with previously published biological hypotheses of centrosome structure (Fig. 5b). Our model gives these three structures a common model and may explain the recently reported progression of centrosomes from a condensate to a lattice[9].

FUTURE DIRECTIONS

Expanding *in vivo* & *in silico* Work to New Factors

We will investigate the recruitment, recovery, and maturation of more centrosomal factors. Of particular interest will be factors granting the centrosome its strength.

With a larger data set we will also be able to expand our mathematical model to include more terms and more dynamic interactions.

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