In silico reconstitution of spindle assembly: speed and error of search and capture
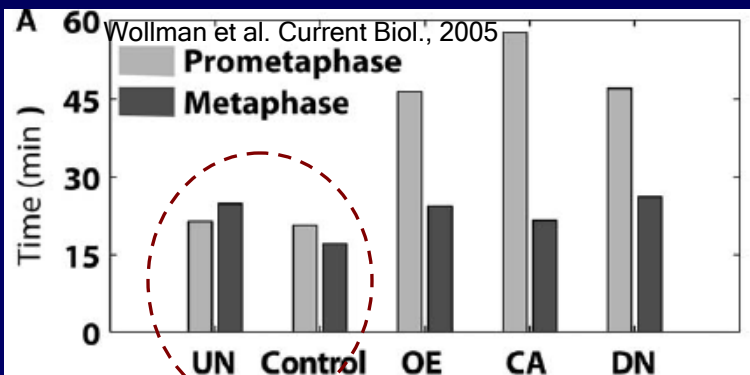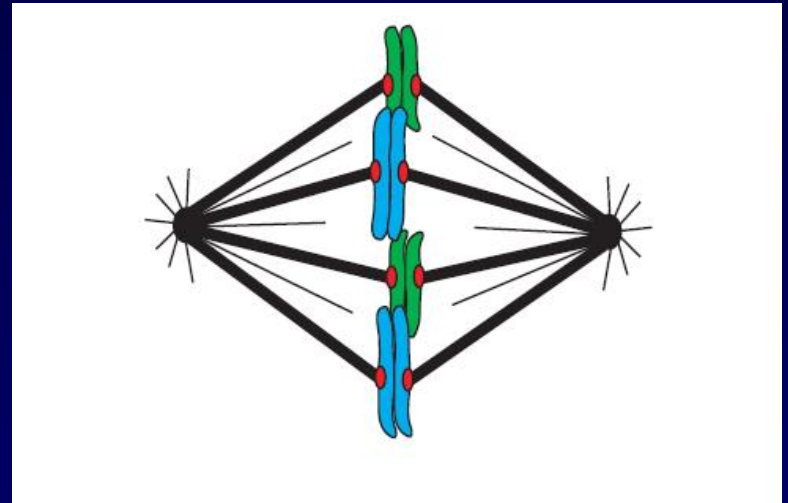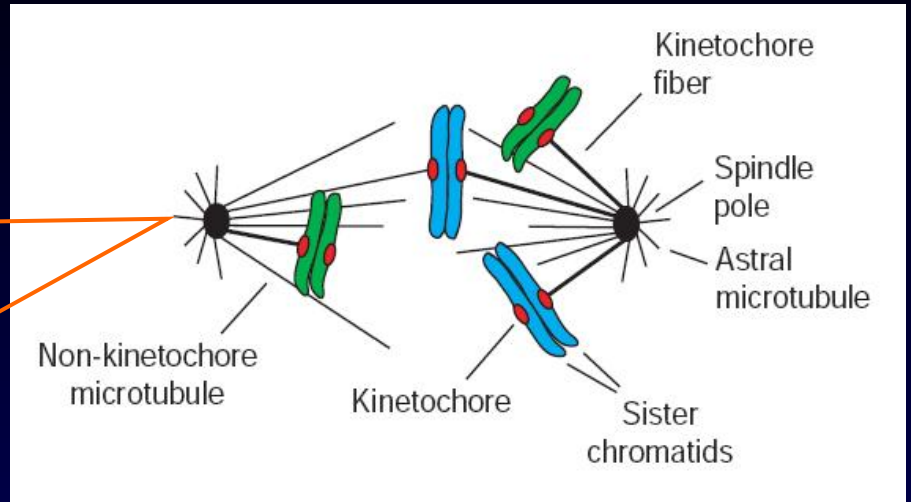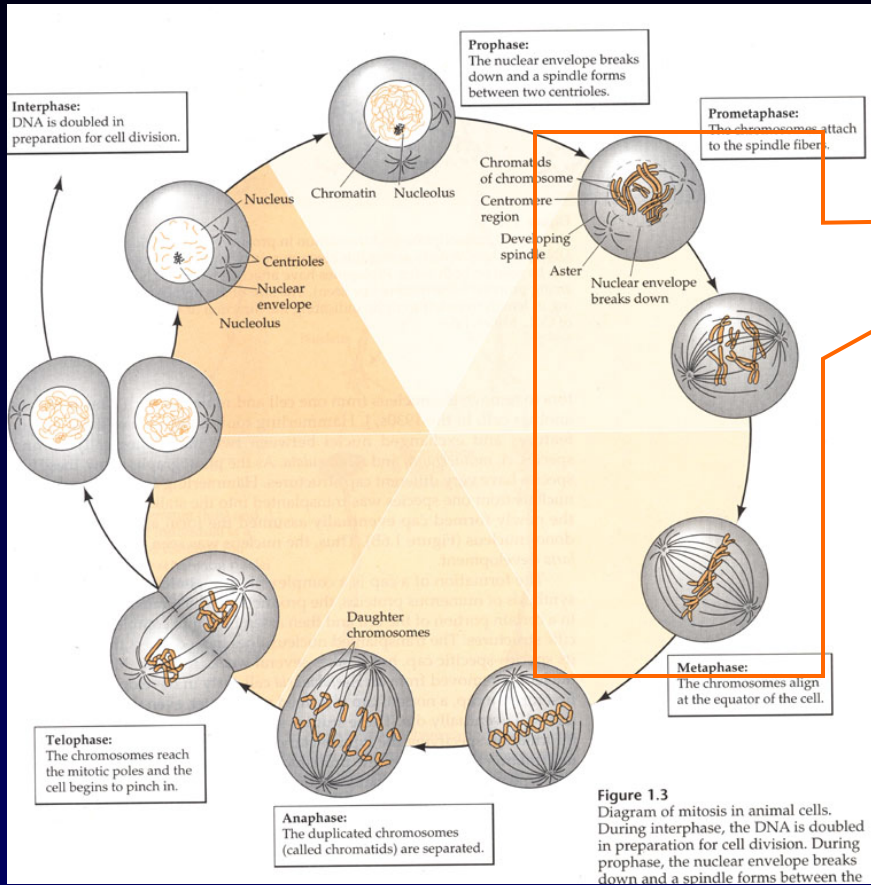
Raja Paul, IACS, Kolkata

February 11, 2010

Different stages of mitosis

Search and Capture (S&C)

Interphase:
DNA is doubled in preparation for cell division.

Prophase:
The nuclear envelope breaks down and a spindle forms between two centrioles.

Prometaphase:
The chromosomes attach to the spindle fibers.

Nucleus Chromatin Nucleolus

Chromatids of chromosome

Centromere region

Developing spindle

Aster

Nuclear envelope breaks down

Centrioles

Nuclear envelope

Nucleolus

Daughter chromosomes

Metaphase:
The chromosomes align at the equator of the cell.

Telophase:
The chromosomes reach the mitotic poles and the cell begins to pinch in.

Anaphase:
The duplicated chromosomes (called chromatids) are separated.

Figure 1.3
Diagram of mitosis in animal cells. During interphase, the DNA is doubled in preparation for cell division. During prophase, the nuclear envelope breaks down and a spindle forms between the

Kinetochore fiber
Spindle pole
Astral microtubule
Non-kinetochore microtubule
Kinetochore
Sister chromatids

Wollman et al. Current Biol., 2005

Prometaphase
Metaphase

Time (min)

60
45
30
15
0

UN Control OE CA DN

Dynamic Instability of MT

capture

KT

grow → shrink → grow …

grow → shrink → rescue → grow …

Rescue length

Polymerization Phase

CATASTROPHE   RESCUE

GDP

GTP

Depolymerization Phase

GTP-Tubulin   GDP-Tubulin

from Fygenson et al., Phys Rev E, 50 :1579 (1994).

catastrophe

growth

shortening

rescue

Length (μm)

Time (min)
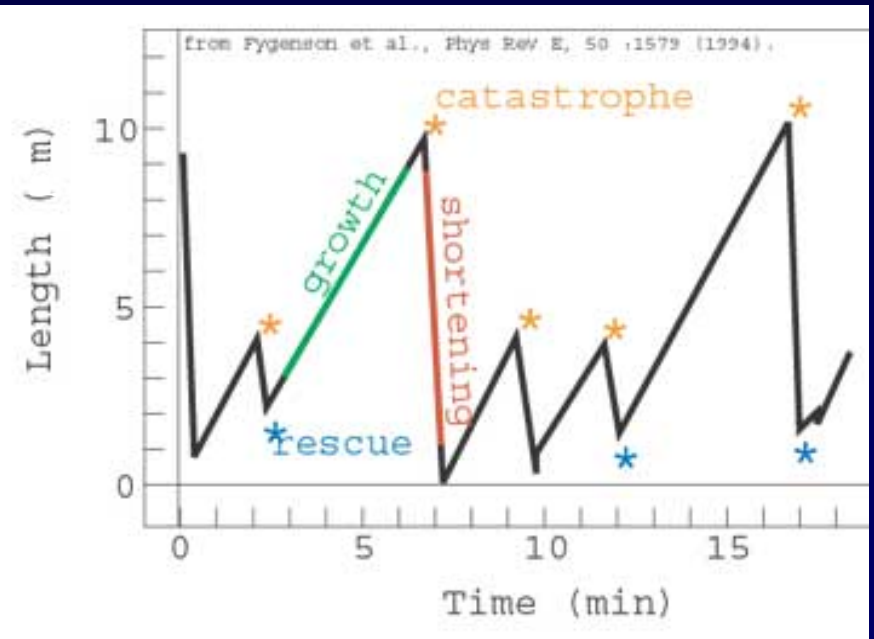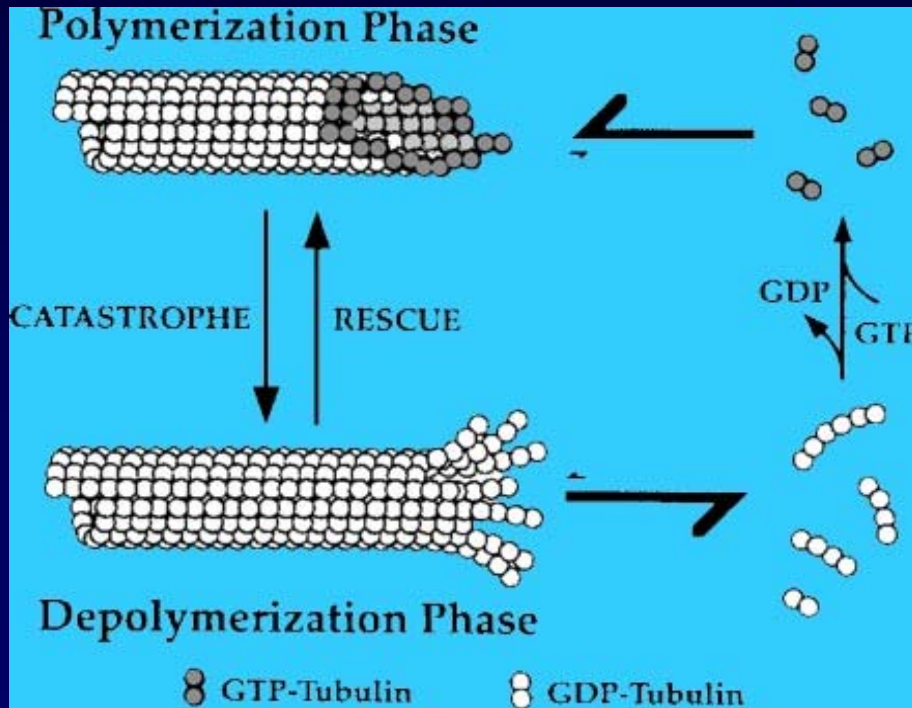
MT dynamics described by 4 parameters: $\mathbf{v_g}$, $\mathbf{v_s}$, f_{cat}, f_{res}

Basic question that we will address

What is the Fast & Accurate method of capturing all chromosomes ?

Part-I: minimal capture time

Part-II: capture accuracy

Efficient Search & Capture requires MT's dynamic instability (Holy & Leibler, PNAS, 1994)

Dynamical instability of MTs are essential for efficient search and capture.

1 MT searching for 1 KT

microtubule

centrosome   target, KT

cell membrane
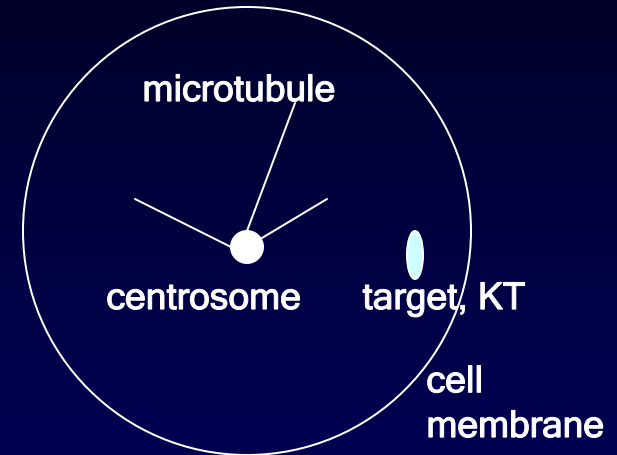
Search time is Minimum if :

    1 - Average length of MT = distance of the KT

    2 - MTs are not rescued when they undergo catastrophe.

Efficient chromosome capture requires a biased MT dynamics (Wollman et al. Current Biol., 2005)

Many MTs and many KTs

Unbiased versus biased S&C

- High RanGTP inside the nucleus stabilize MTs.

- MTs catastrophe is high outside the nucleus compared to inside.
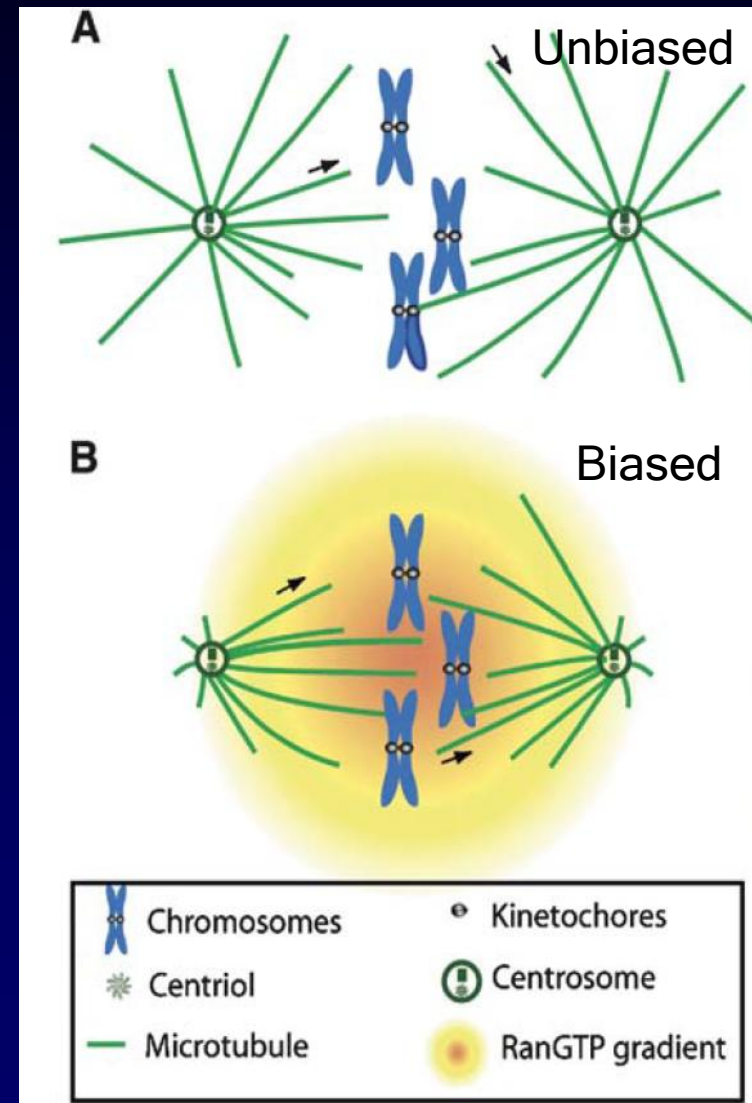
Efficient chromosome capture requires a biased S&C (Wollman et al. Current Biol., 2005)
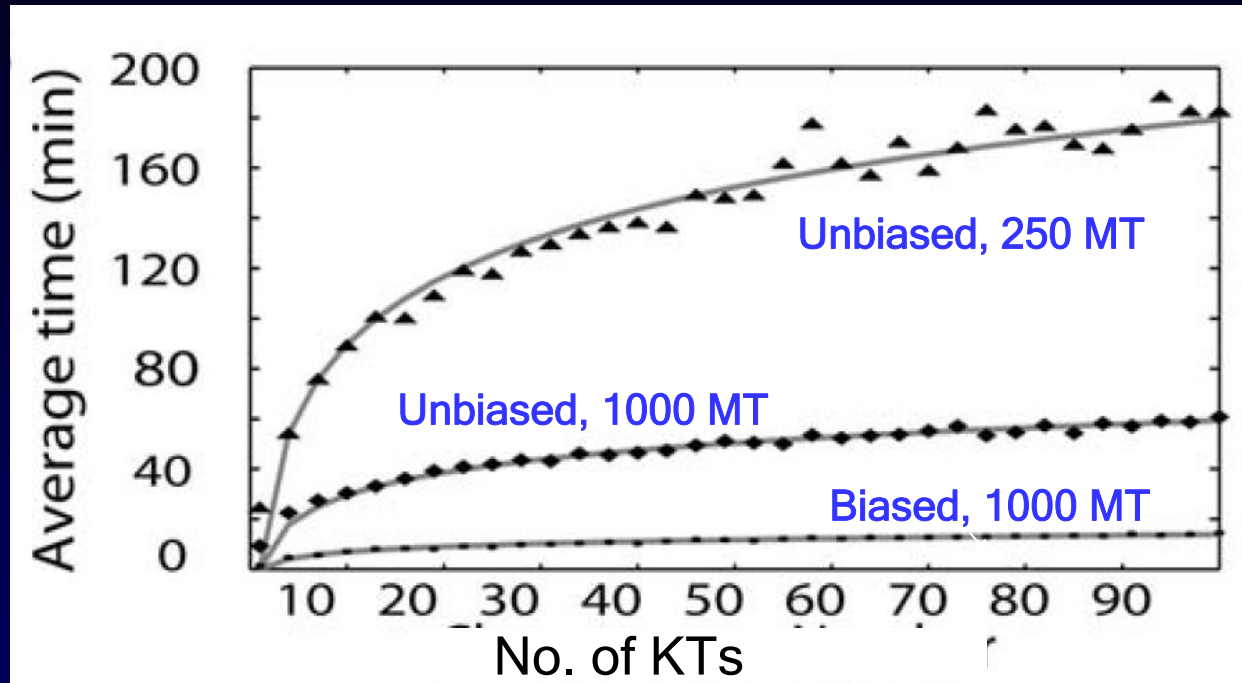
- Avg. cap. time is small for biased capture.
- Capture time is logarithmic in Chromosome number.

Assumption: MTs are not obstructed by Chromosomes

Previous analysis considered…

Chromosomes are transparent

Chromosomes are static

Finite volume effect of chromosome
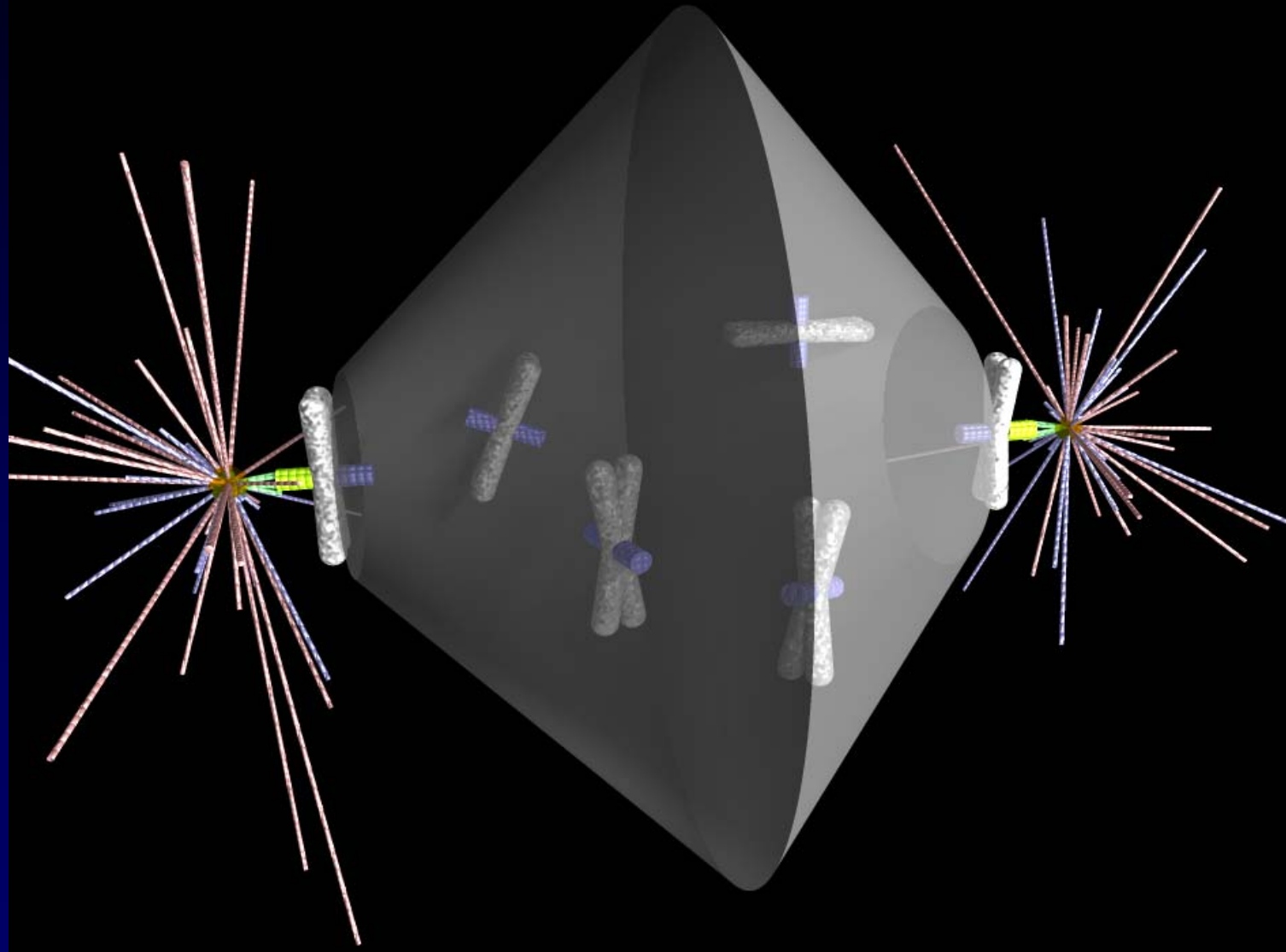
Visibility decreases drastically with increasing chromosome number
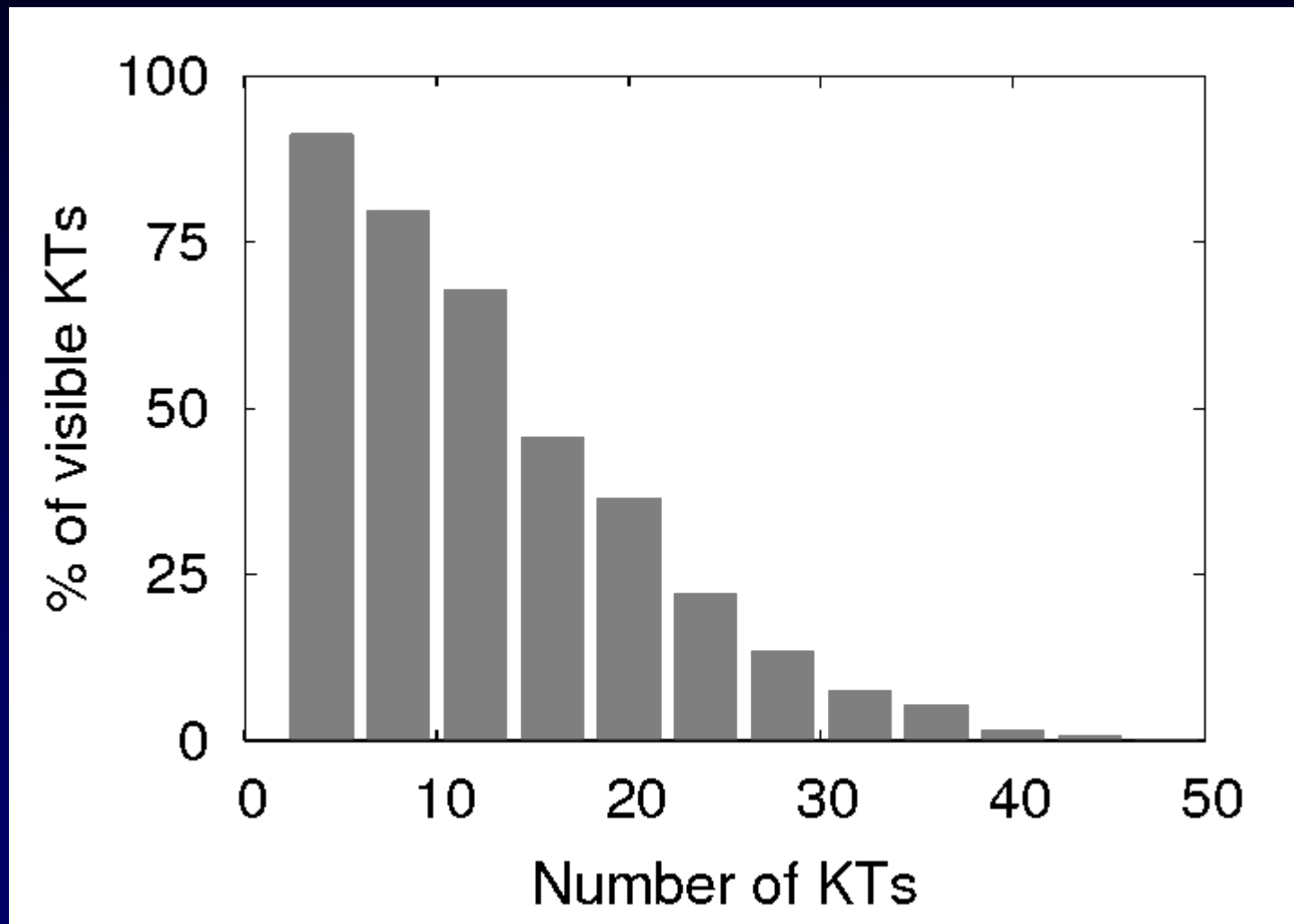
Part-I: Optimal capture time ?

Two different S&C scenarios

1 **Static positioning of chromosomes** – chromosomes are fixed at their initial locations.

2 **Dynamic positioning of chromosomes** – chromosomes are fixed at their initial locations.

Realistic to assume finite volume of chromosomes
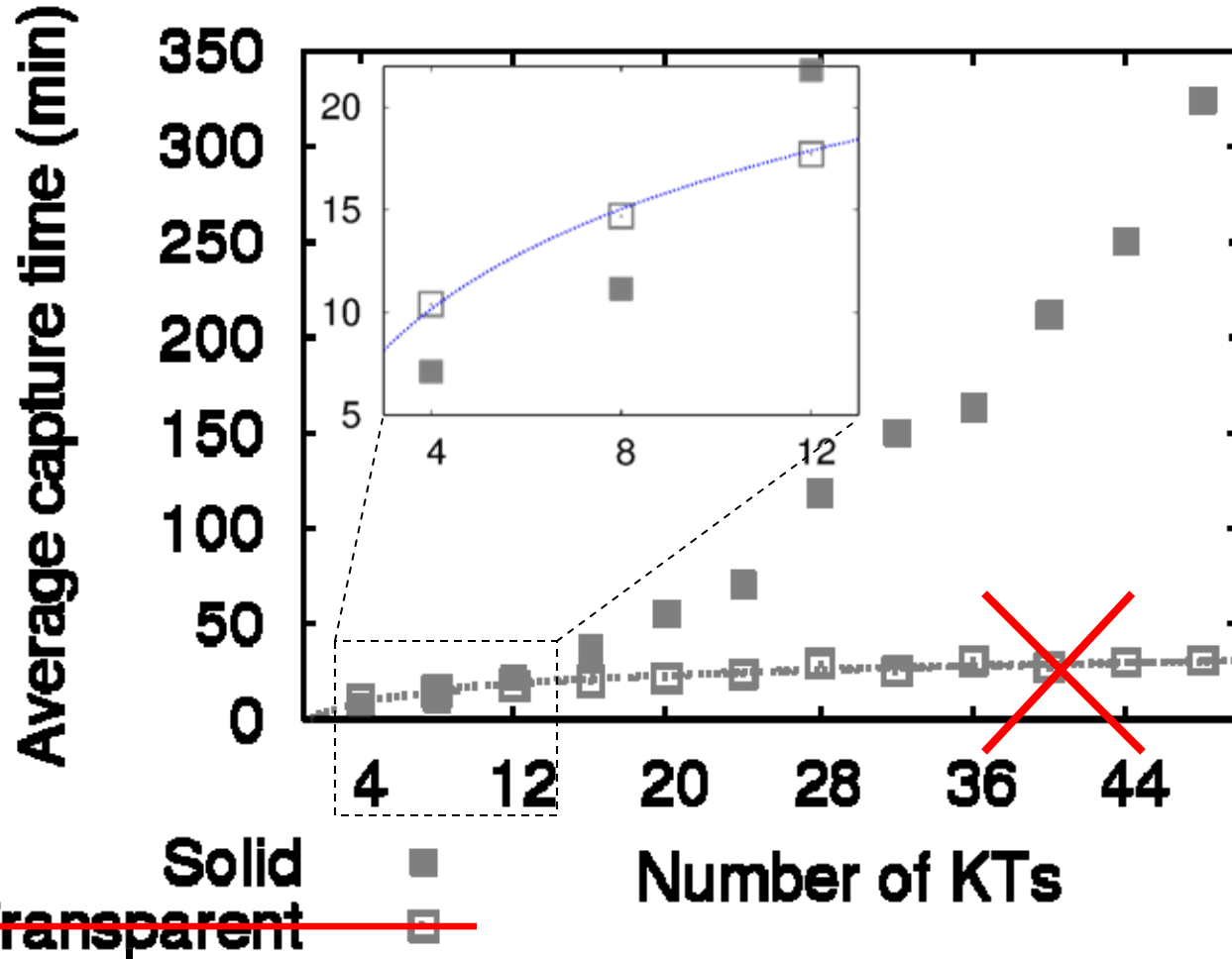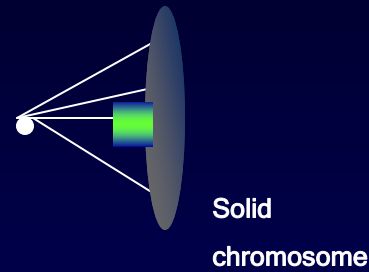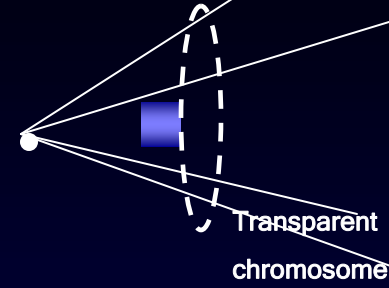
Two different S&C scenarios

Random walk of chromosomes

1 **Static positioning of chromosome** – chromosomes are fixed at their initial locations.

2 **Dynamic positioning of chromosomes** – chromosomes are fixed at their initial locations.
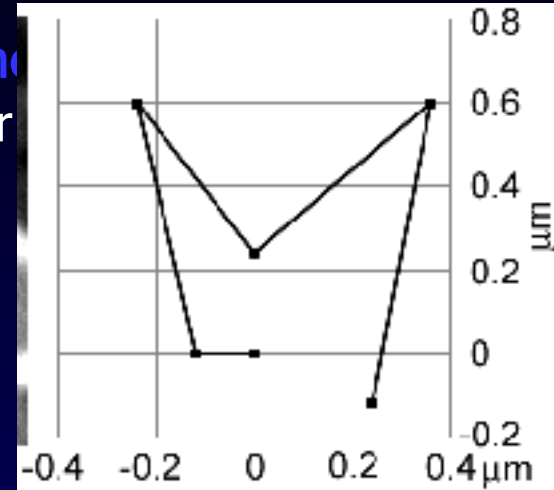
Compare capture time between model static & dynamic positioning of chromosomes
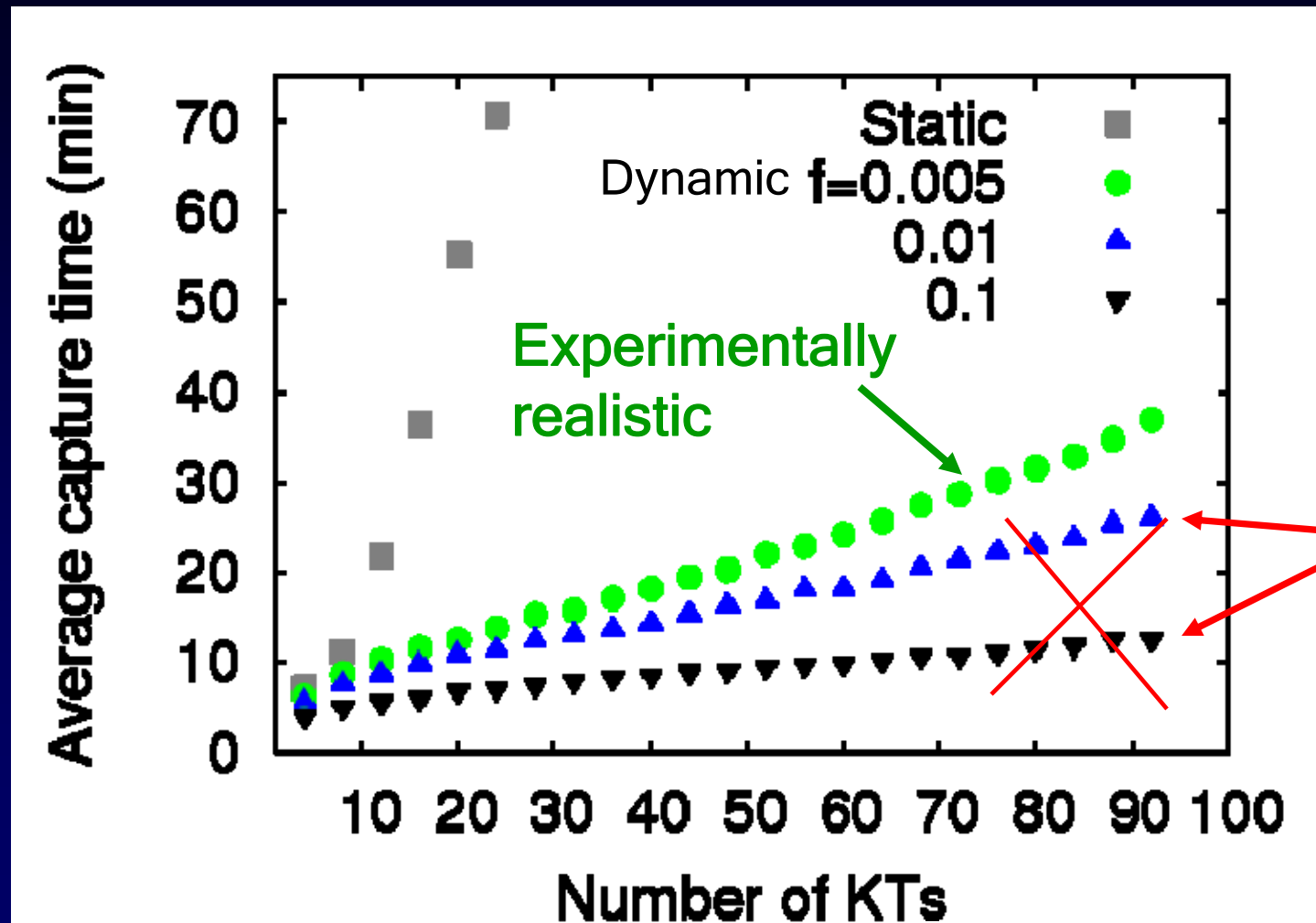
Pathways of S&C

Are the centrosomal and chromosomal pathways of MT dynamics integrated and coordinated for accurate spindle assembly ?
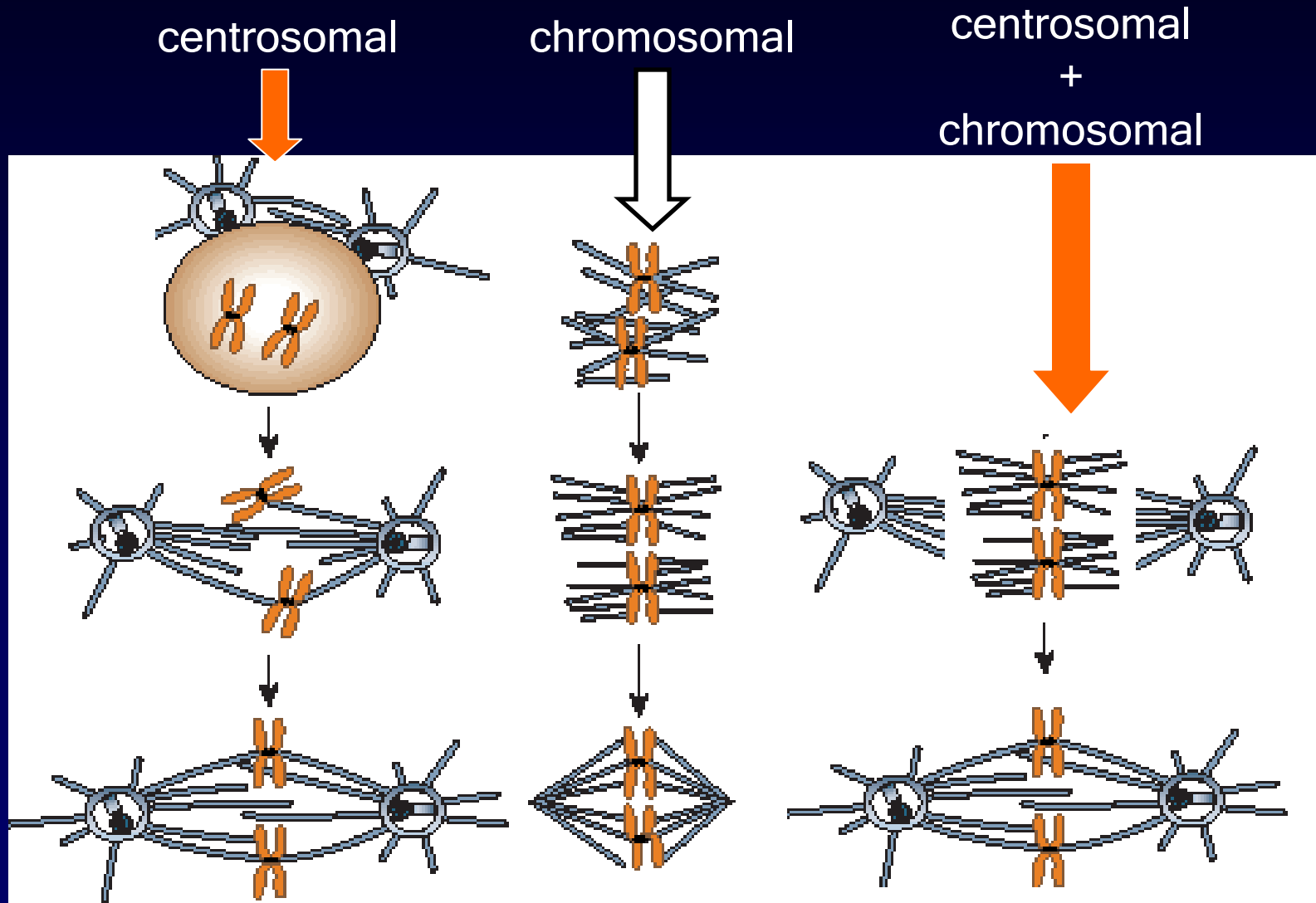
Longer the KT-fiber, smaller the capture time
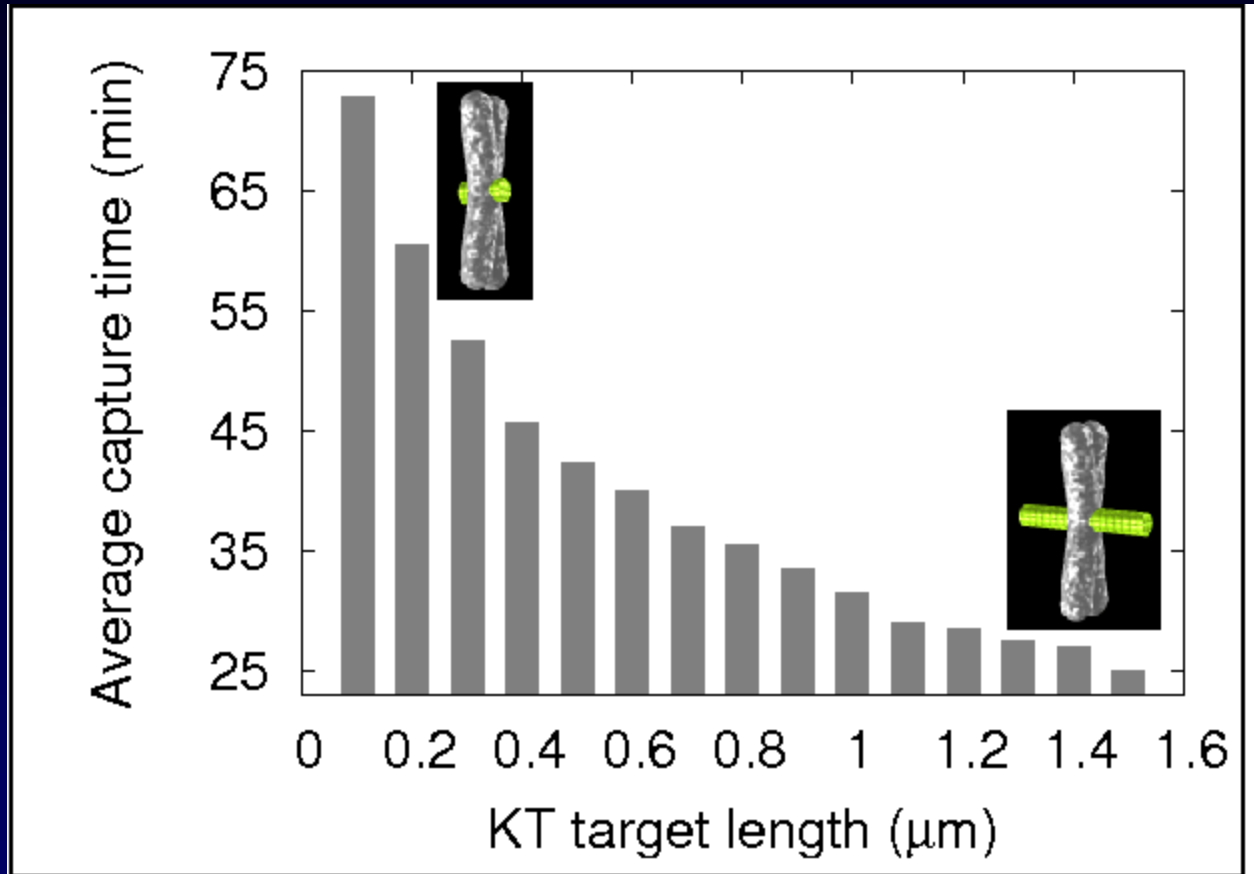
Biased Search & Capture DOES THE JOB! even for slow chromosomal jiggling
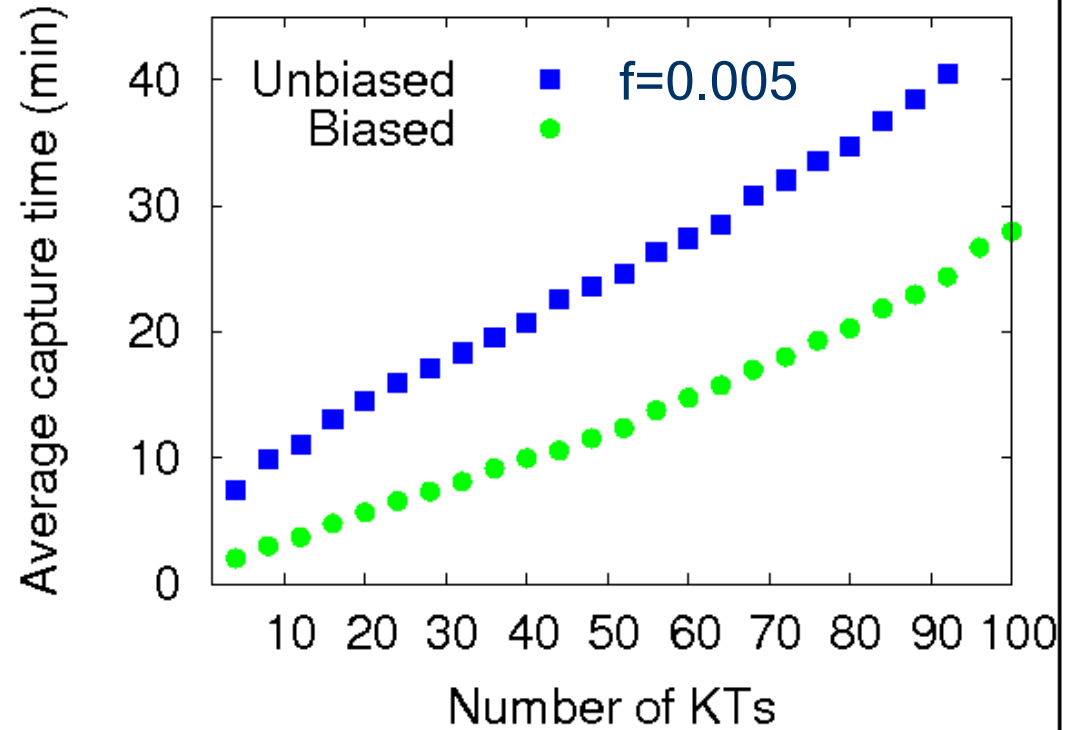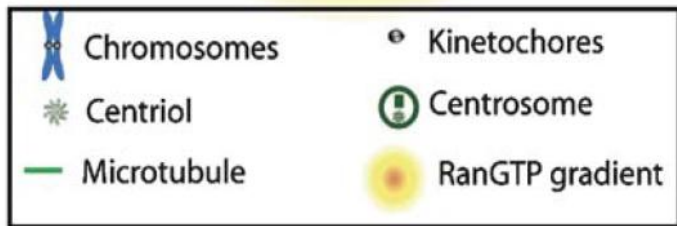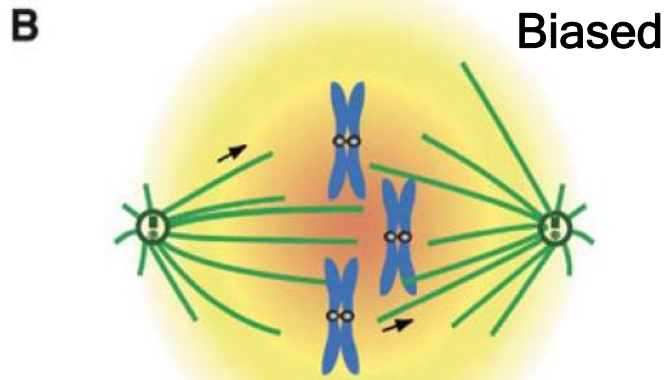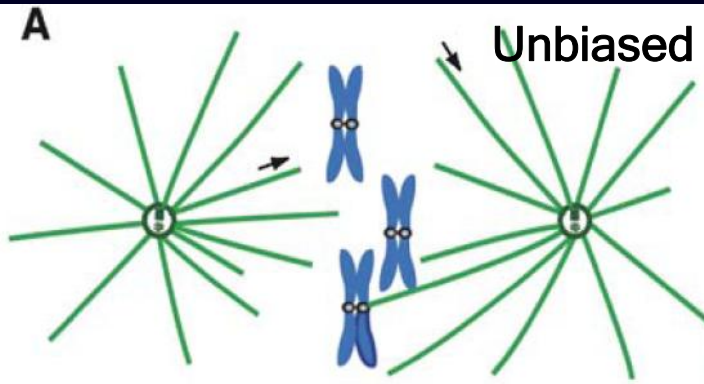
So far I have shown you

- Static positioning of chromosome is not efficient.

- Capture process is way more efficient for the dynamic positioning of the chromosomes.

- Biased microtubule dynamics required for fast capture.

Part-II: Accuracy

Incorrect attachment & consequence

(a) Amphitelic kinetochore orientation
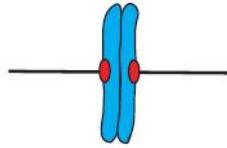
(b) Monotelic kinetochore orientation
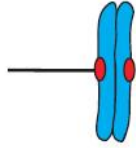
(c) Syntelic kinetochore orientation
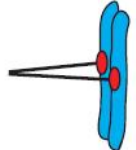
(d) Merotelic kinetochore orientation
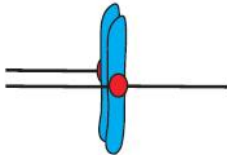
TRENDS in Cell Biology

(a) Amphitelic
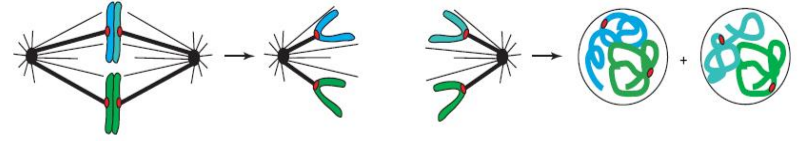
(b) Syntelic

(c) Monotelic
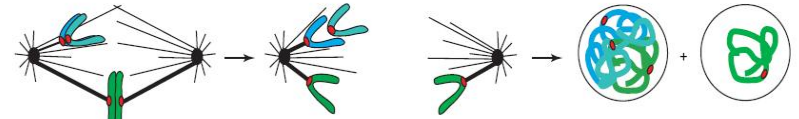
(d) Merotelic
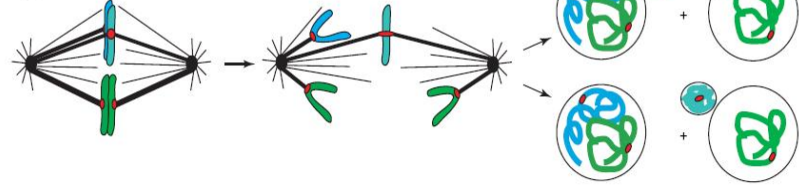
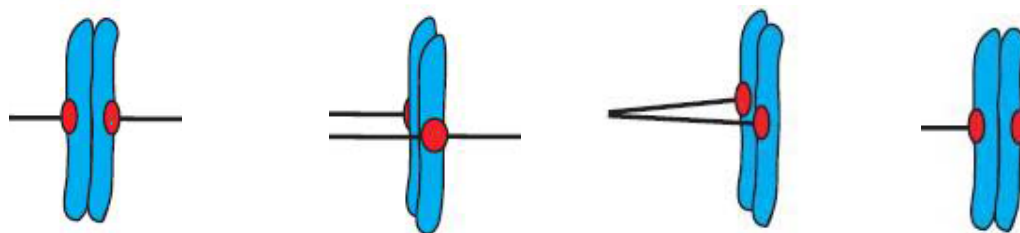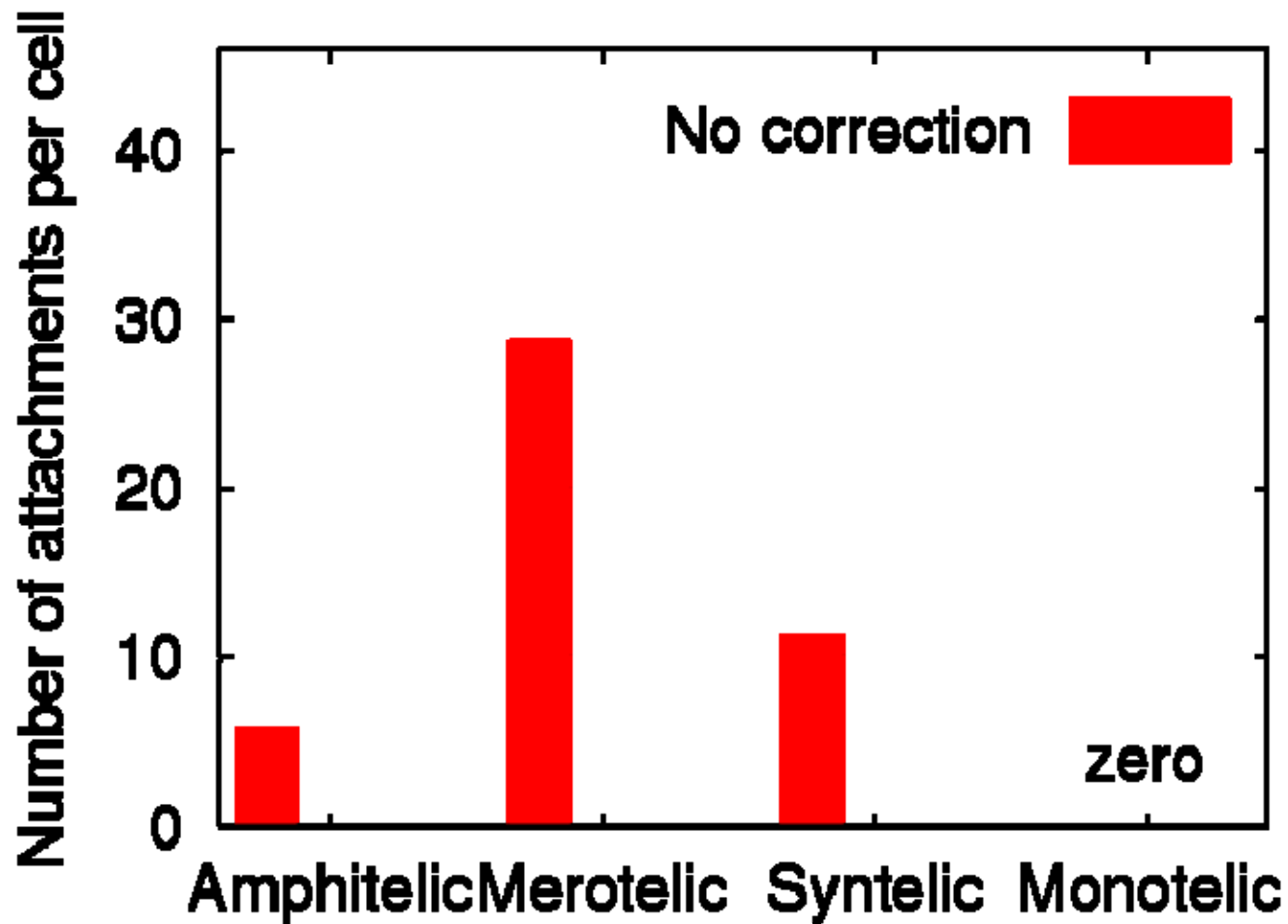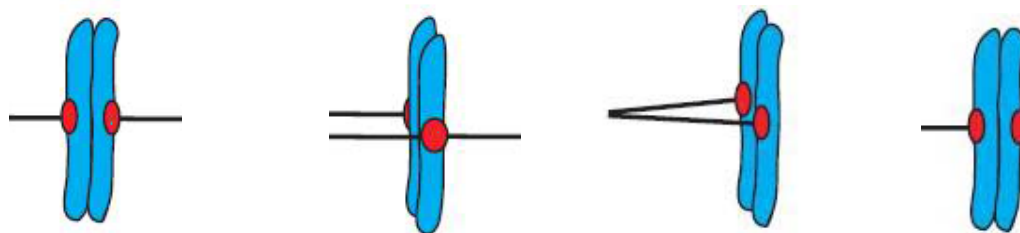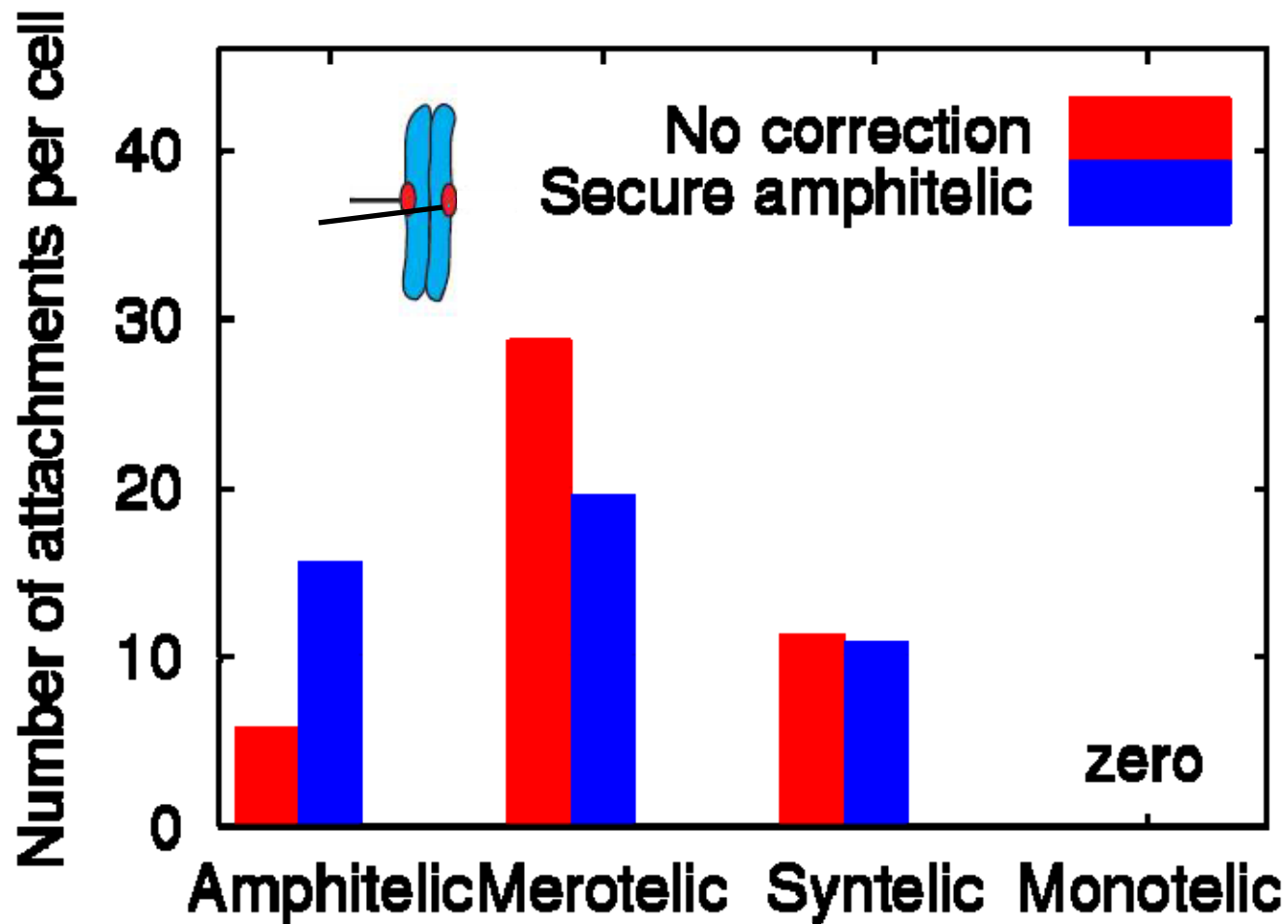Metaphase

Anaphase

Daughter cells

TRENDS in Cell Biology

Probability of different attachments

Probability of different attachments
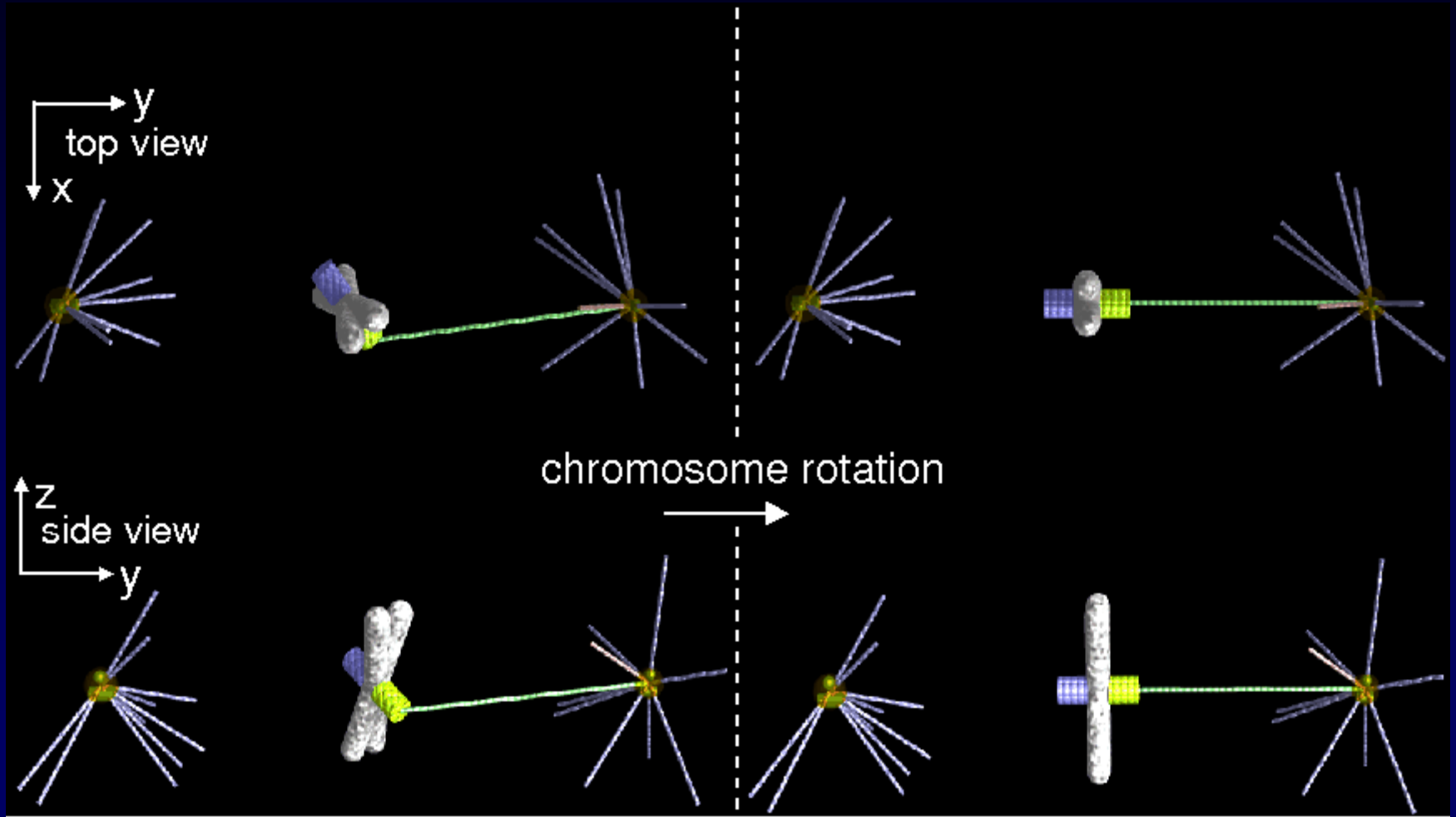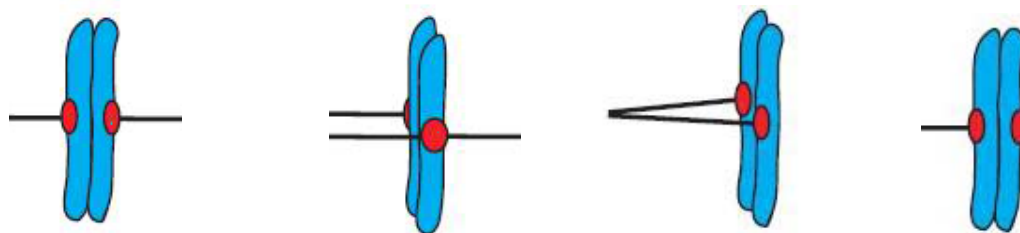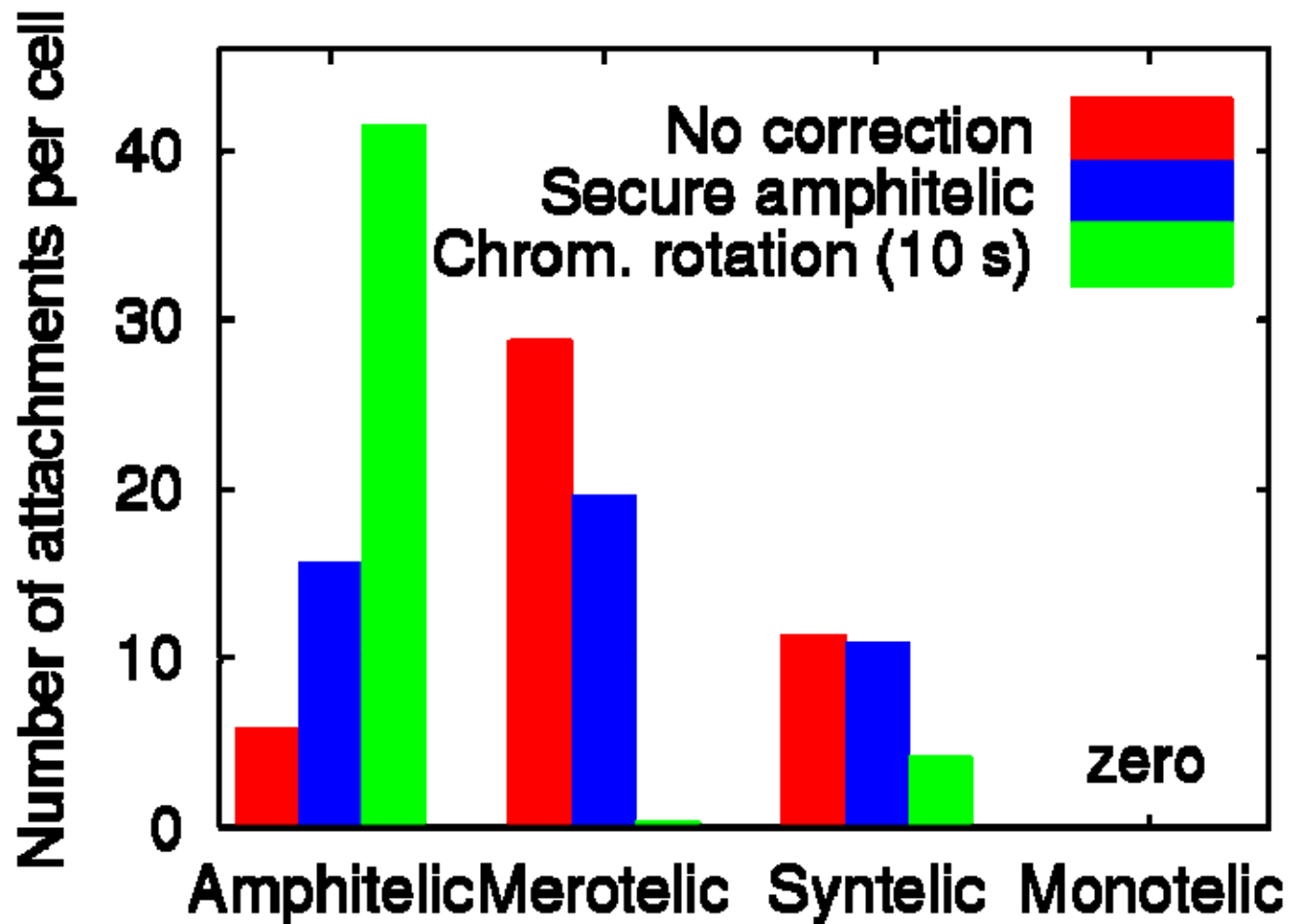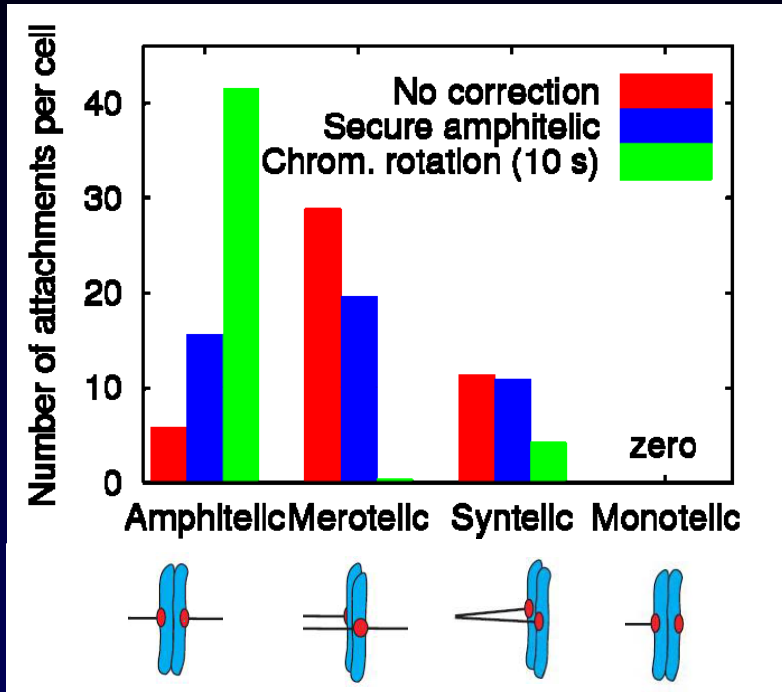
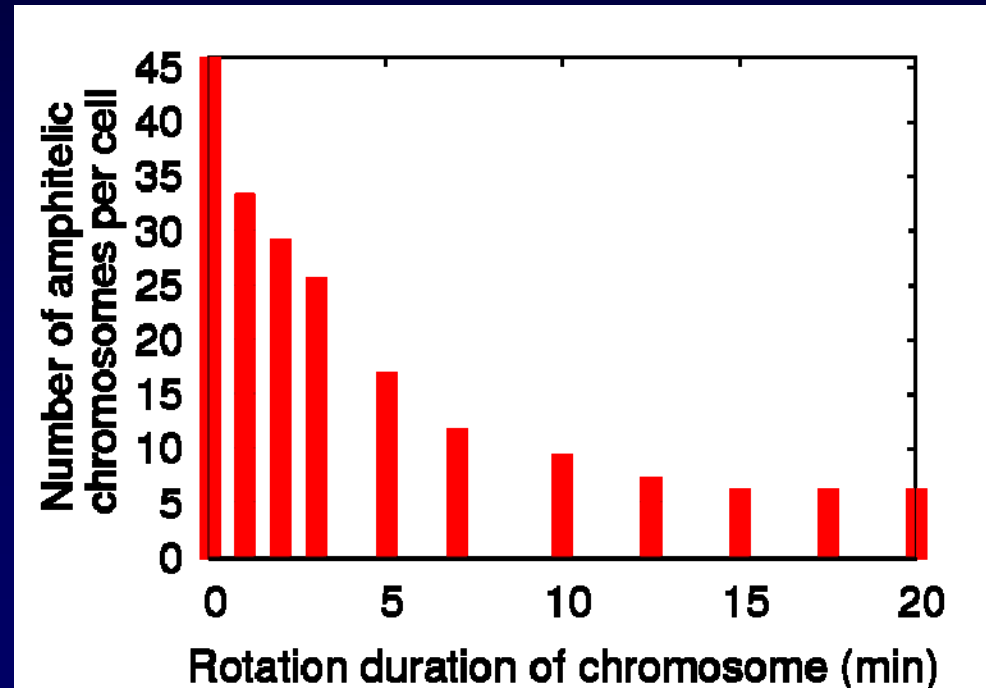# Chromosome rotates after initial capture
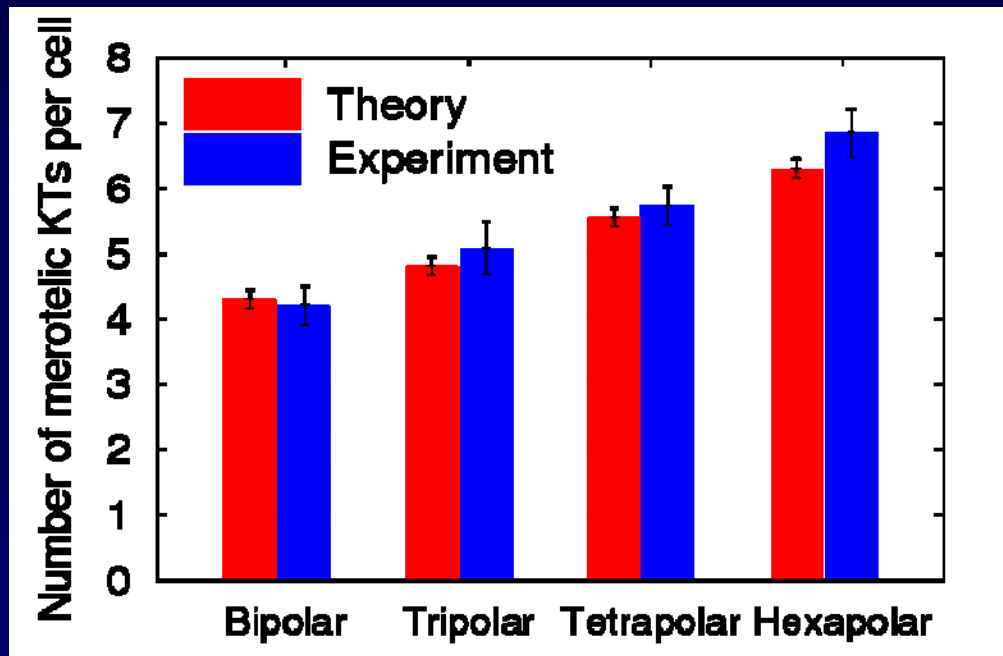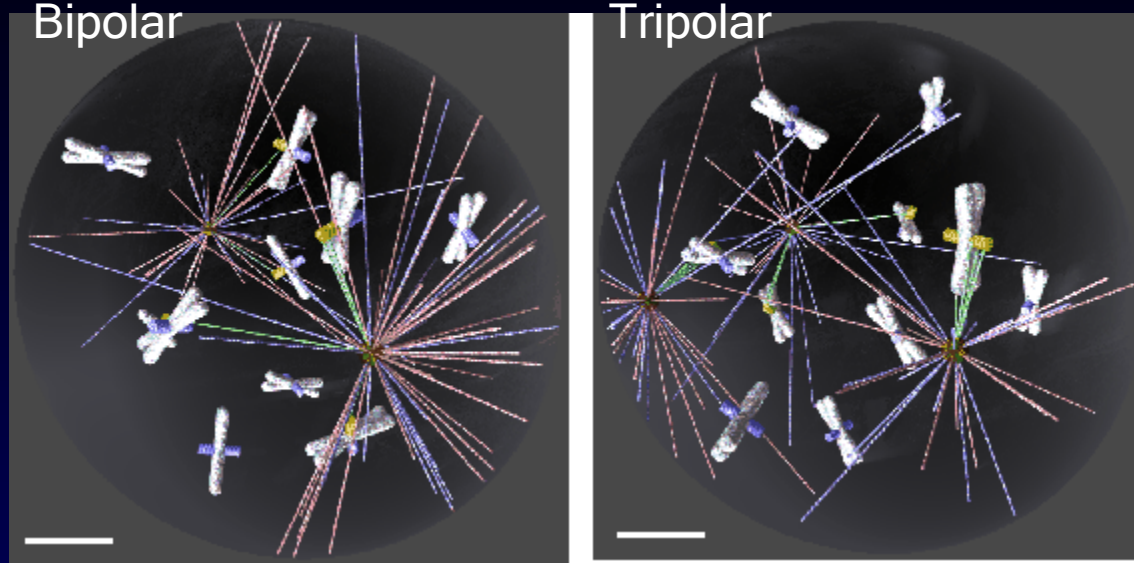
Probability of different attachments

Probability of different attachments

Long rotation decrease correct attachments

Predicting Error-statistics for multipolar cells

Summary

- Meretolic attachment is most likely to occur for flexible MT-kinetochore attachments.

- **Alignment of KT axis along the MT** and its stabilization rescues the captured KT to be meretolically attached. Therefore amphitelic attachment is most probable in this case.

Thank you

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