Segregating the replicated chromosomes

What happens to the replicated chromosomes?
… depends on the goal of the division

- to make more "vegetative" cells: mitosis

  daughter cells' chromosome set should be identical to parental cell's

- to make gametes: meiosis

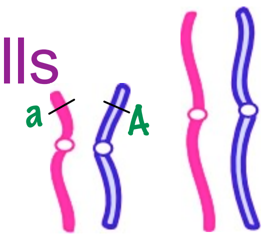
  each daughter cell should have half the number of chromosome sets as the parental cell

  If parental cell was diploid (2N)... daughters should be haploid (1N)

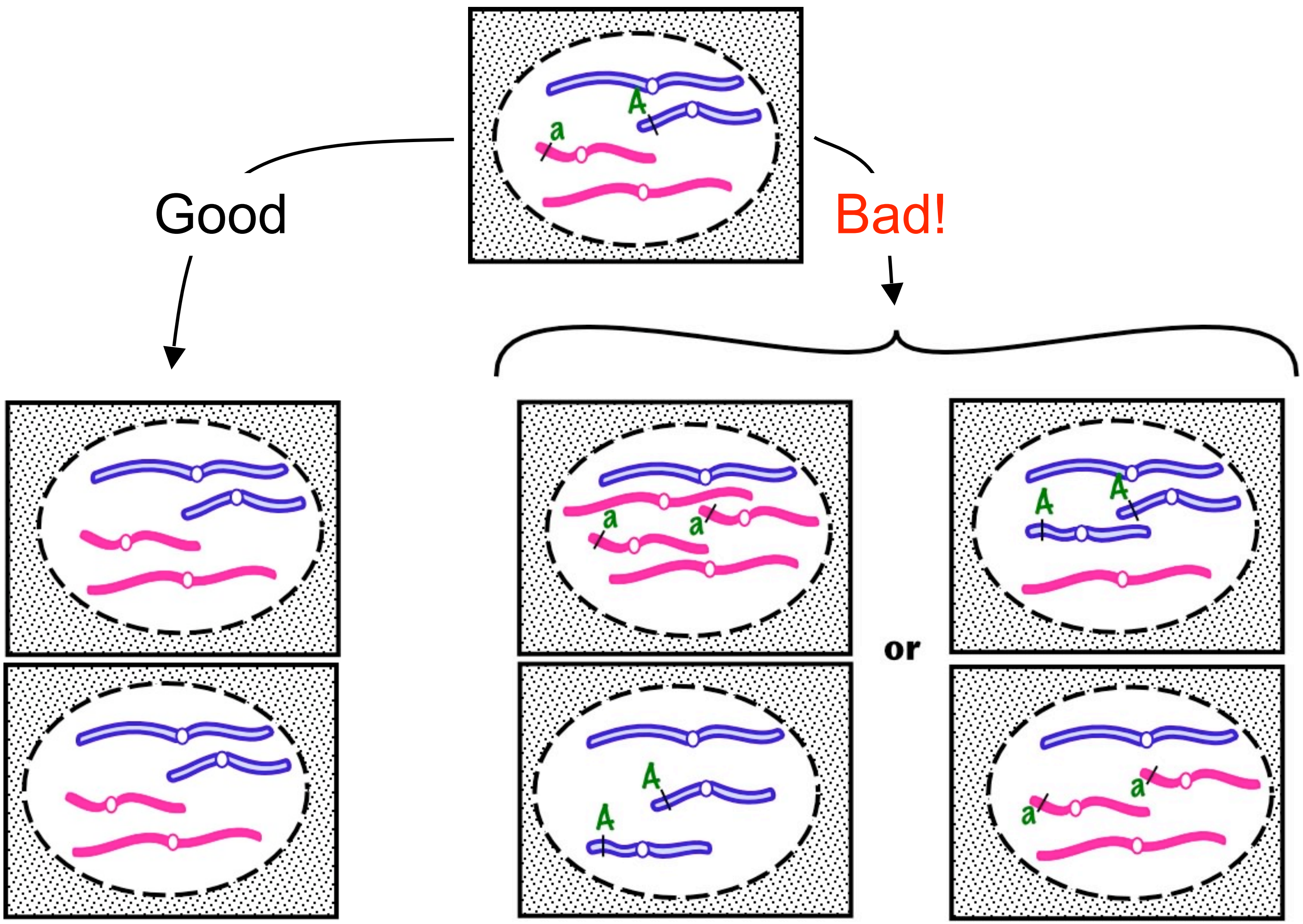
  Will a normal haploid cell undergo meiosis? No

Mitosis

…segregating replicated chromosomes in somatic cells



Diploid cell…
homologue pairs



or any outcome where each daughter cell does not have exactly one copy of each parental chromosome

Mitosis (cont'd)

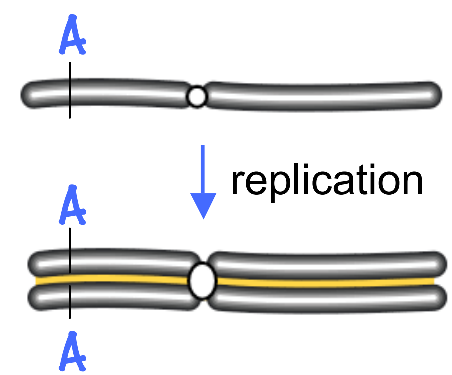
The problem

Partitioning replicated chromosomes so that each daughter cell gets one copy of each chromosome

The solution

After replication of a chromosome…

- hold the two sister chromatids together
- target them to opposite poles
- **then** separate the sisters

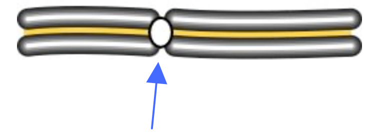


Mitosis (cont'd)

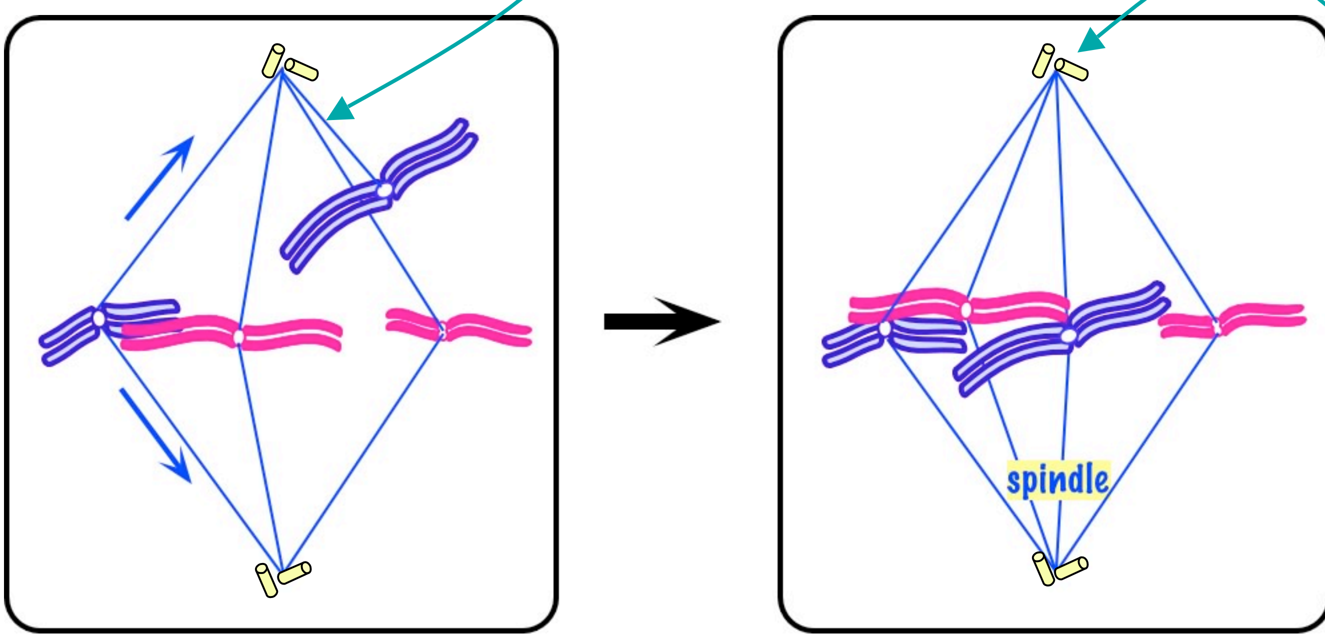
At Metaphase . . .

Chromosomes line up at cell's "equatorial plate"

Mechanism? Spindle fibers exerting tension on kinetochores



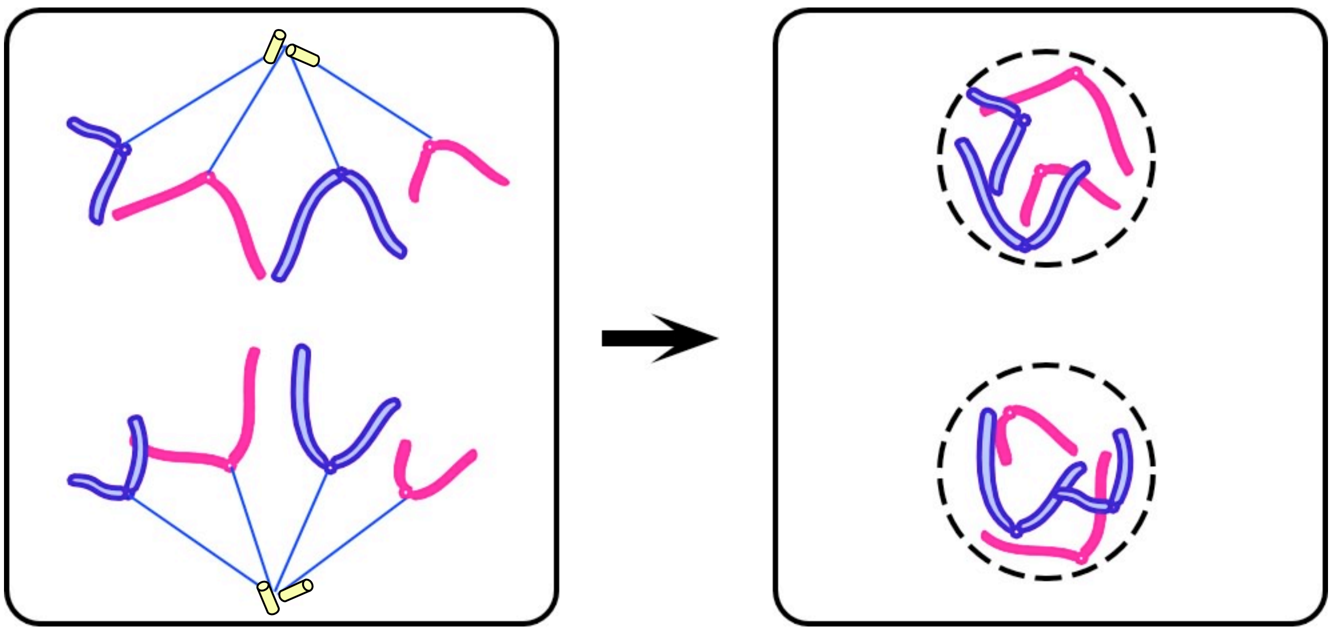
Centromere: DNA sequence on which kinetochore is built



Centriole
= Spindle pole body (yeast)
= MTOC (microtubule organizing center)

Mitosis (cont'd)

At anaphase… cohesion between sister chromatids dissolved, sisters pulled to opposite poles

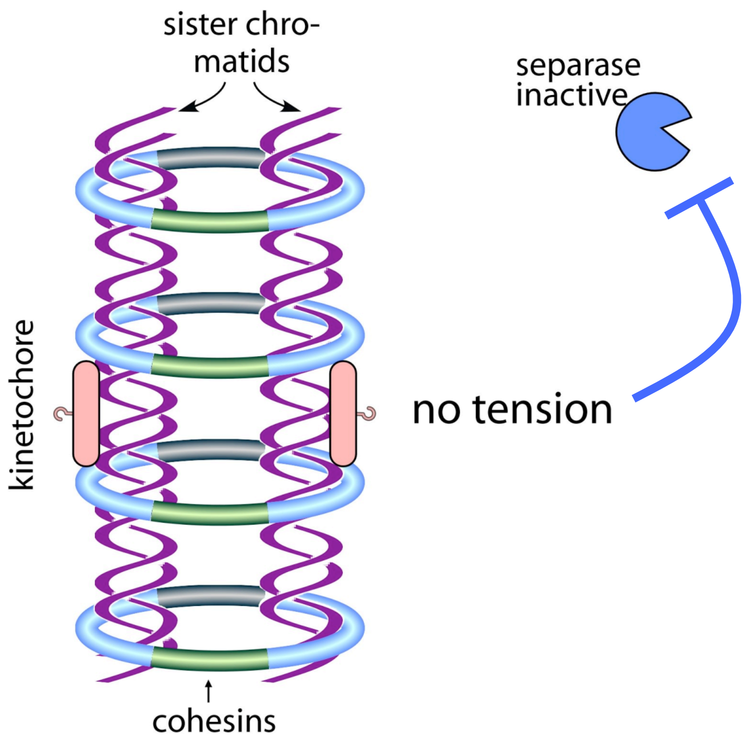


Anaphase Telophase

Monitoring correct attachment to spindle

Sister chromatids are held together by **cohesin** proteins…

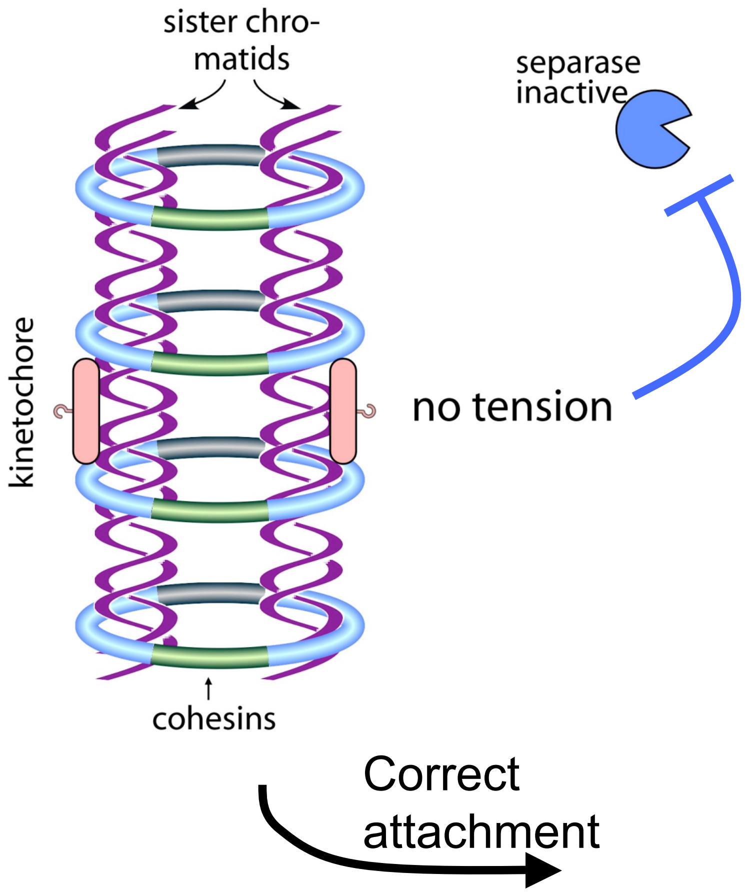
Any kinetochore not experiencing tension → block destruction of cohesins So, no sister separation until all chromosomes are ready!



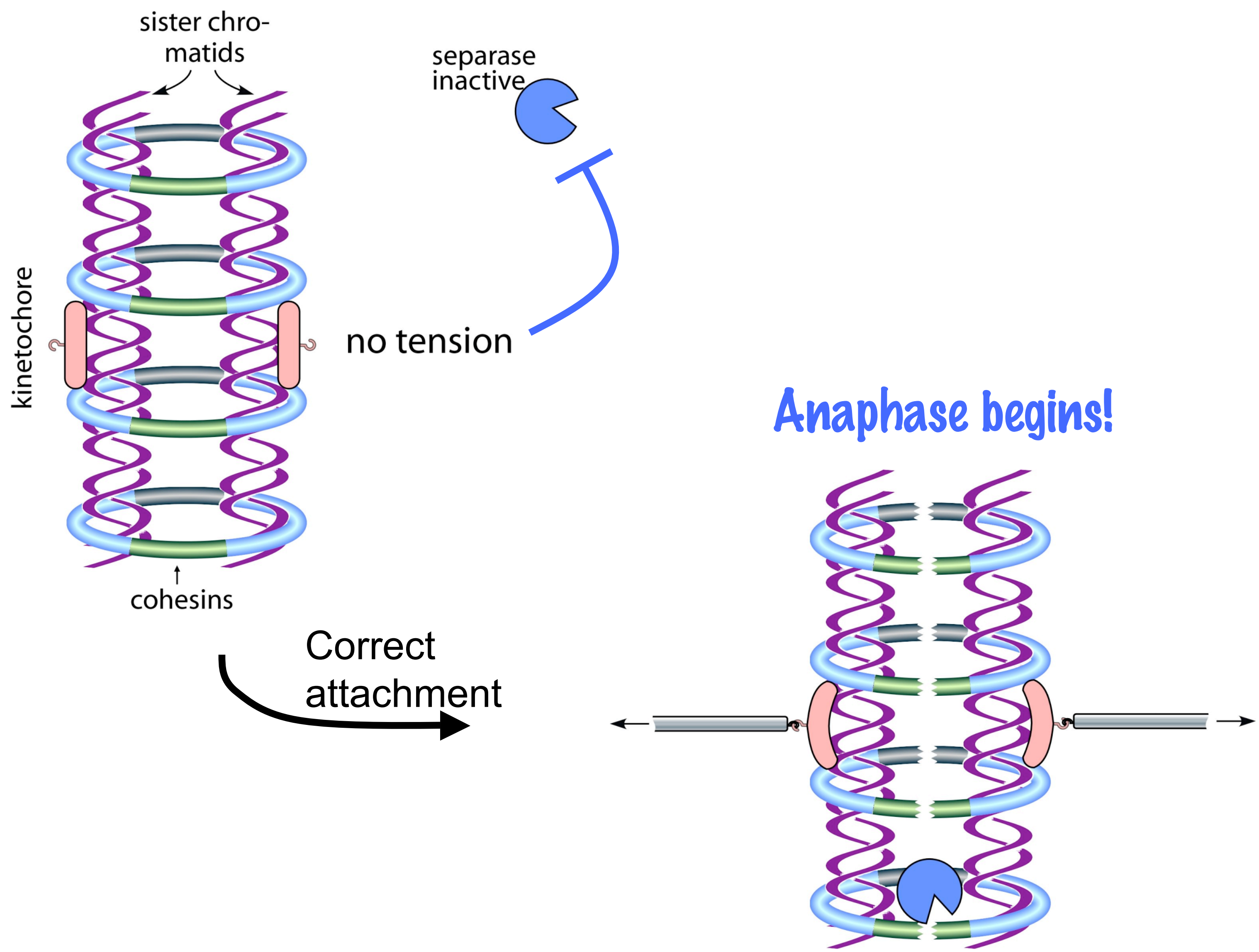
Separase: can destroy cohesins

Unattached kinetochore: blocks separase

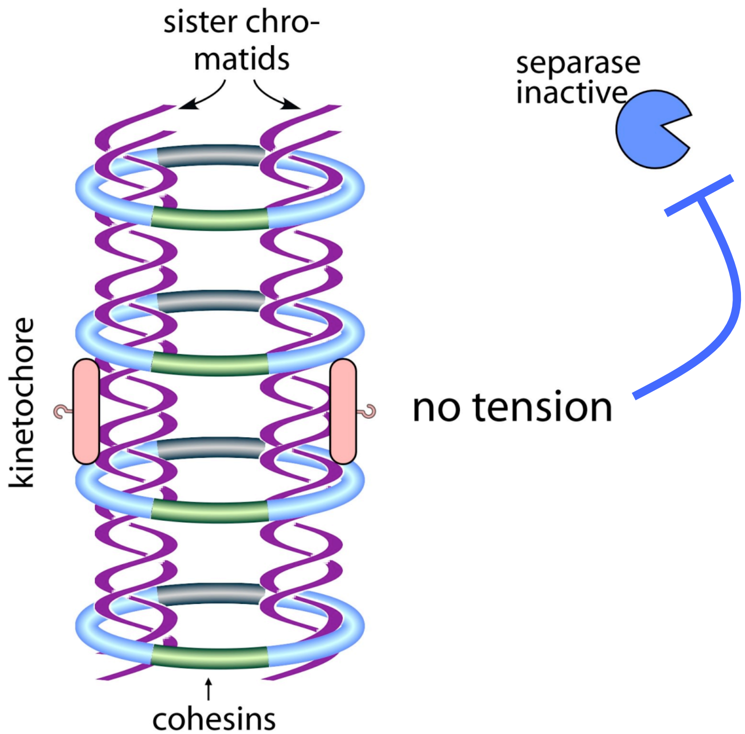
Monitoring correct attachment to spindle (cont'd)



Monitoring correct attachment to spindle (cont'd)



The anaphase entry checkpoint



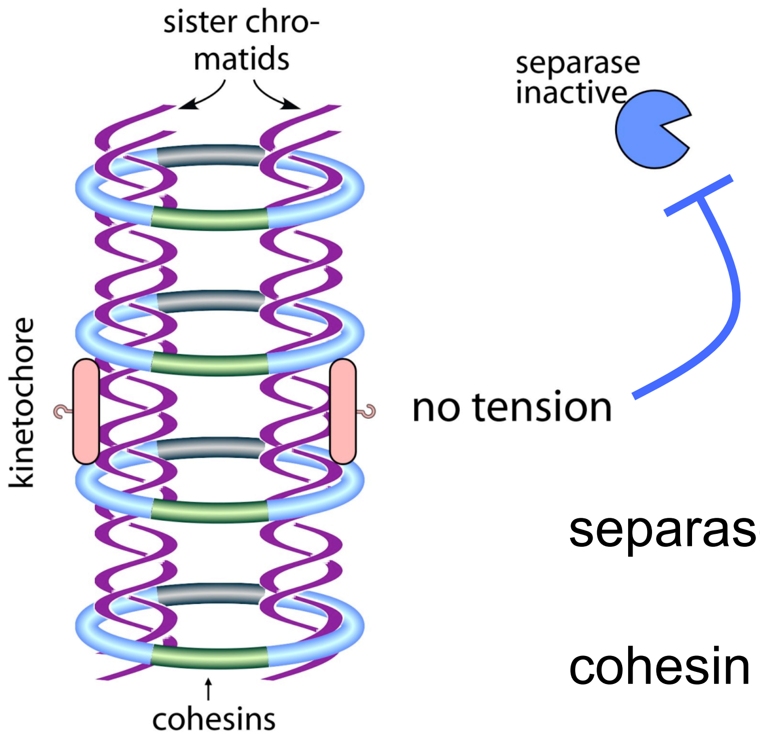
Unattached kinetochore

separase **active!**

cohesins

Sister chromatid separation

The anaphase entry checkpoint—genetic analysis



separase (non-functional) mutation*… phenotype?

cells stuck in metaphase

cohesin (non-functional) mutation*… phenotype?

premature sister separation

Double mutant phenotype?

premature sister separation!

*how to keep the strains alive? …use temperature sensitive mutants

Checkpoints

Cellular surveillance systems to monitor the integrity of the genome and of cellular structures

Enforce the correct order of execution of cellular events.

Examples:

- Chromosomes not attached to spindle → block onset of anaphase
- DNA is damaged → halt the cell cycle to allow repair
- Irreparable DNA damage → trigger cell death

A tiny practice question

The haploid chromosome number in honey bees is 16. Male honey bees are haploid while females are diploid. A single cell isolated from a bee's body was found to have 32 double-stranded DNA molecules. Was the cell from a male, a female, or is it not possible to make a definite conclusion from the information given? Explain BRIEFLY.

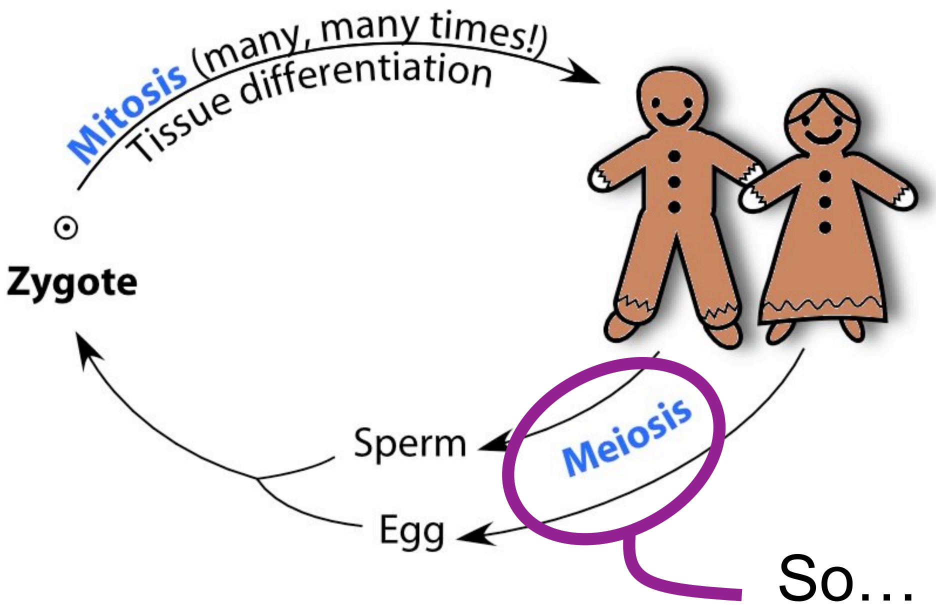
Chromosome segregation-2

Inheritance of traits from parent to offspring

Mitosis

Meiosis

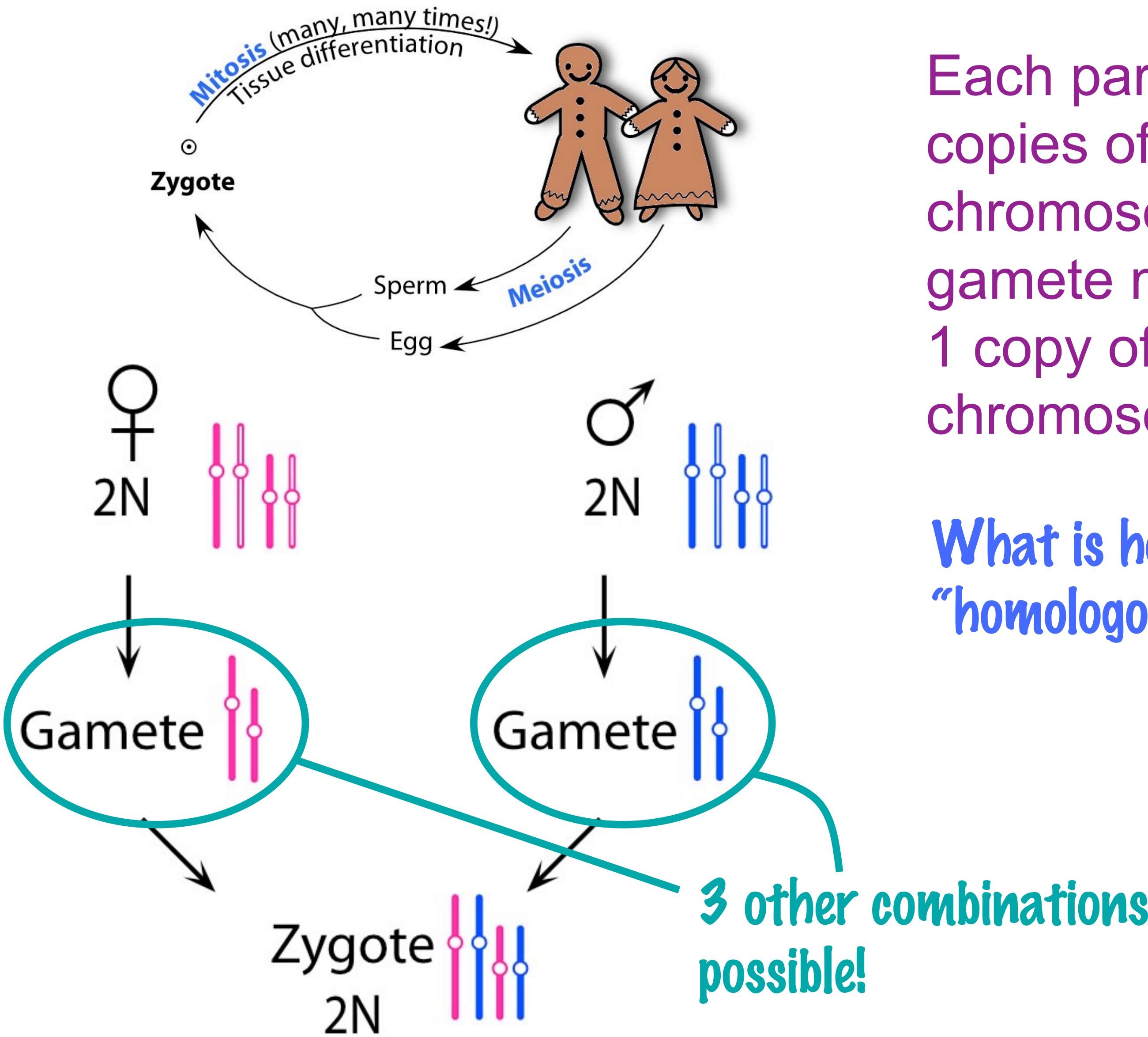
Meiosis—to halve the ploidy for gametes



- Both parents are diploid (2N).
- Unless something is done—gametes will be 2N
  and offspring will be 4N!

So… a specialized form of cell division to cut the ploidy by exactly half

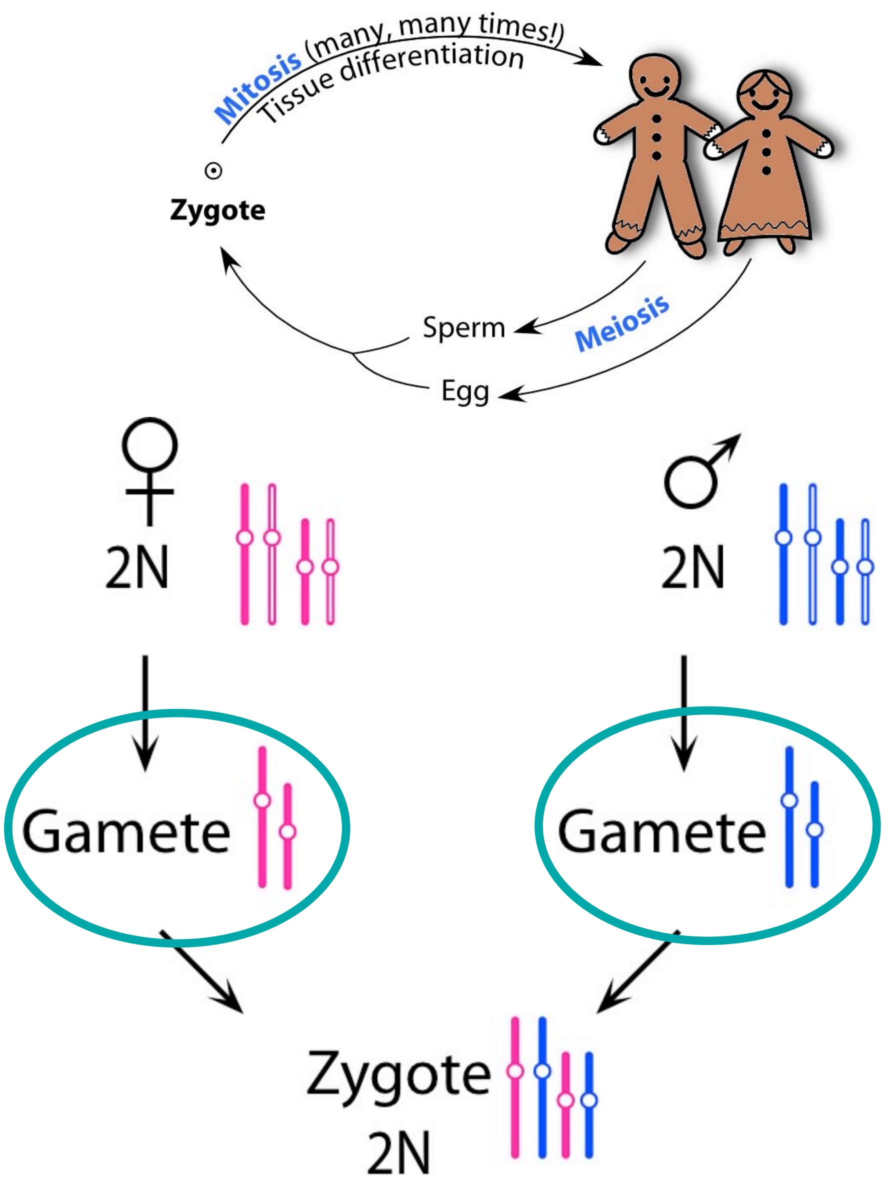
Meiosis—to halve the ploidy for gametes

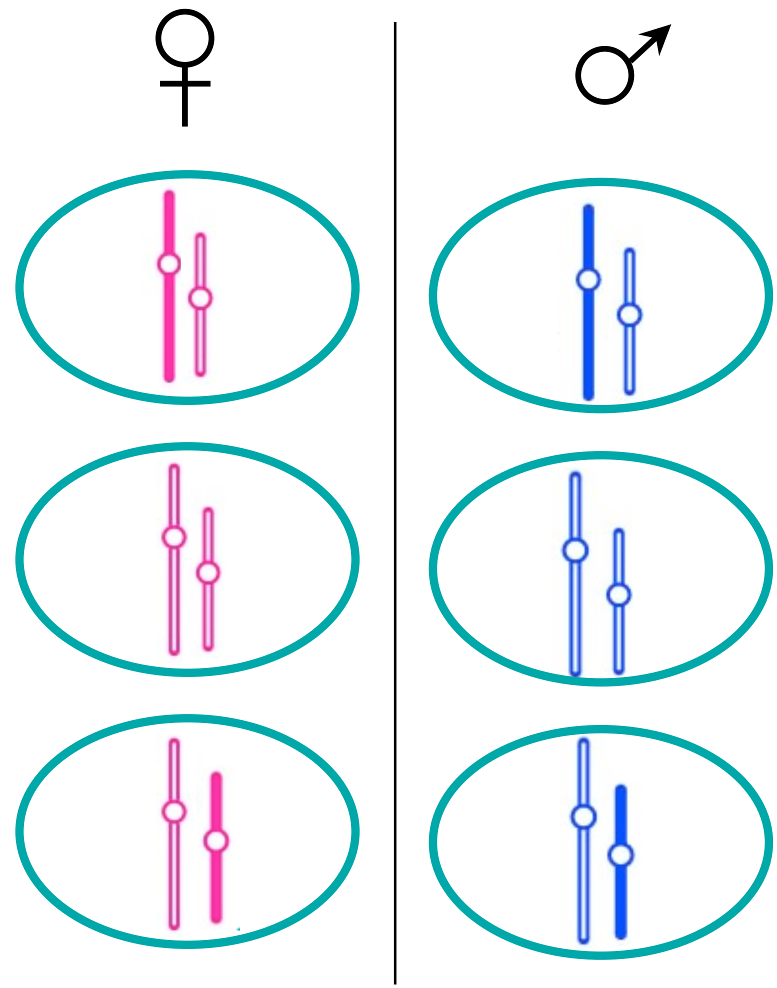


Each parent has 2 copies of every chromosome… but each gamete must have only 1 copy of each chromosome

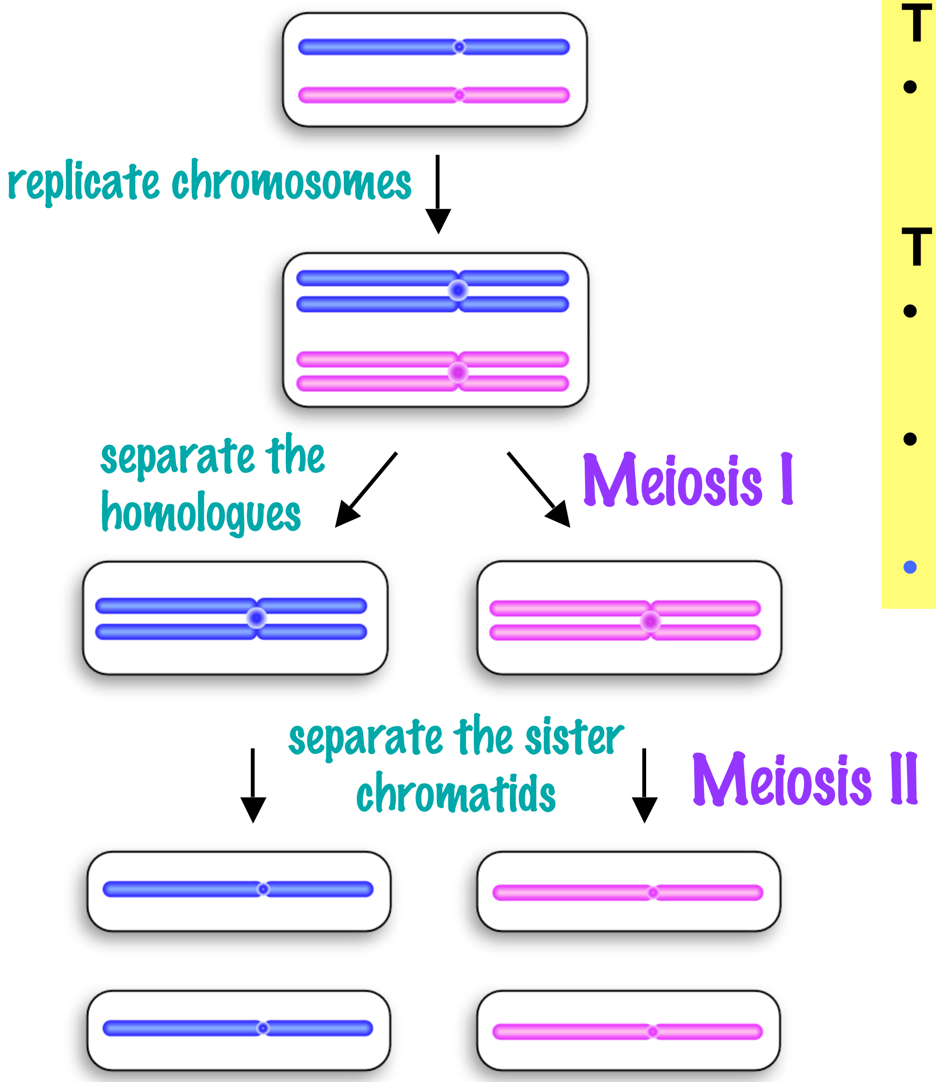
What is homologous about "homologous chromosomes"?

Meiosis—to halve the ploidy for gametes





Overview of meiosis

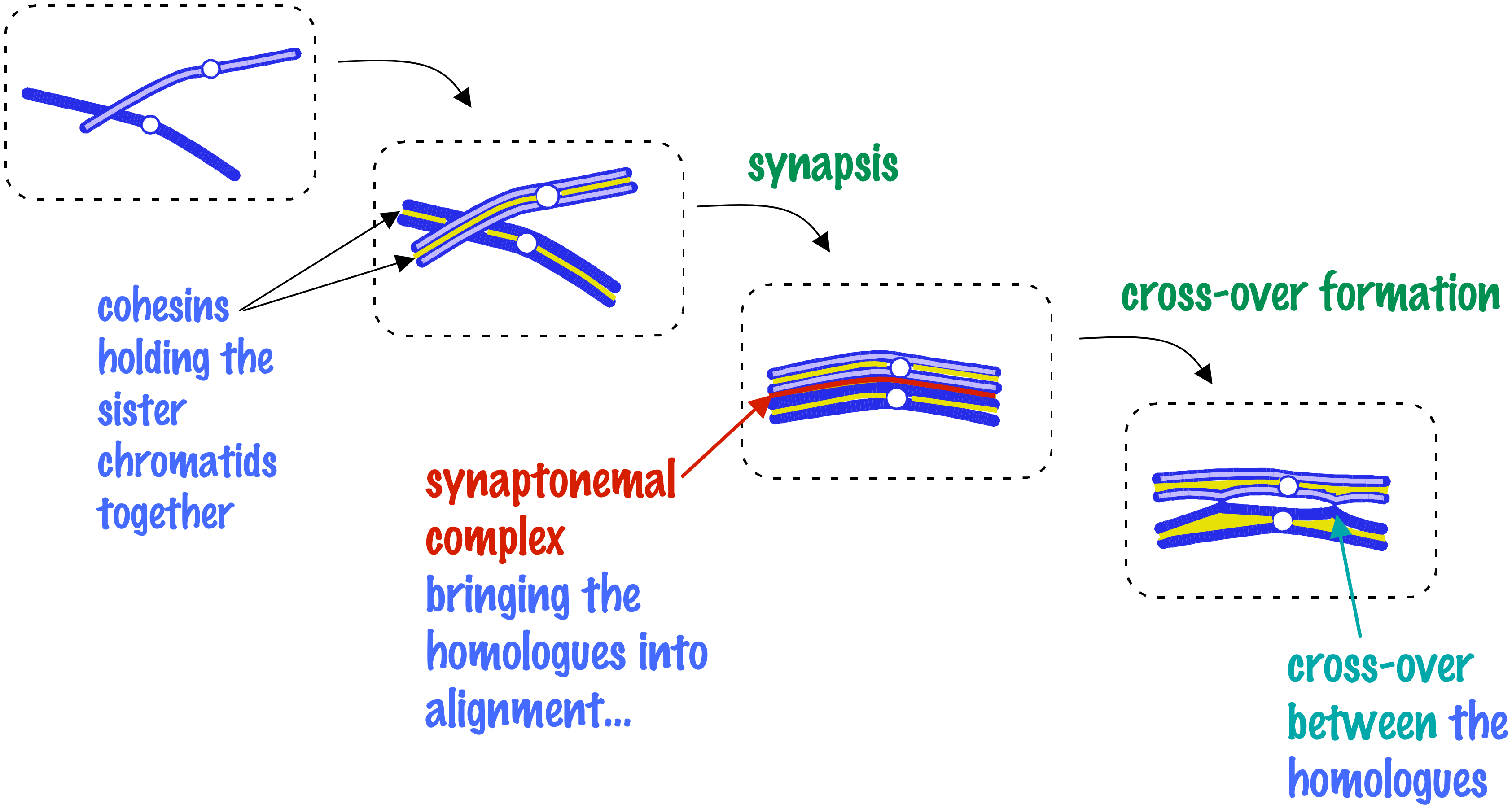


The problem:

- ensuring that homologues are partitioned to separate gametes

The solution:

- Hold homologous chromosomes together by **some means**
- target homologues to opposite poles…
- **then** separate the homologues



How do the homologues find each other? DNA sequence!

How does a cross-over hold homologues together? cohesins!

Beyond the Basics

How do homologues pair up?

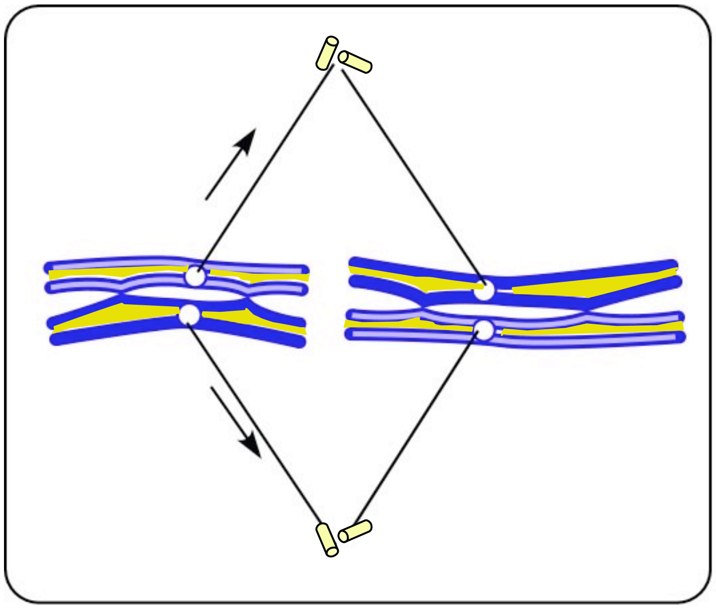
"Homologue recognition is absolutely necessary for the subsequent correct segregation of the homologues and thus the production of viable gametes, yet we have very little understanding of how it actually occurs."

Improving the chances of finding the right partner
G. Moore and P. Shaw (2009)
Current Opinion in Genetics & Development **19:** 99-104

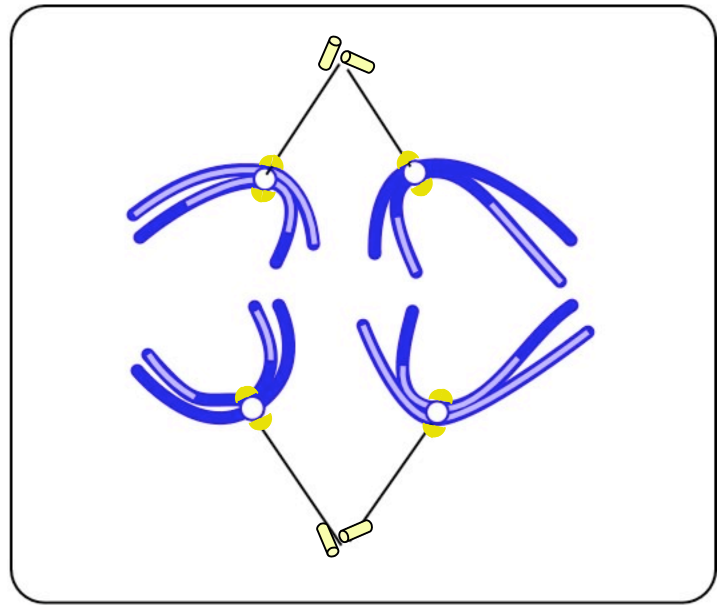
Roles for:
- double-stranded DNA breaks
- specific pairing sites, including centromeres & telomeres
- pairing in premeiotic S phase
- other mechanisms

Meiosis I — reductional division

Crossovers hold the homologues together—again, tension on kinetochores indicates proper attachment



Metaphase I



Anaphase I

Cohesin near centromeres is maintained

Homologues are separated, so ploidy is halved

Sister centromeres/kinetochores stay together through meiosis I

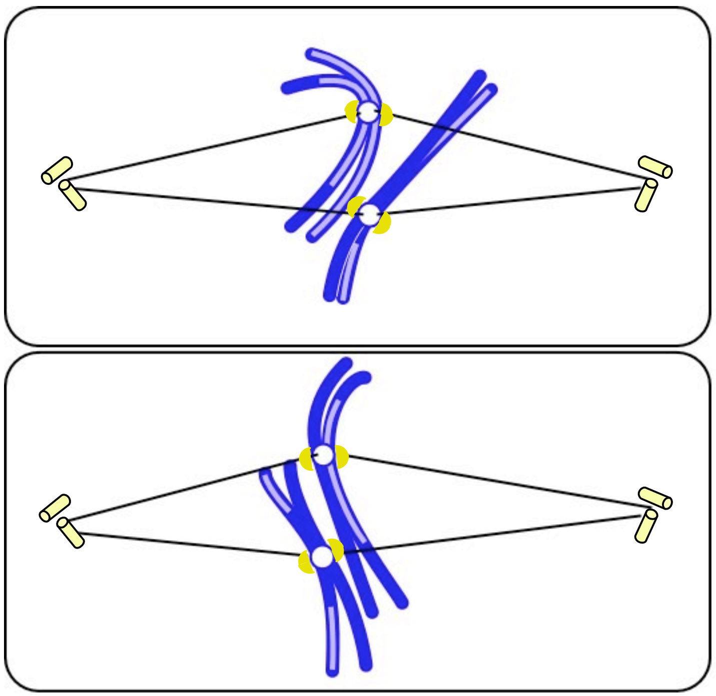
Meiosis II — equational division

Two daughter cells from meiosis I → go directly into meiosis II

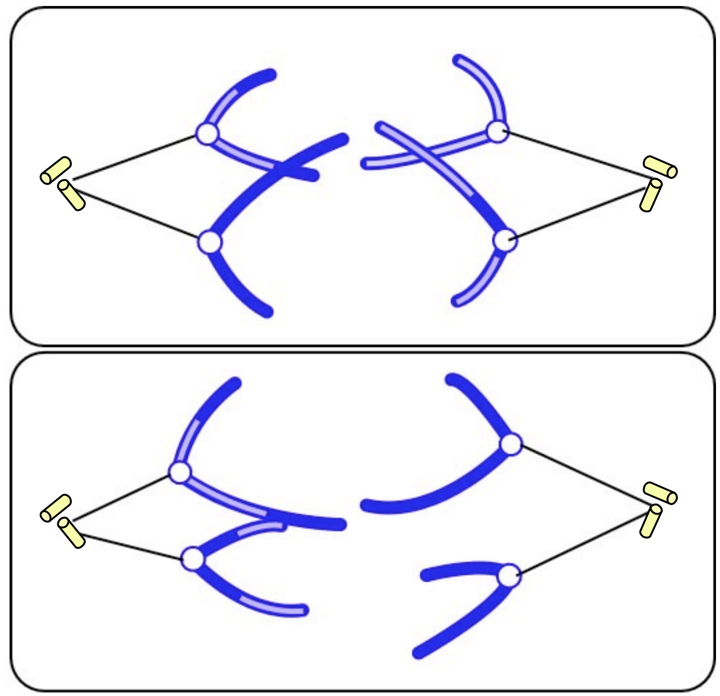
Tension on kinetochores is monitored

Cohesin near centromere is destroyed

Sister centromeres/kinetochores separate in meiosis II

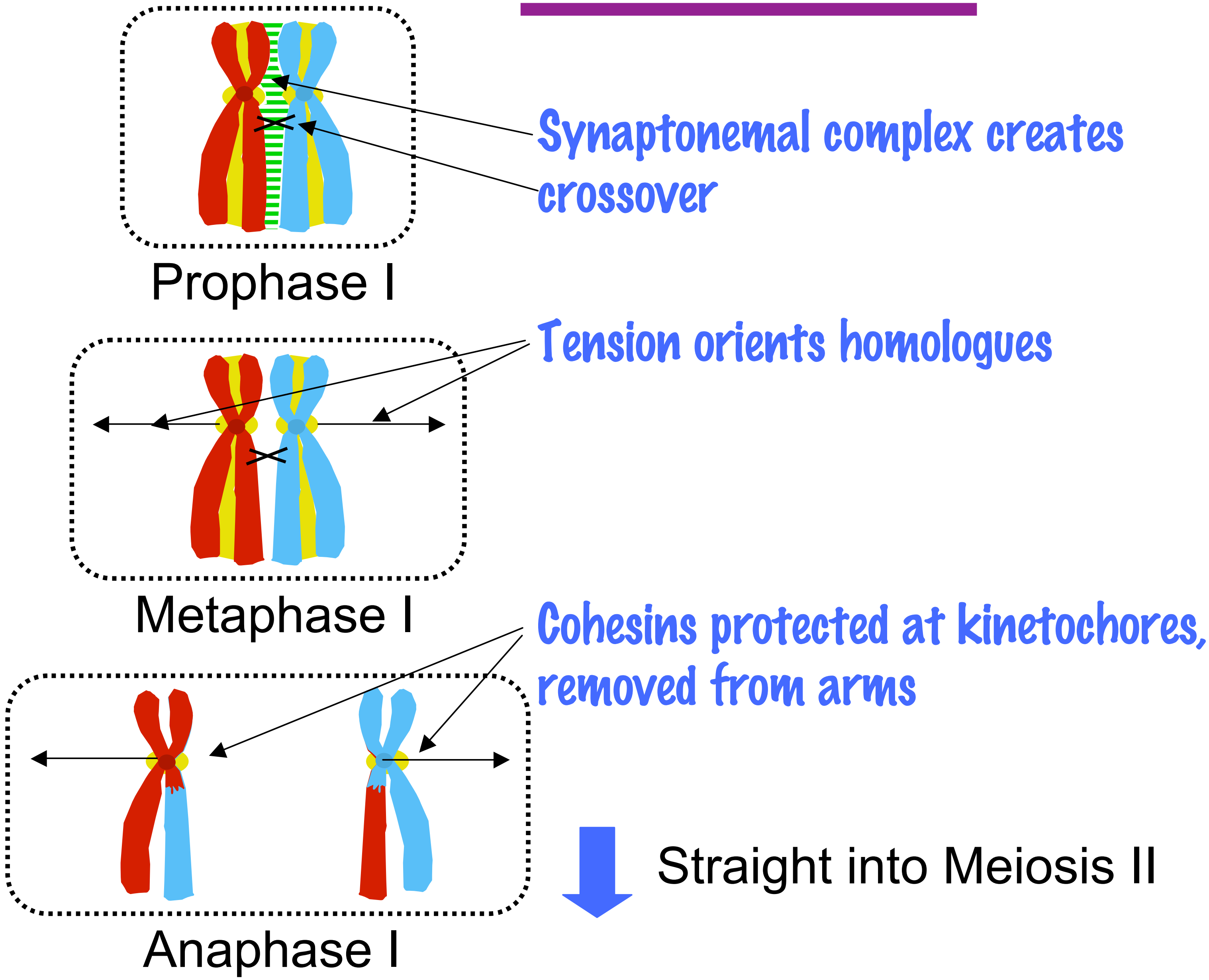


Metaphase II



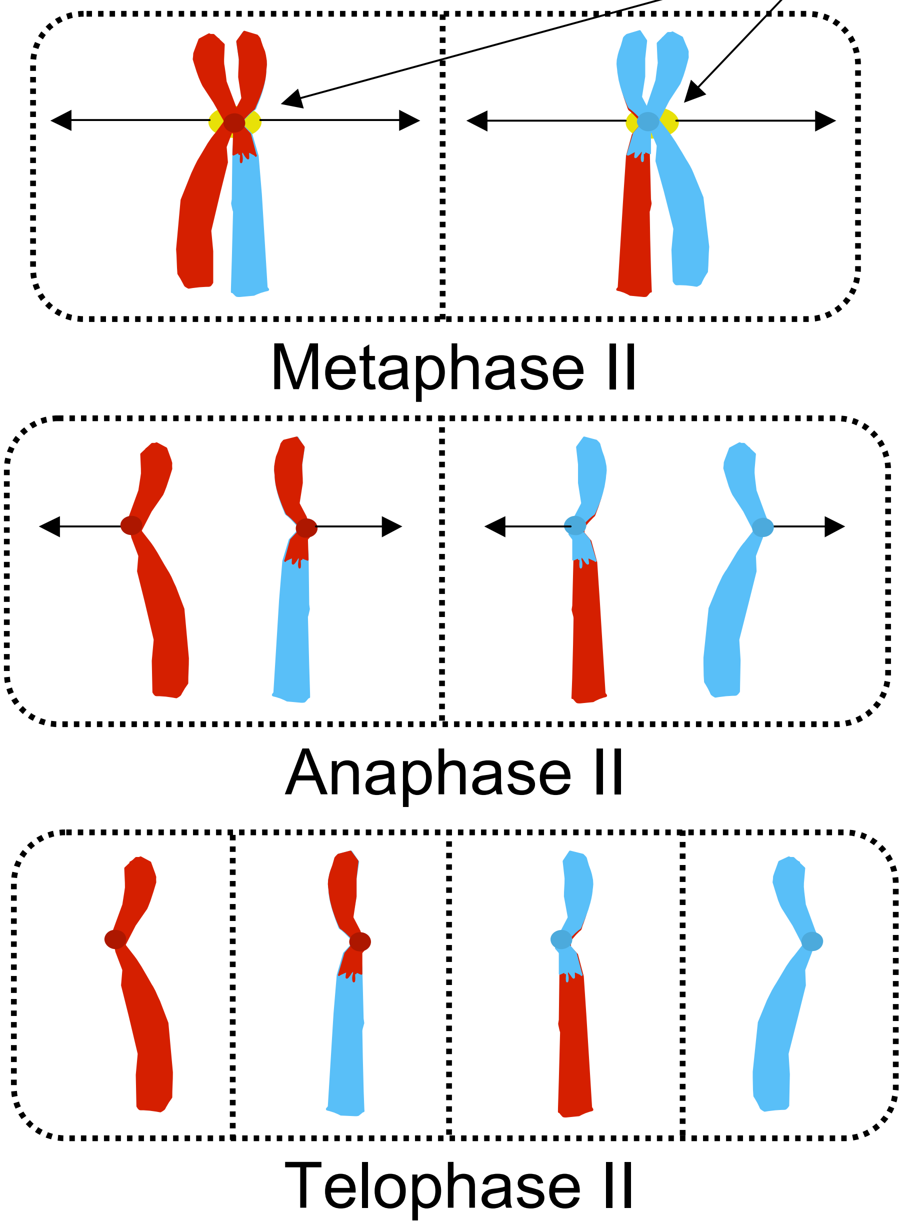
Anaphase II

In summary



Synaptonemal complex creates
crossover
Prophase I
Tension orients homologues
Metaphase I
Cohesins protected at kinetochores,
removed from arms
Anaphase I
Straight into Meiosis II

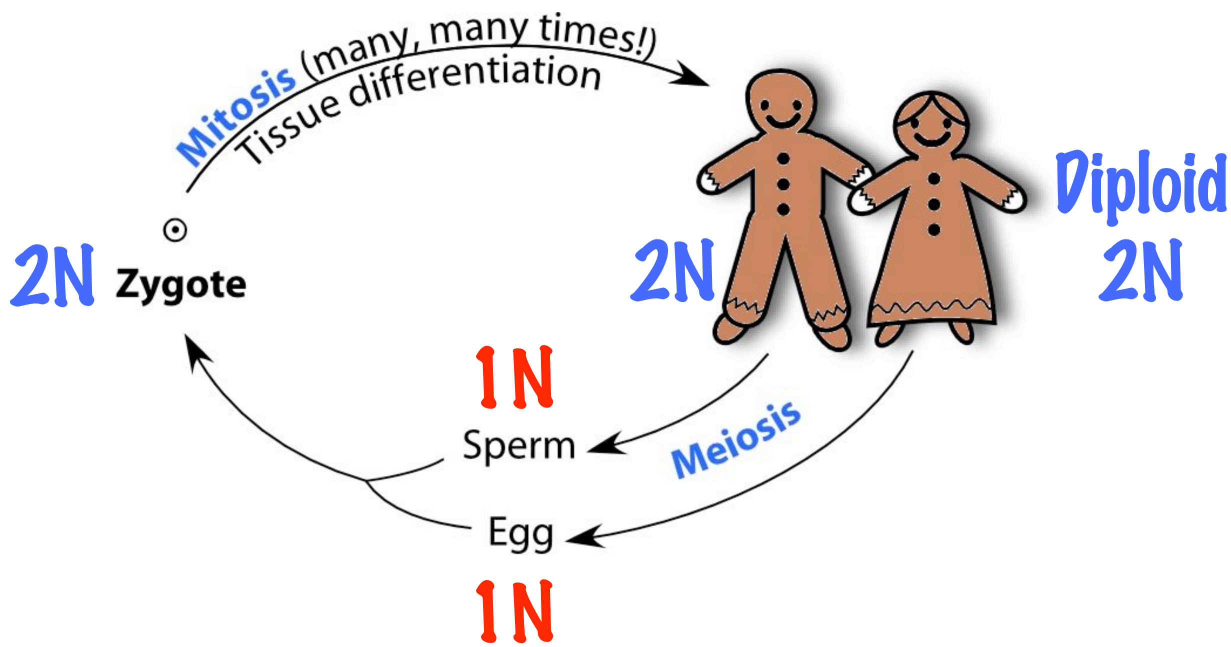
Tension orients sister centromeres



Cohesins removed from kinetochore region; sister centromeres segregate

Result: 4 cells
Each haploid
Chromosomes have a single chromatid (unreplicated)

Mitosis	vs.	Meiosis
Somatic cells		Germ cells
Haploids and diploids		Only diploids
One round of division		Two rounds of division
Homologous chromosomes do not pair		Homologous chromosomes pair along their length
Sister chromatids attach to spindle fibers from opposite poles		Homologous chromosomes attach to spindle fibers from opposite poles
Produces 2 new daughter cells, identical to each other and original cell		Produces 4 haploid cells, none identical to each other or original cell, because of recombination



- ★ What happens if there is a segregation error?
- ★ What happens to junior when mom and dad carry different alleles of a gene?

Chromosomal abnormalities

"Chromosome mutations"

~15% of human conceptions end in spontaneous abortion

Chromosomal abnormalities in ~1/2 of those

Defects in chromosome number

Aneuploidy

Defects in chromosome structure

Chromosomal rearrangements and deletions

Changes in chromosome number

Euploidy vs. aneuploidy

Complete chromosome sets

1N, 2N, 3N, etc.

Incomplete (unbalanced) chromosome sets

monosomy, trisomy, etc.

Monosomy (2N - 1)… only one kind tolerated in humans

Turner syndrome (XO)

Aneuploidy

Trisomy (2N + 1)

Most common at birth—trisomy 21 (Down syndrome)

1 in 750 live births

Less common

Trisomy 18 (Edward syndrome, 1 in 10,000)

Trisomy 13 (Patau syndrome, 1 in 20,000)

Why is trisomy 21 tolerated better than other trisomies?

Small chromosome → fewer genes → less imbalance

Aneuploidy hierarchy of tolerance

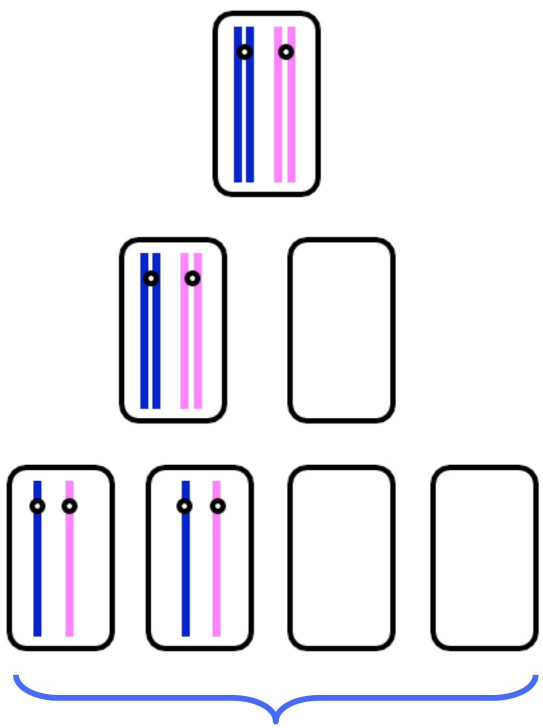
- sex chromosome aneuploidy > autosome aneuploidy
- autosome trisomy > autosome monosomy

Aneuploidy (cont'd)

Major cause of aneuploidy—meiosis nondisjunction

failure to separate chromosomes correctly

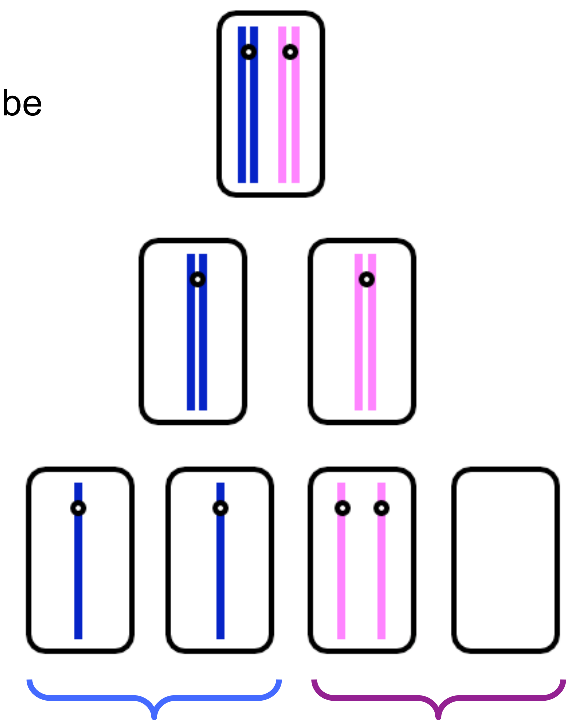
Meiosis I nondisjunction



All 4 products defective

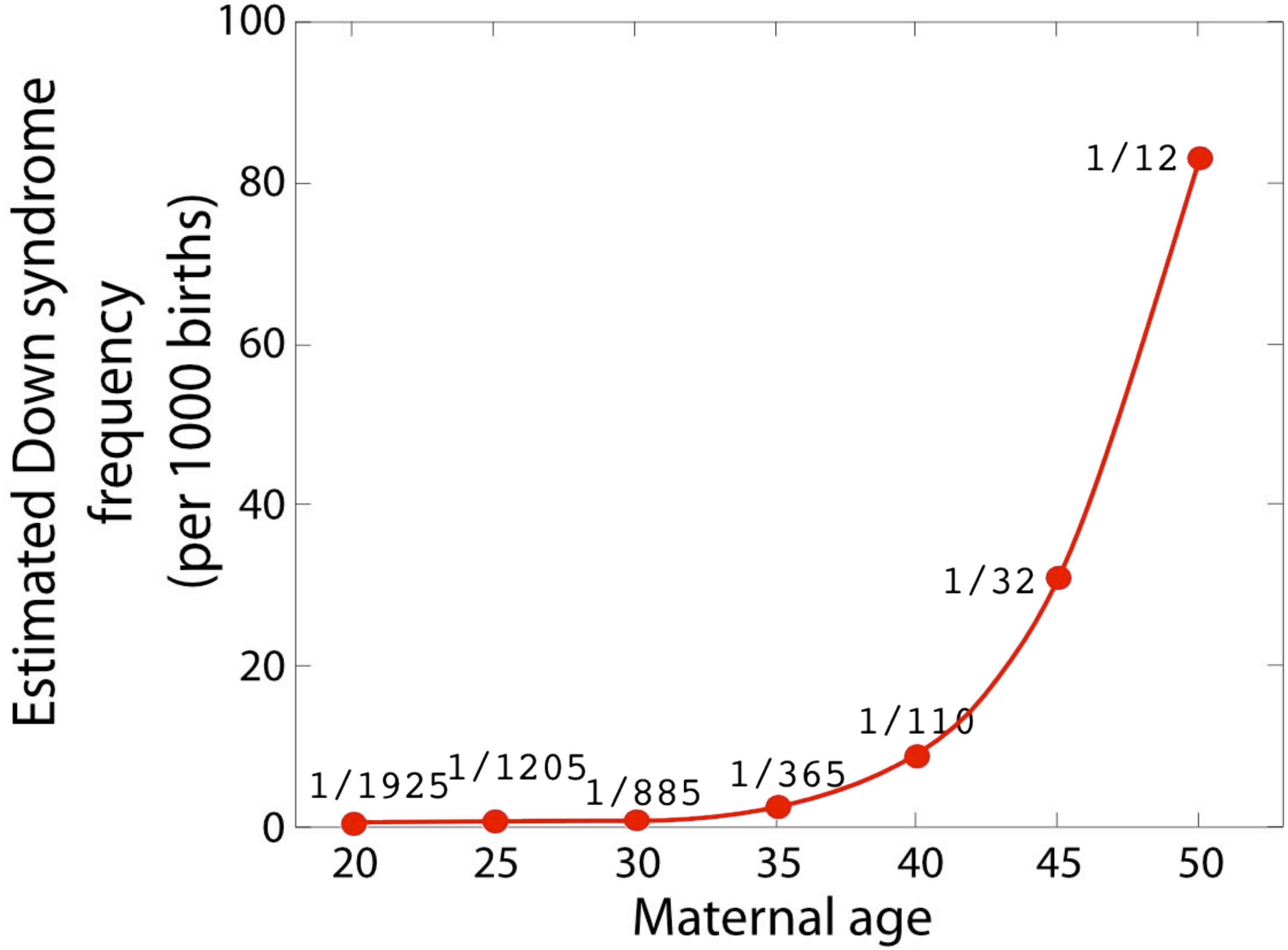
(only showing the problem chromosome… others could be perfectly normal)

Meiosis II nondisjunction



2 normal 2 defective

Aneuploidy and maternal age



Nature Genetics **37**, 1351 - 1355 (2005)
Published online: 30 October 2005; |
doi:10.1038/ng1672

cohesin subunit

SMC1$_\beta$-deficient female mice provide evidence that cohesins are a missing link in age-related nondisjunction

Craig A Hodges[1], Ekaterina Revenkova[2], Rolf Jessberger[2, 3], Terry J Hassold[4] & Patricia A Hunt[4]

Aneuploidy and maternal age (cont'd)

Why the increase in ND with age?

Keep in mind...

- Humans... oocytes begin meiosis before birth
- Arrested in prophase I of meiosis until ovulation

- checkpoint loss in older oocytes?
- less robust spindle?
- "good" oocytes used first?