Combining Quantitative Genetics and Cellular Biophysics

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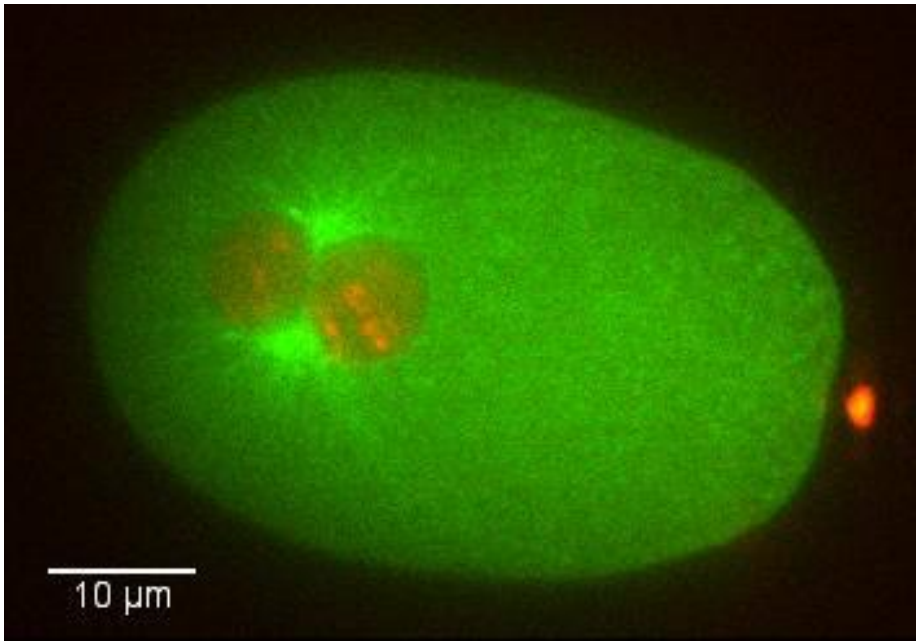
With help from: Gunar Fabig, Matt Rockman, Elaine Angelino

Funding: HFSP, BSF, NSF, NIH

Cell Division and The Spindle

First Mitotic Division in *C. elegans*



Tubulin (Microtubules)
Histones (Chromosomes)

Approach:

- Quantitative Measurements
- Technique Development
- Comparison with Theory

How Does The Spindle

Assemble?
Peter Foster, Bryan Kaye, Doogie Oh,
Sebastian Furthauer, Jan Brugues (now at MPI)

Position Itself?
Hai-Yin Wu, Manqi Deng

Elongate?
Che-Hang Yu

Segregate Chromosomes?
Tae Yeon Yoo

Consequences For

Medicine: Tim Sanchez
infertility and assisted reproductive technologies

Evolution: Reza Farhadifar
micro and macro evolution of cell division

Quick Summary of My Last Talk

Our Approach to Understanding Spindle Evolution

spontaneous mutation is the ultimate source of variation

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selection, population dynamics, genetic drift, . . .

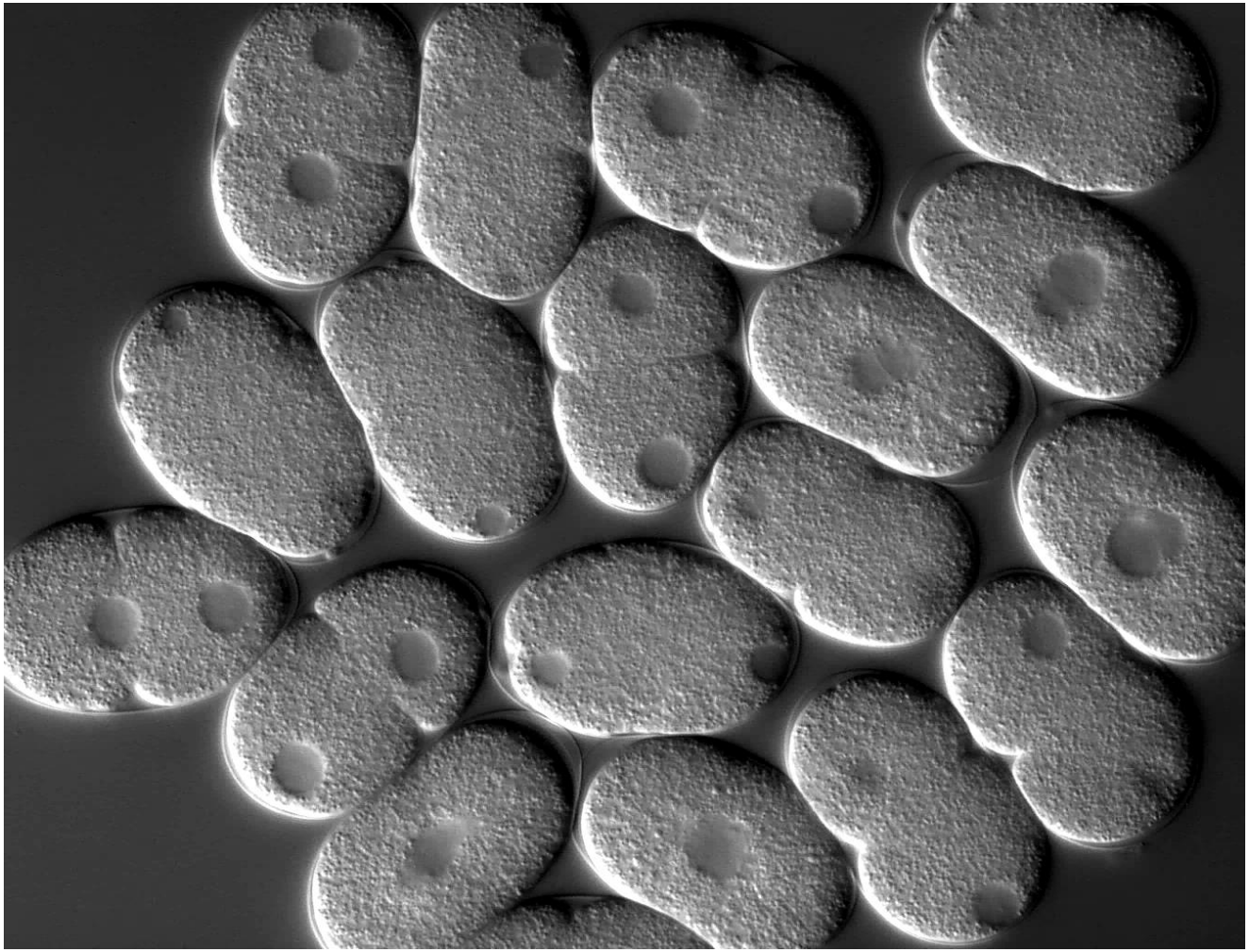
↓

within species variations of the spindle

↓

between species variations of the spindle

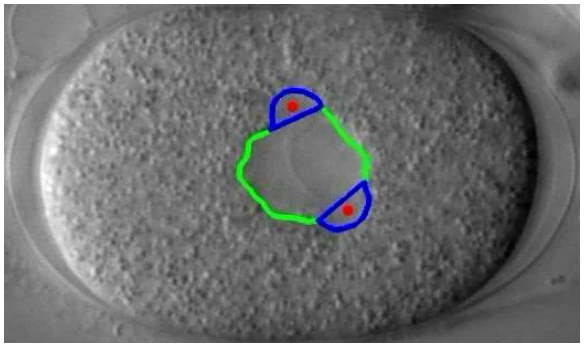
High Throughput Imaging of the First Mitotic Spindle in *C. elegans*



Imaged more than 20,000 embryos

Automated Segmentation and Tracking of the First Mitotic Spindle in *C. elegans*

Tracking

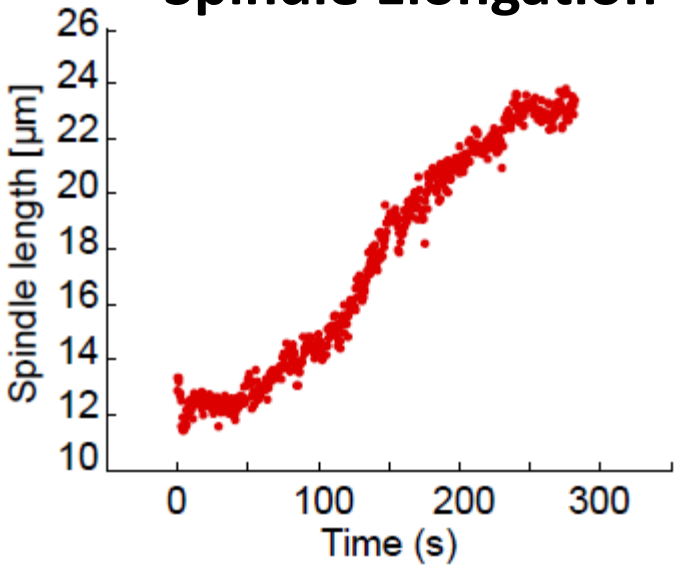


Quantify

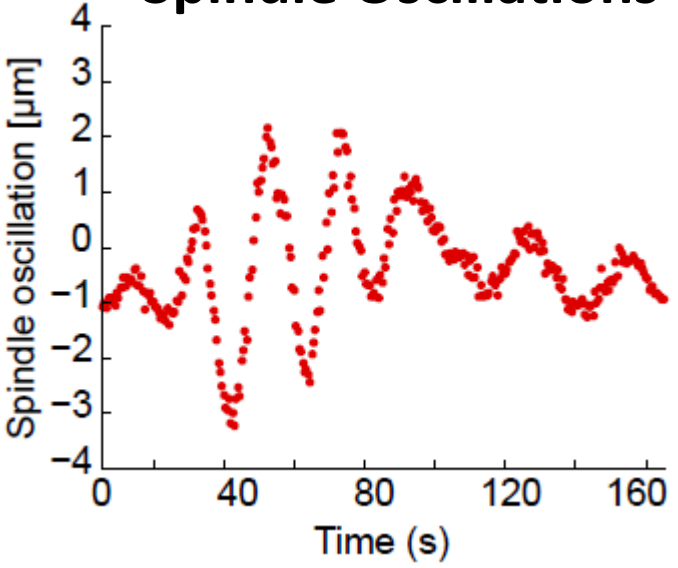
- Spindle Elongation
- Oscillations
- Centrosome Size
- Division Plane

etc. . .

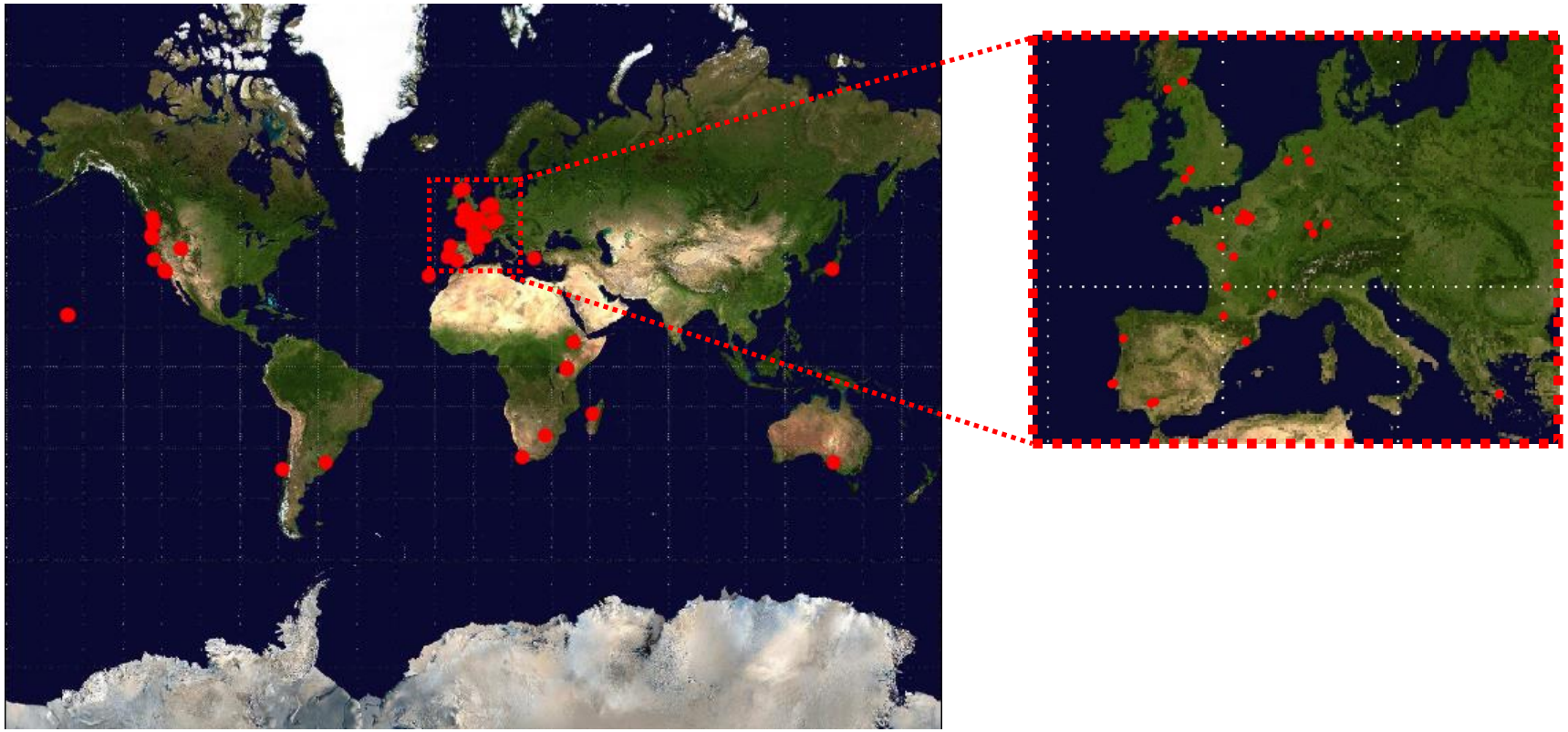
Spindle Elongation



Spindle Oscillations



Studied the First Mitotic Spindle in Many *C. elegans* Wild Isolates From Around the World

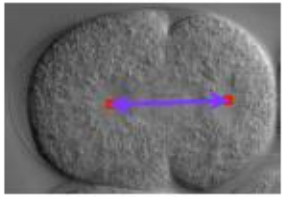


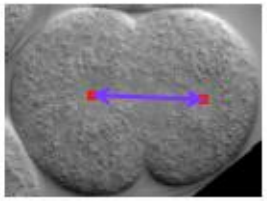
Isolated collected by Marie-Anne Felix, Erik Andersen, and many others

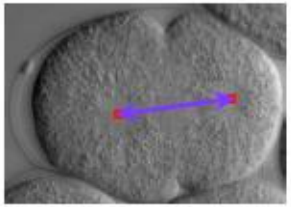
- ~100 *C. elegans* wild isolates collected from around the globe
- wild isolates sequenced by Erik Anderson and Leonid Kruglyak

Extensive Standing GENETIC Variation For Spindle Dynamics and Morphology In *C. elegans* Wild Isolates

CB4932







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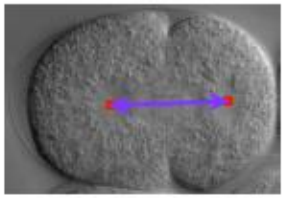
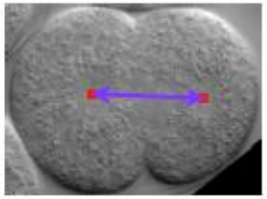
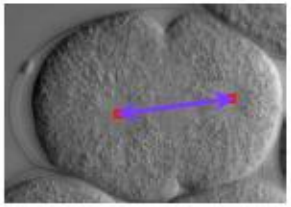
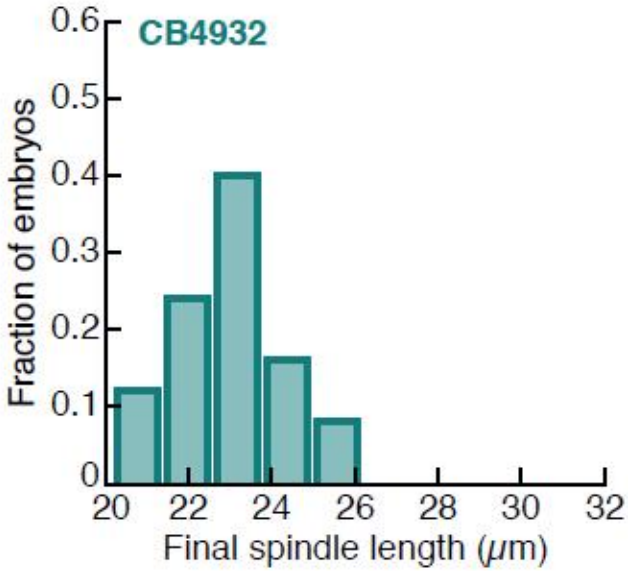
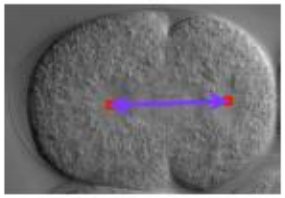
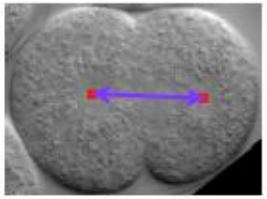
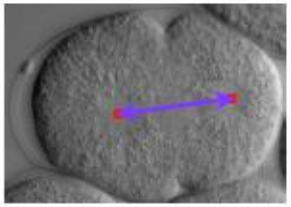







CB4932
Fraction of embryos
0.6
0.5
0.4
0.3
0.2
0.1
0
20
22
24
26
28
30
32
Final spindle length (μm)

CB4932

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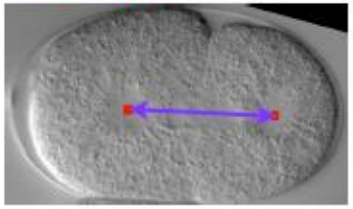
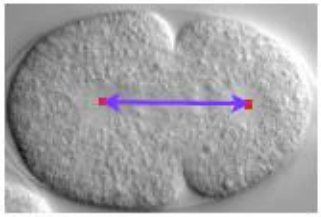
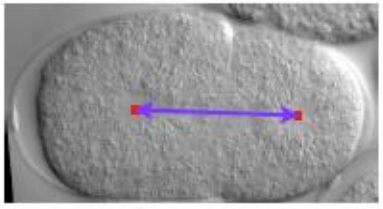

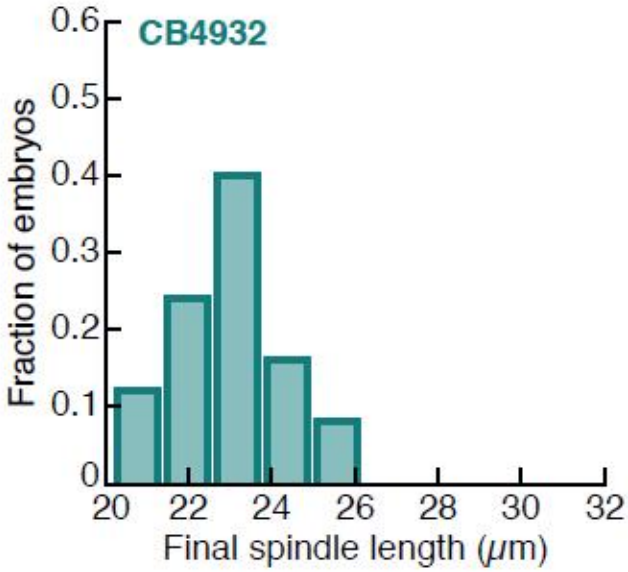

Final spindle length differs in different wild isolates

There is GENETIC variation for final spindle length in *C. elegans*

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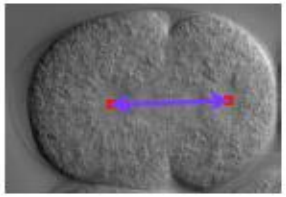
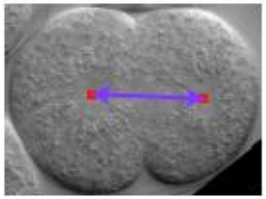
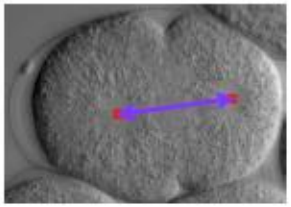

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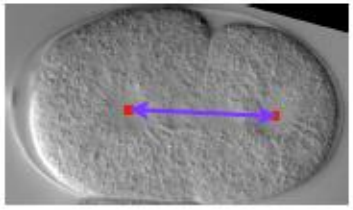
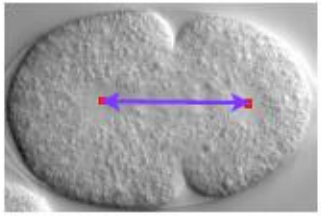
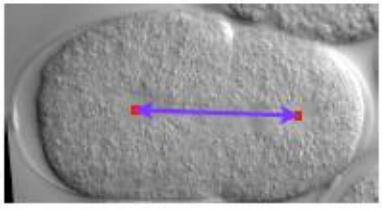
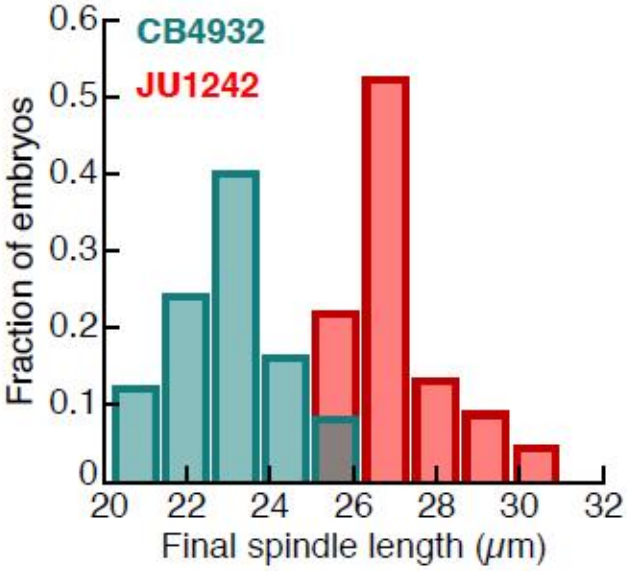
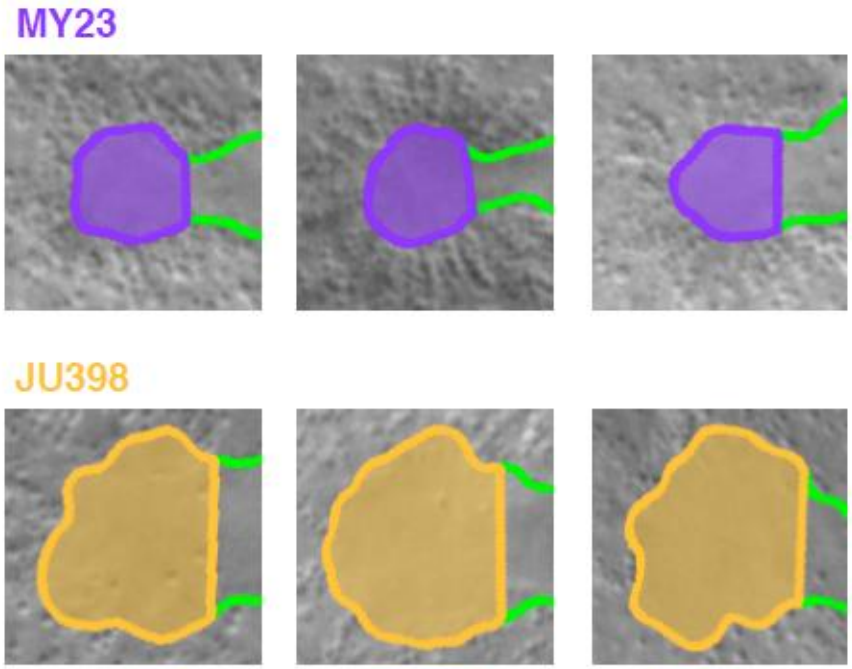
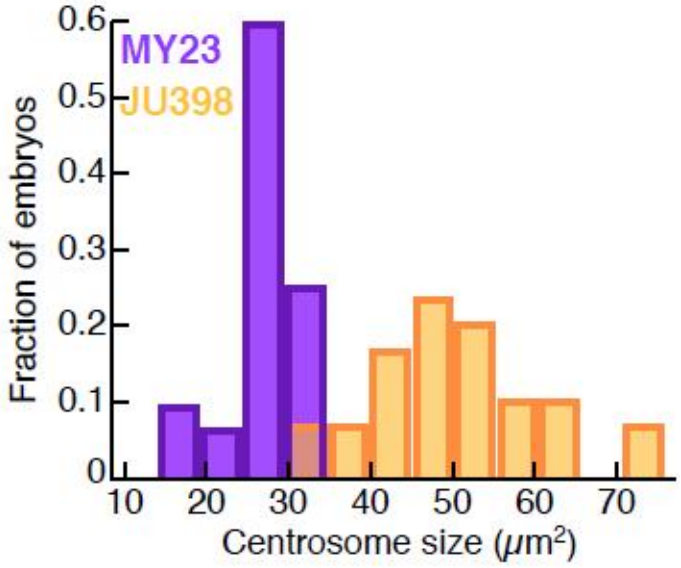






Centrosome size differs in different wild isolates

There is GENETIC variation for centrosome size in *C. elegans*





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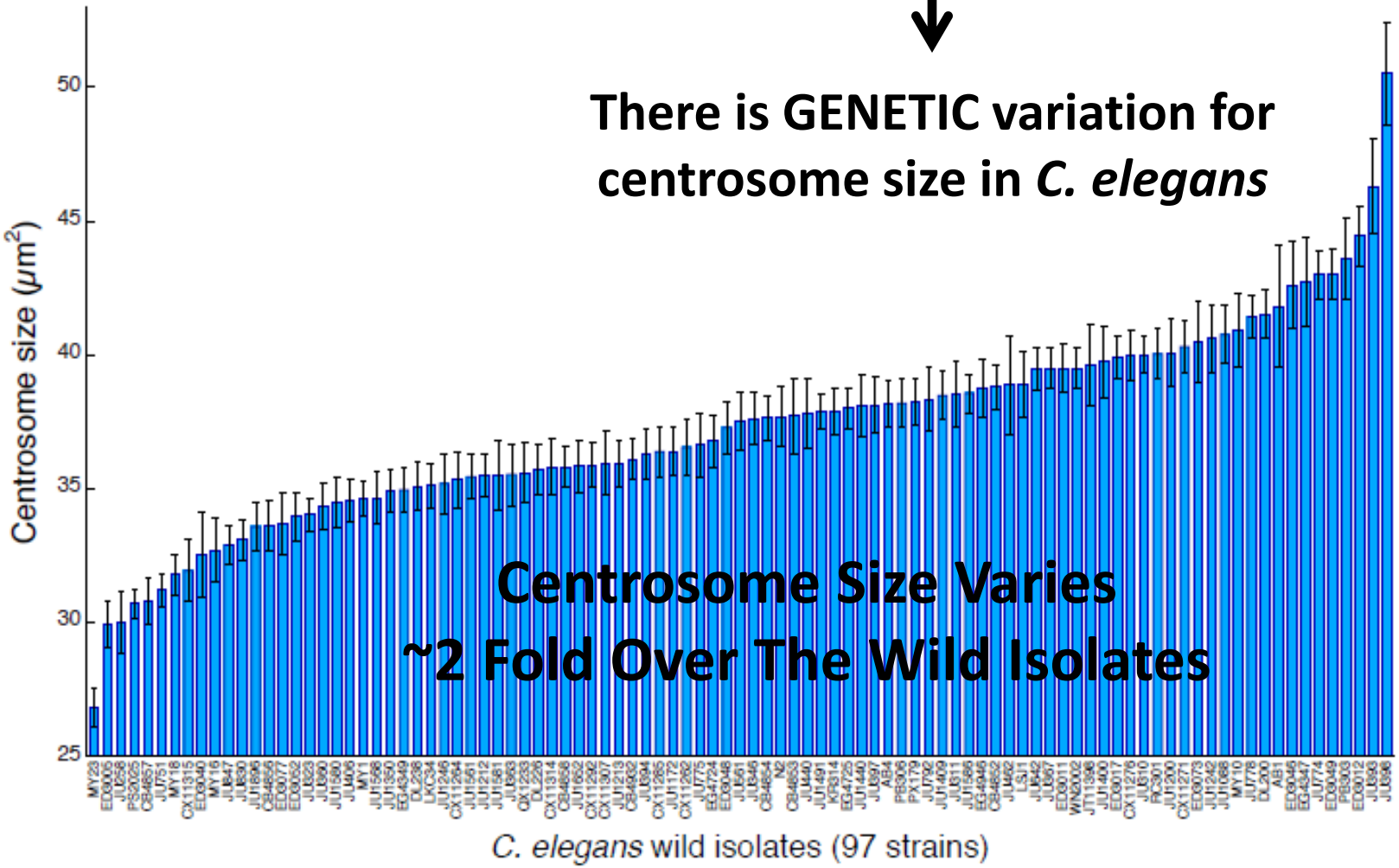


Our Approach to Understanding Spindle Evolution

spontaneous mutation is the ultimate source of variation

↓

selection, population dynamics, genetic drift, . . .

↓

within species variations of the spindle

↓

between species variations of the spindle

characterized effects of spontaneous mutations on cell division traits

stabilizing selection on embryo size

explains within species variation for cell division traits in *C. elegan*

explains between species variation for cell division traits in nematodes

This Discussion:

Combining Quantitative Genetics and Cellular Biophysics

Quantitative Genetics of Cell Division

Interesting from multiple perspectives:

1) Genetics

2) Biophysics

3) Casual Analysis

Investigate Genetic Basis of Cell Division Using Recombinant Inbred Advanced Intercrossed Lines (RAILS)

Imaging *C. elegans* RAILs

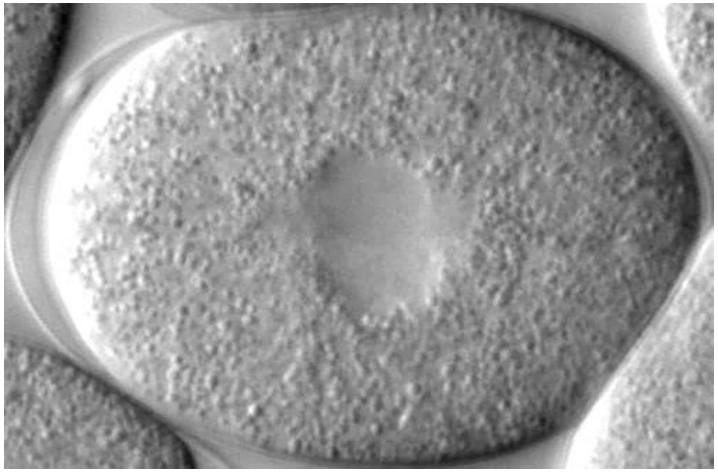
Lines created by Matt Rockman

Cross Between N2 and CB4856
10 generations of intercrossing followed by 10 generations of selfing

- **Imaged ~200 RAILS** (all of which are genotyped)
- **Imaged ~50 Embryos per line**

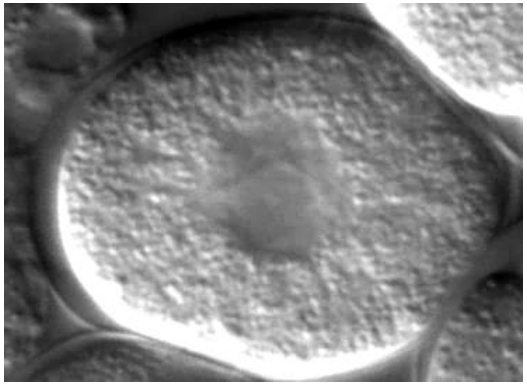
Little Variation Between Parent Lines
Extensive Variation Between Intercrossed Lines

Parent Line: CB4856

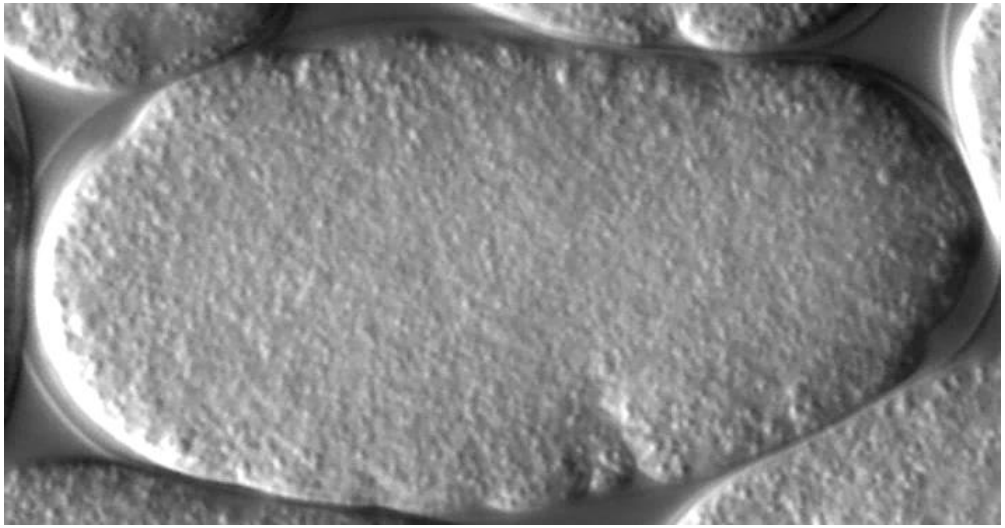


Parent Line: N2

Intercross: QX51



Intercross: QX52



Quantitative Genetics of Cell Division

Interesting from multiple perspectives:

1) Genetics

Are variations in cell division caused by variations in canonical "cell division genes"?

Preliminary Mapping Results

- **Multiple QTLs**
- **Some QTLs shared between traits**

Quantitative Genetics of Cell Division

Interesting from multiple perspectives:

1) Genetics

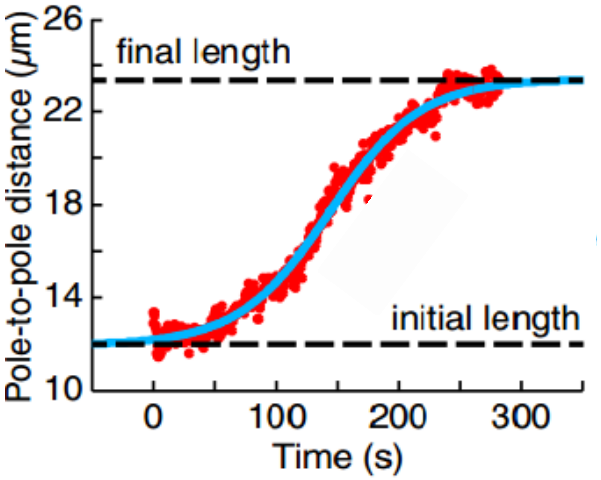
2) Biophysics

I) “Taylor expansion” in theories parameters

II) Models must be consistent with observed statistics

Models must be consistent with observed statistics

Spindle Length



Why Does Spindle Final Length Depend on Cell Size?

What Determines Spindle Final Length?

Timer?

One mechanism sets initial length

Another mechanism determines the duration of anaphase

Constraint?

One mechanism sets initial length

The spindle elongates until it "hits" the edge of the cell

Limiting Component?

One mechanism sets initial length

The spindle elongates until all tubulin is in the spindle

Models must be consistent with observed statistics

What Determines Spindle Final Length?

~~Timer?~~

Constraint?

Limiting Component?

. . .

lack of correlation between Initial and Final Spindle Length rules out Timer model

Pairwise Correlations Across RAILS

Cell Length

Final Spindle Length

Initial Spindle Length

	Initial Spindle Length	Final Spindle Length	Cell Length

Quantitative Genetics of Cell Division

Interesting from multiple perspectives:

1) Genetics

2) Biophysics

- **I) “Taylor expansion” in theories parameters**
- **II) Models must be consistent with observed statistics**

3) Casual Analysis

Casual Analysis

Infer Casual Relationship Between Traits By Studying Their Correlations and Partial Correlations Across Lines

If **Then**

$A \rightarrow B \rightarrow C$

Conditioning on B makes A and C uncorrelated

EXAMPLE

If Cell Size → Centrosome Size → Spindle Length

Then Spindle Length will be independent of Cell Size when Centrosome Size is held fixed

Casual Analysis

Infer Casual Relationship Between Traits By Studying Their Correlations and Partial Correlations Across Lines

If

$A \rightarrow B \rightarrow C$

$A \leftarrow B \leftarrow C$

$A \leftarrow B \rightarrow C$

Then

Conditioning on B makes A and C uncorrelated

If

$A \rightarrow B \leftarrow C$

Then

Conditioning on B Makes A and C MORE correlated

"colliders" are special

Casual Analysis

Infer Casual Relationship Between Traits By Studying Their Correlations and Partial Correlations Across Lines

1) Colliders are special

2) Genes cause phenotypes (not the other way around)

The Same Statistics

Casual Analysis

Infer Casual Relationship Between Traits By Studying Their Correlations and Partial Correlations Across Lines

1) Colliders are special

2) Genes cause phenotypes (not the other way around)

Different Statistics

Casual Analysis

Infer Casual Relationship Between Traits By Studying Their Correlations and Partial Correlations Across Lines

1) Colliders are special

2) Genes cause phenotypes (not the other way around)

Currently using to investigate the mechanism of spindle scaling with cell size. . .

What Determines Spindle Final Length?

~~Timer?~~

Constraint?

Limiting Component?

. . .

Final Spindle Length is correlated with both Cell Length and Cell Volume

Pairwise Correlations Across RAILS

Cell Volume

Cell Length

Final Spindle Length

Initial Spindle Length

	Initial Spindle Length	Final Spindle Length	Cell Length	Cell Volume