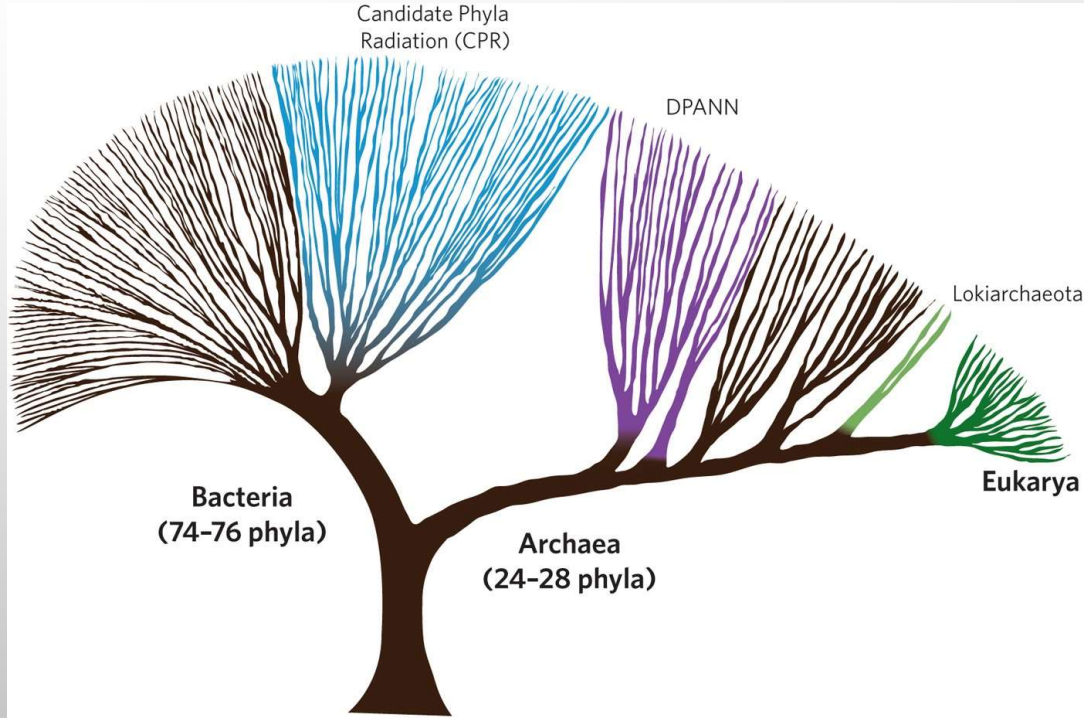
MOLECULAR INVENTIONS AND THE TREE OF LIFE

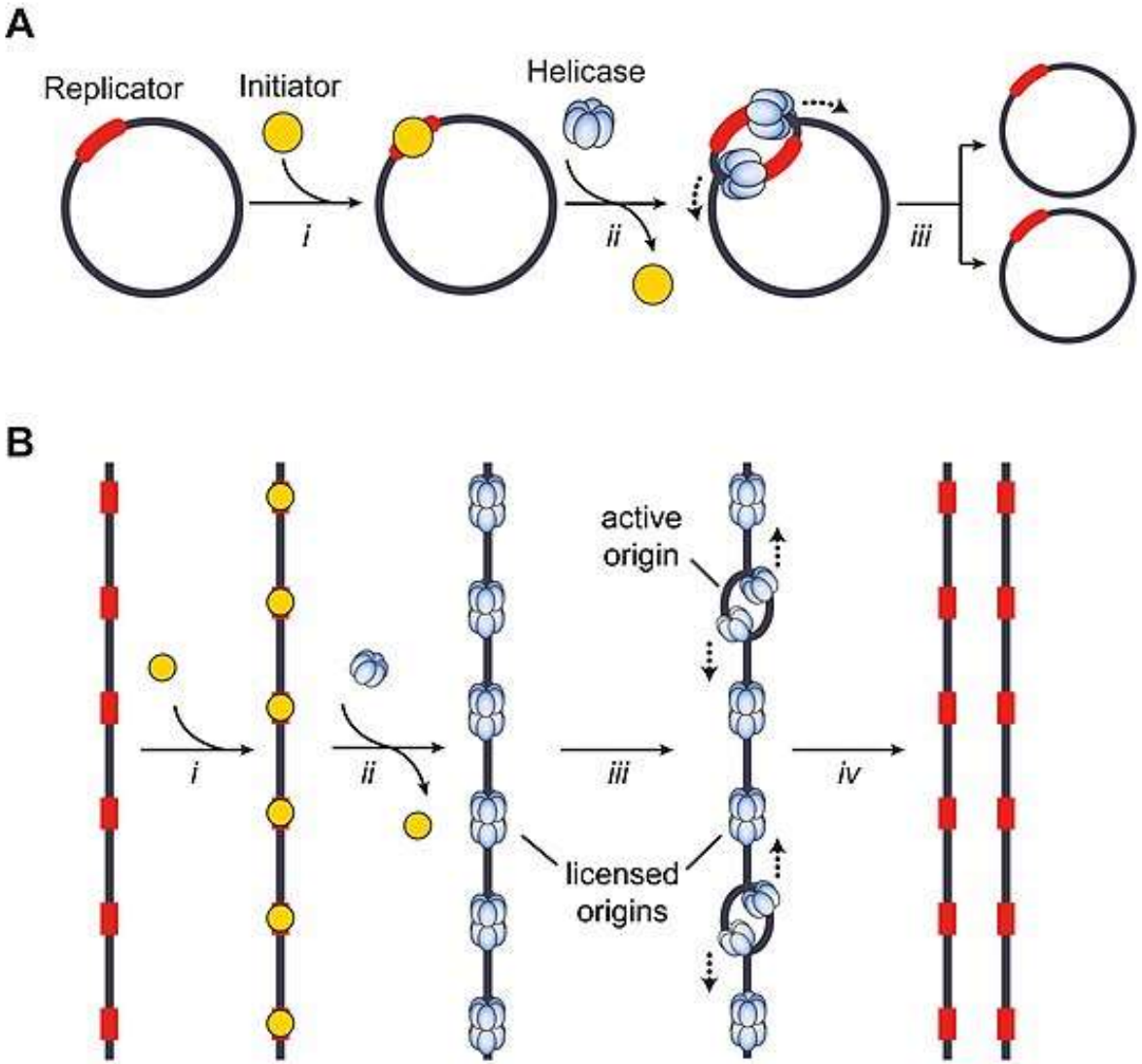
SPRING 2024



UP TO THIS POINT

- EUKARYOTES EVOLVED FROM AN ASGARD ARCHAEAN ANCESTOR, AND
- ENDOSYMBIOSIS WITH AN OXYGEN-RESPIRING ALPHAPROTEOBACTERIUM
- LATER, A BRANCH OF THESE EARLY EUKARYOTES ACQUIRED A CYANOBACTERIA AS AN ENDOSYMBIONT
- THUS, THE ANIMAL/FUNGI AND THE PLANT LINES OF DESCENT WERE ESTABLISHED

- THESE WERE FAR MORE COMPLEX ORGANISMS, WHO
- NEEDED A BIGGER GENOME TO CODE FOR ALL THE ADDED FUNCTIONALITIES
- LINEAR CHROMOSOMES, IN PAIRS


A
Replicator
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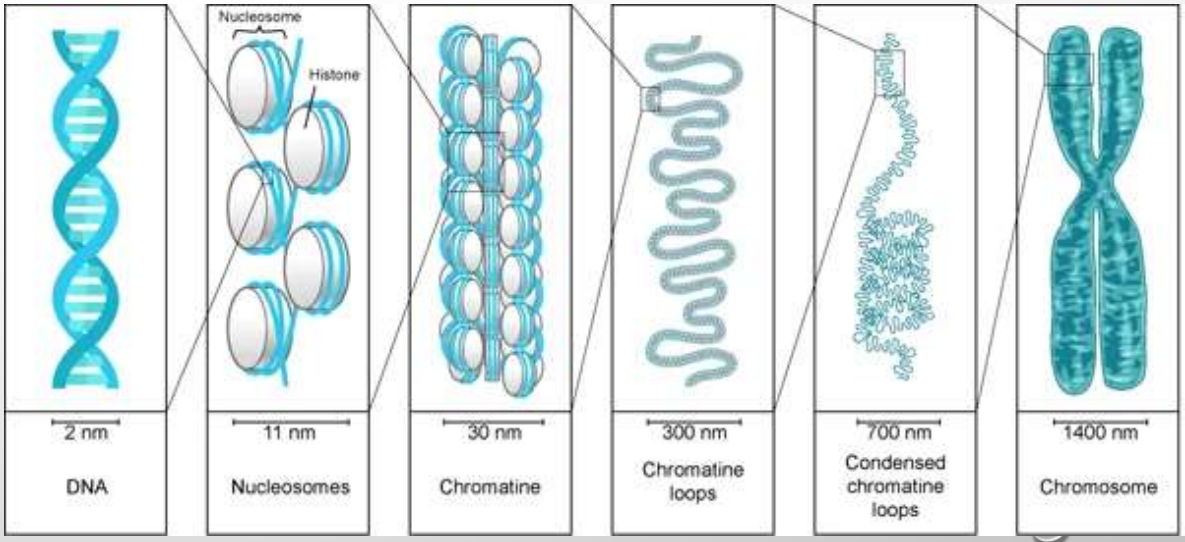
ENSURING PROGENY: MITOSIS – THE NEXT MOLECULAR INVENTION

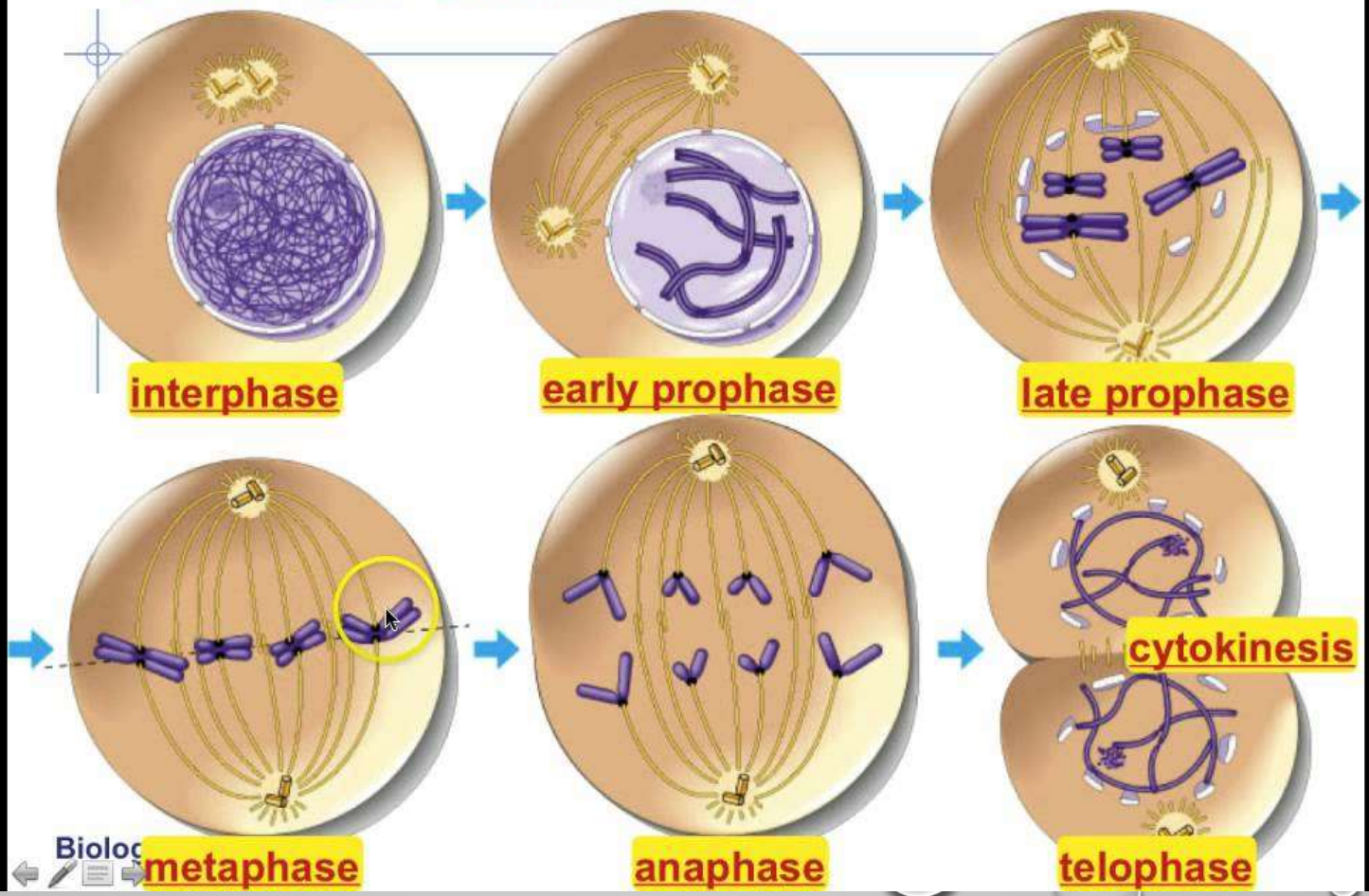
- THE PROCESS BY WHICH REPLICATED DNA IS SEPARATED INTO 2 NUCLEI, EACH ONE GETTING IDENTICAL COPIES OF THE GENOME
- FIRST, DNA IS REPLICATED
- THE SISTERS REMAIN ATTACHED
- NEXT, THE CHROMOSOMES, WHICH HAVE ALREADY DUPLICATED, CONDENSE
- EACH CHROMOSOME IS NOW 2 SISTERS
- THE CHROMOSOMES ALIGN ALONG THE EQUATORIAL PLANE OF THE CELL

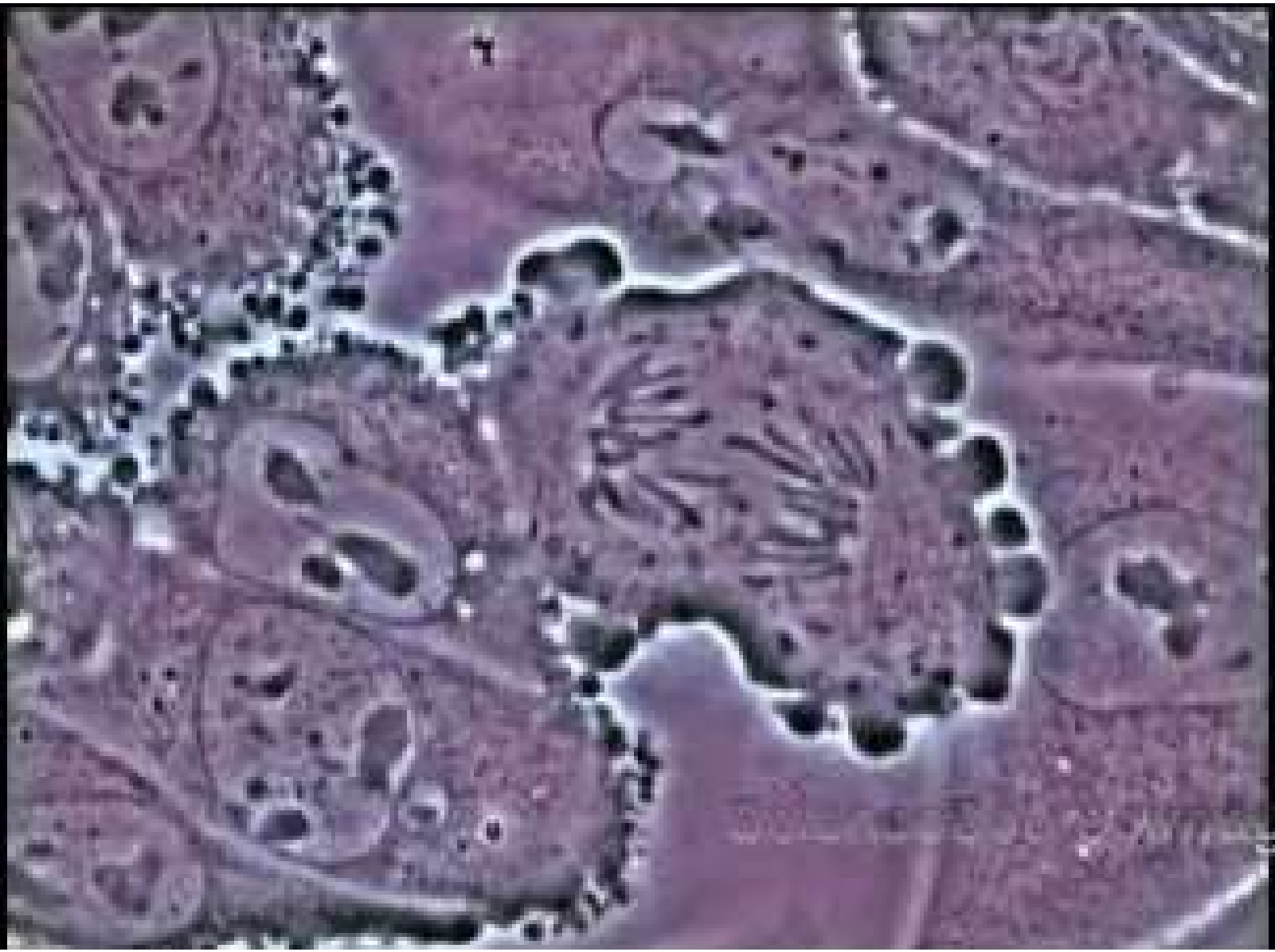


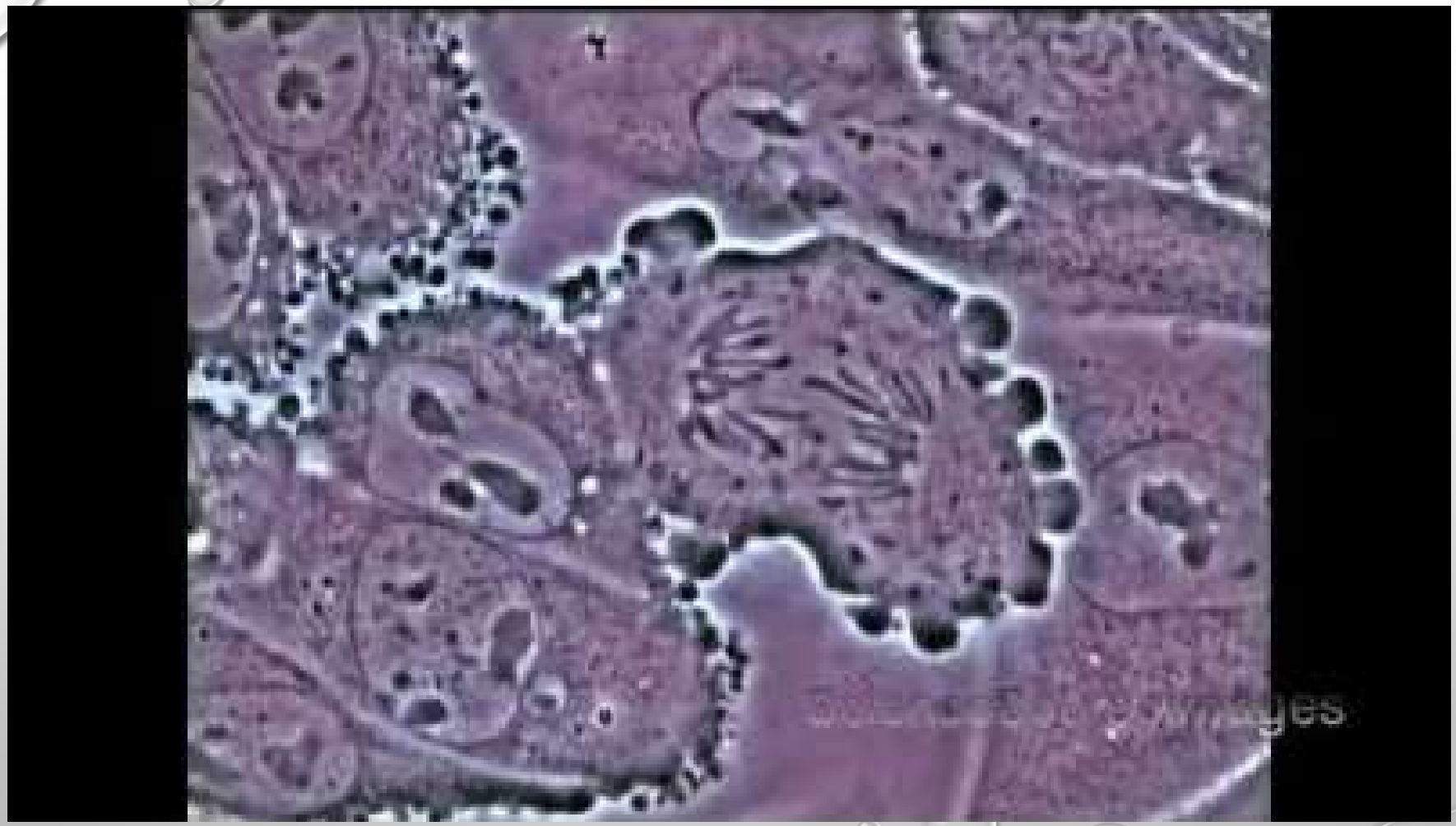
THE CYTOSKELETON STEPS IN

- MICROTUBULES ATTACH TO THE CHROMOSOMES
- THE 'GLUE' KEEPING THE SISTERS TOGETHER DEGRADES
- THE MICROTUBULES BEGIN PULLING THE SISTERS AWAY FROM EACH OTHER TOWARDS THE TWO POLES OF THE CELL
- THIS CAUSES THE CELL TO ELONGATE
- NOW AT THE POLES, THE CHROMOSOMES START TO RELAX AND DECONDENSE
- NEXT, A CONTRACTILE RING DEVELOPS WHERE THE EQUATORIAL PLANE USED TO BE, PINCHING OFF THE SEPARATED NUCLEI

Overview of mitosis

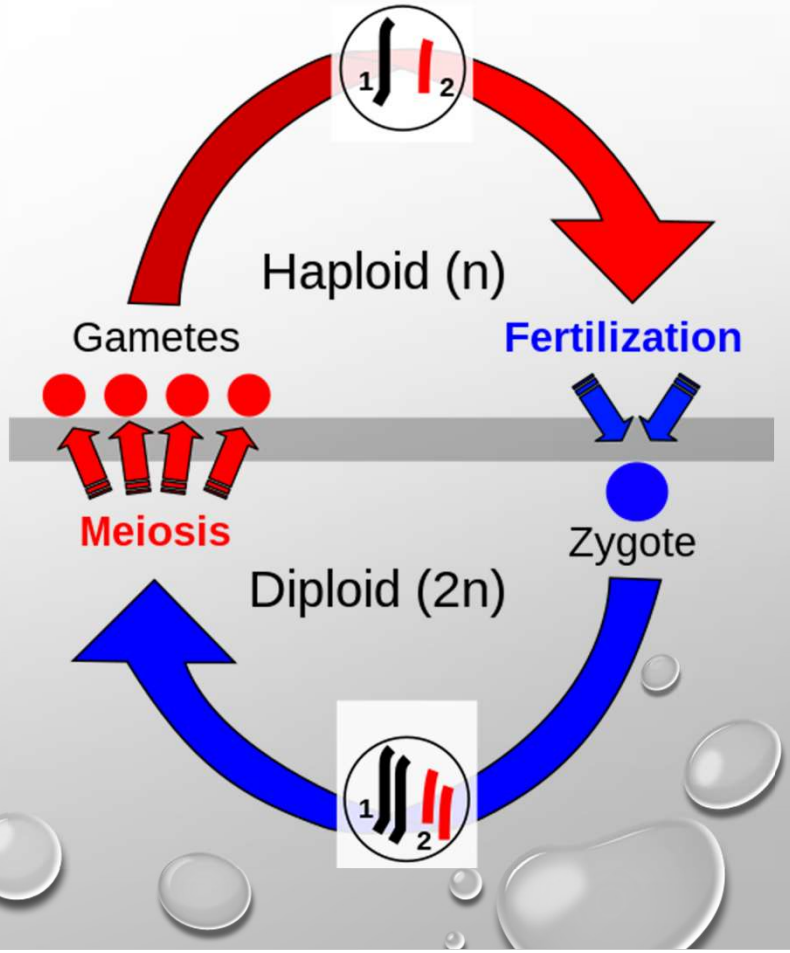






AND ALL EUKARYOTES HAVE SEX – THE NEXT MOLECULAR INVENTION

- **SEXUAL REPRODUCTION** IS A TYPE OF REPRODUCTION IN WHICH A GAMETE (REPRODUCTIVE CELLS, SUCH AS A SPERM OR OVUM) WITH A SINGLE SET OF CHROMOSOMES (HAPLOID) COMBINES WITH ANOTHER GAMETE TO PRODUCE A FERTILIZED EGG THAT DEVELOPS INTO AN ORGANISM COMPOSED OF CELLS WITH TWO SETS OF CHROMOSOMES (DIPLOID)



A COST/BENEFIT ANALYSIS OF SEX

- ASEXUAL REPRODUCTION SHOULD IN PRINCIPLE OUTPERFORM SEX:
  - EVERY ORGANISM CAN BEAR ITS OWN YOUNG
  - A MORE STREAMLINED PROCESS → FASTER GROWTH
  - YOU PASS ON **ALL** YOUR GENETIC INFORMATION TO THE PROGENY

- MAJOR ADVANTAGE:
  - IMPEDES THE ACCUMULATION OF DELETERIOUS MUTATIONS
  - INCREASES GENETIC DIVERSITY BY GENERATING RECOMBINANT OFFSPRING VIA INDEPENDENT ASSORTMENT AND CROSSING OVER
  - GREATER RATES OF EVOLUTION ALLOW ORGANISMS TO BETTER COPE WITH ENVIRONMENTAL STRESSES

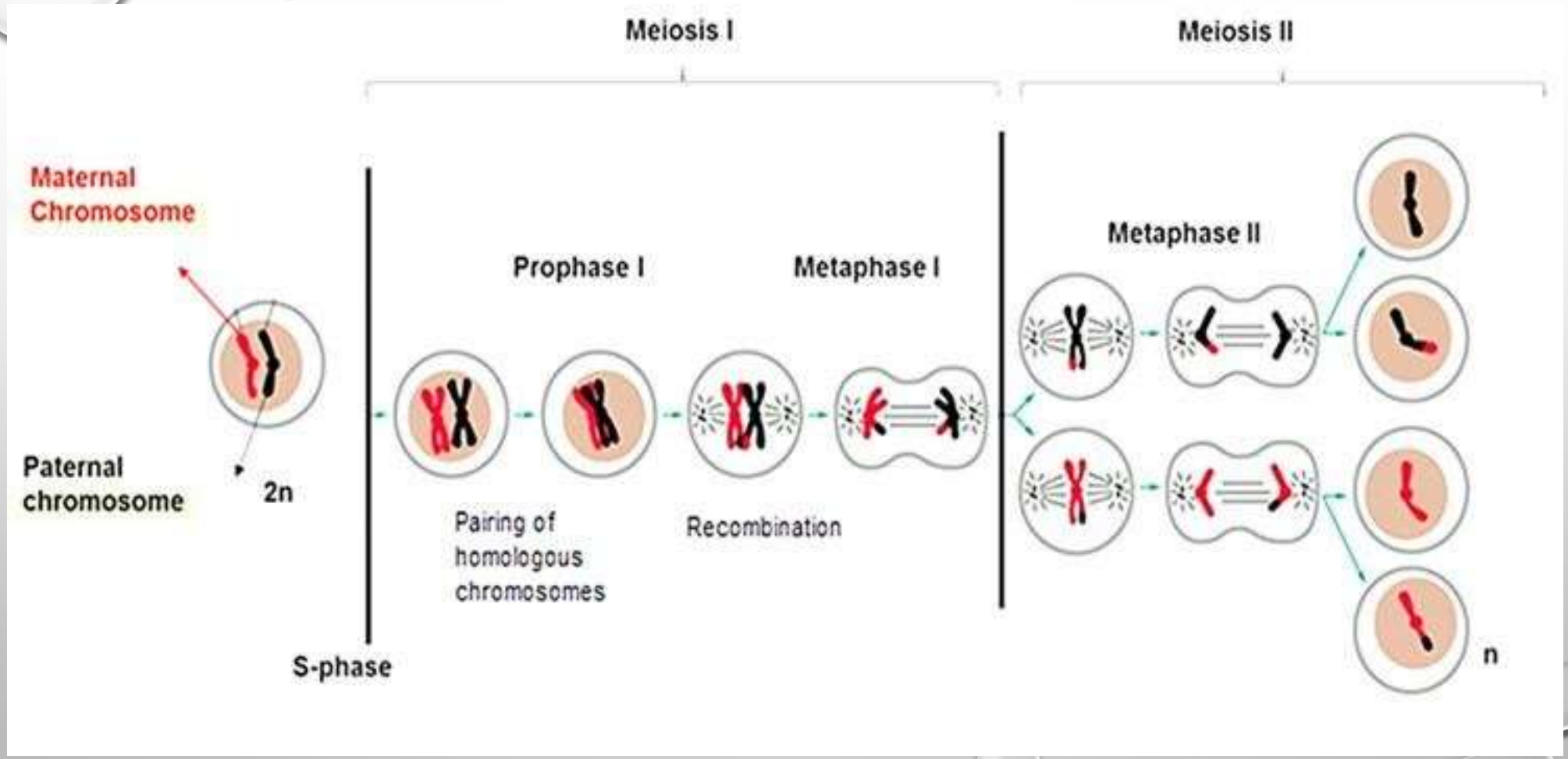
MAKING GAMETES: MEIOSIS

- IT INVOLVES TWO ROUNDS OF DIVISION THAT ULTIMATELY RESULT IN FOUR CELLS, EACH WITH ONLY ONE COPY OF EACH CHROMOSOME
- IN MEIOSIS, ONE DNA REPLICATION EVENT IS FOLLOWED BY TWO ROUNDS OF CELL DIVISION
- THIS RESULTS IN FOUR DAUGHTER CELLS, EACH WITH HALF THE NUMBER OF CHROMOSOMES AS THE ORIGINAL PARENT CELL

- THE ENTIRE COMPLEMENT OF CHROMOSOMES WILL BE RESTORED DURING FERTILIZATION

HOW DOES IT WORK?

- DNA OF EACH CHROMOSOME IS REPLICATED SO THAT IT CONSISTS OF TWO IDENTICAL SISTERS, THE CHROMATIDS, WHICH REMAIN HELD TOGETHER
- HOMOLOGOUS CHROMOSOMES PAIR WITH EACH OTHER (THAT MAKES 4 CHROMATIDS TOGETHER, A TETRAD)
- AT THIS POINT, THE SISTERS (CHROMATIDS) EXCHANGE PIECES OF THEIR DNA → GENETIC RECOMBINATION
- THE HOMOLOGOUS CHROMOSOMES PULL AWAY FROM EACH OTHER, RESULTING IN 2 CELLS, EACH WITH AN HAPLOID NUMBER OF CHROMOSOMES (BUT EACH CHROMOSOME COMPOSED OF TWO SISTER CHROMATIDS)
- IN A SECOND DIVISION, AND JUST AS IN MITOSIS, THE SISTER CHROMATIDS ARE SEPARATED AND SEGREGATE FROM ONE ANOTHER.


Meiosis I
Meiosis II
Maternal Chromosome
Paternal chromosome
2n
S-phase
Prophase I
Metaphase I
Pairing of homologous chromosomes
Recombination
Metaphase II
n

- IT'S A UNIVERSAL FEATURE IN EUKARYOTES, SO THE LAST EUKARYOTIC COMMON ANCESTOR COULD ALMOST CERTAINLY DO IT
- THE KEY INNOVATION — INDEED, THE HALLMARK OF MEIOSIS — WAS SYNAPSIS BETWEEN HOMOLOGOUS CHROMOSOMES
- MEIOSIS GENERATES GENETIC DIVERSITY IN TWO WAYS:
- (1) LAW OF INDEPENDENT ASSORTMENT: THE INDEPENDENT ORIENTATION OF HOMOLOGOUS CHROMOSOME PAIRS ALLOWS A RANDOM AND INDEPENDENT DISTRIBUTION OF CHROMOSOMES TO EACH DAUGHTER CELL
- (2) CROSSING OVER: THE PHYSICAL EXCHANGE OF HOMOLOGOUS CHROMOSOMAL REGIONS BY RECOMBINATION RESULTS IN NEW COMBINATIONS OF GENETIC INFORMATION WITHIN CHROMOSOMES

THE NEXT FRONTIER, AND OUR LAST MOLECULAR INVENTION: MULTICELLULARITY

- MULTICELLULARITY HAS EVOLVED INDEPENDENTLY AT LEAST 25 TIMES IN EUKARYOTES AND ALSO IN SOME BACTERIA AND ARCHAEA
- HOWEVER, COMPLEX MULTICELLULAR ORGANISMS EVOLVED ONLY IN SIX EUKARYOTIC GROUPS: ANIMALS, FUNGI, BROWN ALGAE, RED ALGAE, GREEN ALGAE, AND LAND PLANTS
- MULTICELLULAR EUKARYOTES MAY HAVE EXISTED AT LEAST 1 BILLION YEARS AGO
- A MAJOR BURST OF DIVERSIFICATION OCCURRED ABOUT 600–700 MYA, AT A TIME OF DRAMATIC INCREASES IN ATMOSPHERIC AND OCEANIC OXYGEN

ORIGIN OF MULTICELLULARITY HYPOTHESES

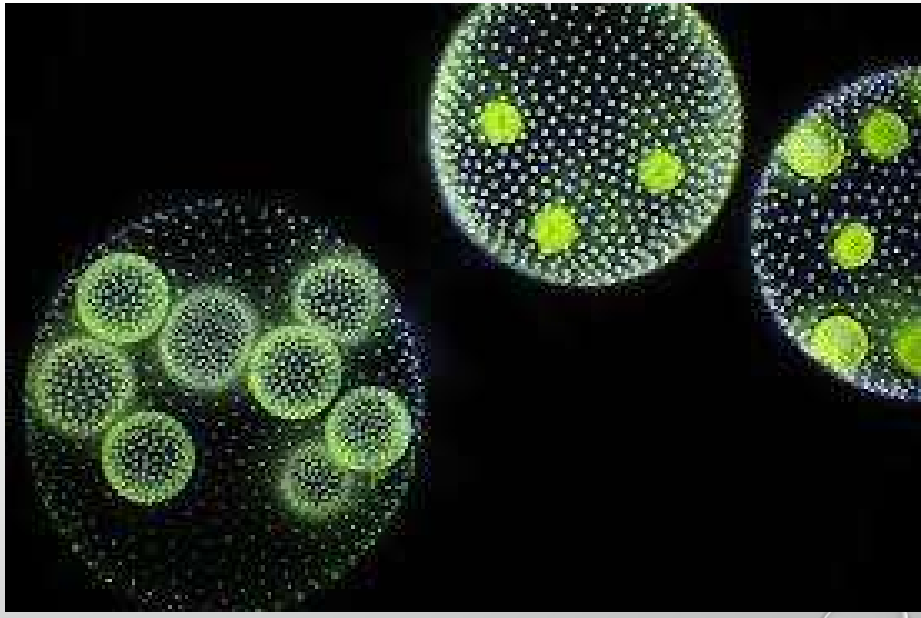
- 1) A GROUP OF FUNCTION-SPECIFIC CELLS AGGREGATED INTO A SLUG-LIKE MASS, WHICH MOVED AS A MULTICELLULAR UNIT. OVER TIME THESE ORGANISMS WOULD BECOME SO DEPENDENT ON EACH OTHER THAT THEY WOULD NOT BE ABLE TO SURVIVE INDEPENDENTLY, EVENTUALLY LEADING TO THE INCORPORATION OF THEIR GENOMES INTO ONE MULTICELLULAR ORGANISM

- 2) A SINGLE UNICELLULAR ORGANISM WITH MULTIPLE NUCLEI COULD HAVE DEVELOPED INTERNAL MEMBRANE PARTITIONS AROUND EACH OF ITS NUCLEI

- 3) MULTICELLULARITY OCCURRED AS A CONSEQUENCE OF CELLS FAILING TO SEPARATE FOLLOWING DIVISION – AND FOR THIS WE DO HAVE EXAMPLES

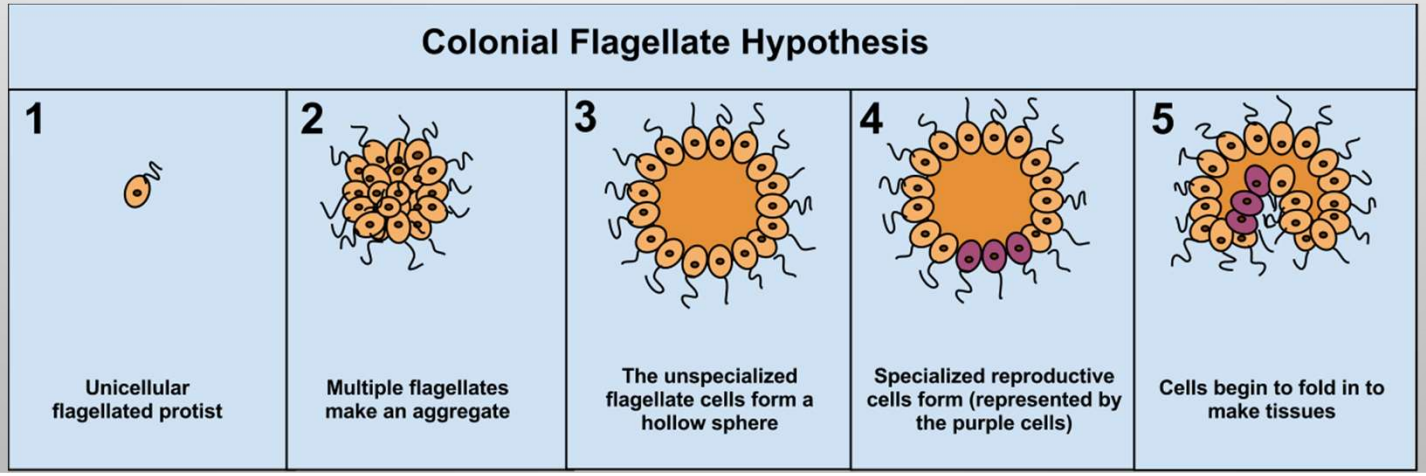
VOLVOX

- FRESH WATER GREEN ALGA
- EACH MATURE *VOLVOX* COLONY IS COMPOSED OF UP TO THOUSANDS OF CELLS FROM TWO DIFFERENTIATED CELL TYPES: NUMEROUS FLAGELLATE SOMATIC CELLS AND A SMALLER NUMBER OF GERM CELLS



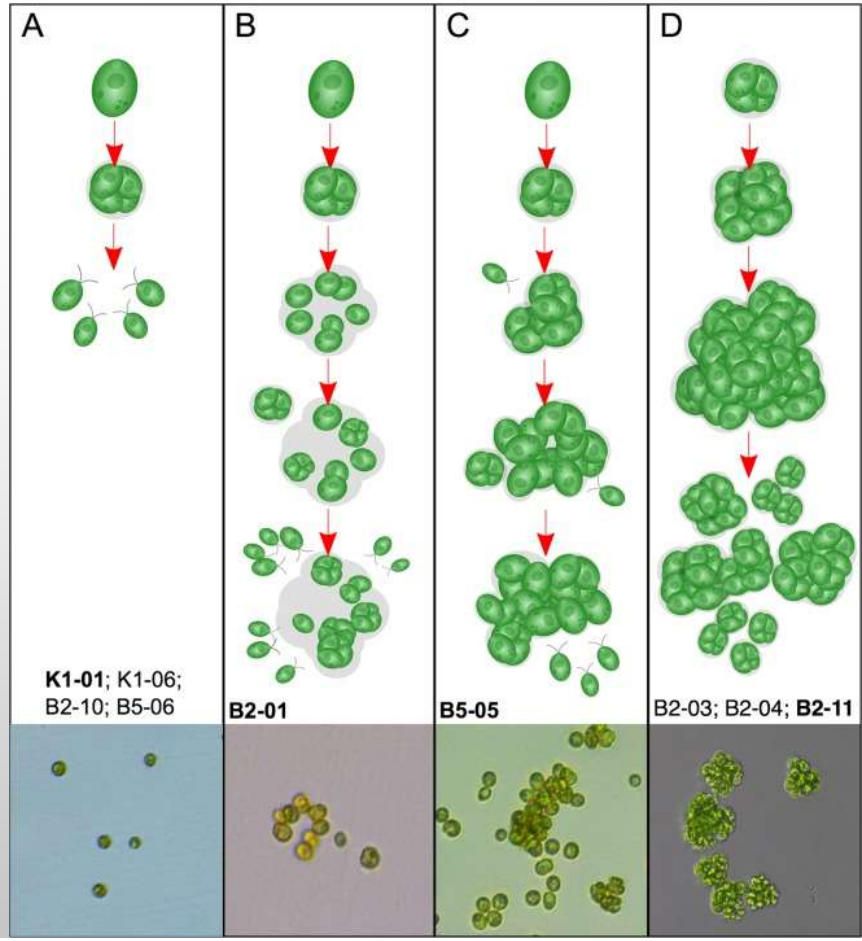
VOLVOX

- THE SPECIALIZATION OF CELLS INTO REPRODUCTIVE GERMLINE VERSUS STERILE SOMA REPRESENTS THE MOST FUNDAMENTAL DIVISION OF LABOR
- DIFFERENTIATING INTO A SOMATIC CELL IS ALTRUISTIC: A SOMATIC CELL SACRIFICES ITS IMMORTALITY, RELYING ON GERM CELLS TO TRANSMIT THEIR GENES TO FUTURE GENERATIONS
- STERILITY CAN ONLY EVOLVE IF THERE IS A NET GAIN IN GENE COPIES PRODUCED, SO SOMATIC AND GERMLINE CELLS MUST BE CLOSELY RELATED



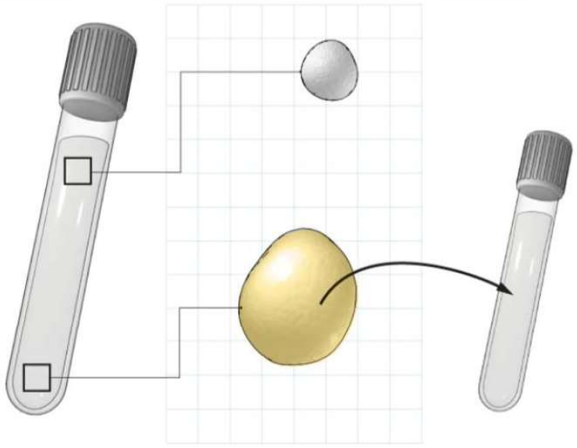
WHY MULTICELLULARITY – PREDATION HYPOTHESIS

- MAKE YOURSELF BIGGER → MORE DIFFICULT TO EAT
- LABORATORY EVOLUTION EXPERIMENTS ON THE SINGLE-CELLED GREEN ALGA, *CHLAMYDOMONAS REINHARDTII*, USING PARAMECIUM AS A PREDATOR
- THEY FOUND THAT IN THE PRESENCE OF THIS PREDATOR, *C. REINHARDTII* DOES INDEED EVOLVE SIMPLE MULTICELLULAR FEATURES



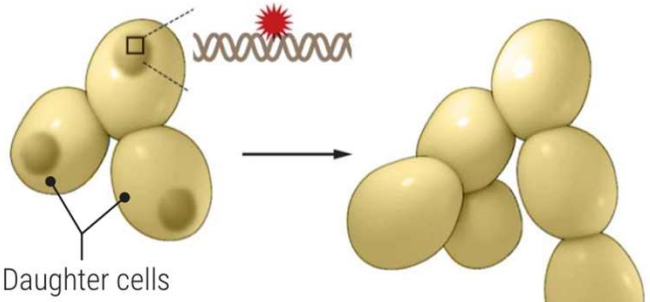
Multicellularity made easy

Researchers got single-cell yeast to evolve multicellularity in the lab, demonstrating the relative ease of the transition.



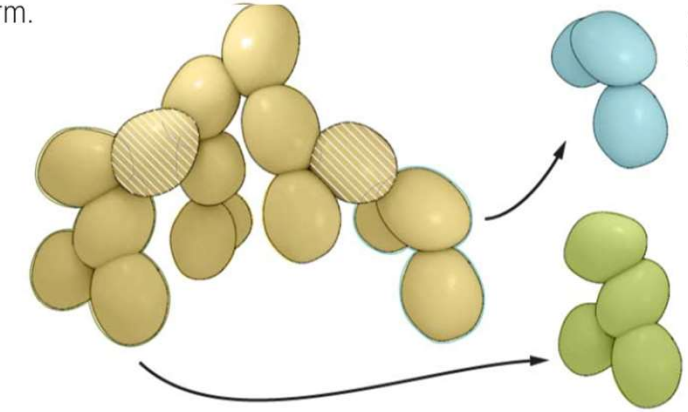
1 Selection

As single yeast cells grow, the larger ones sink faster. Only those cells are allowed to reproduce; repeated rounds of selection result in ever-bigger yeast.



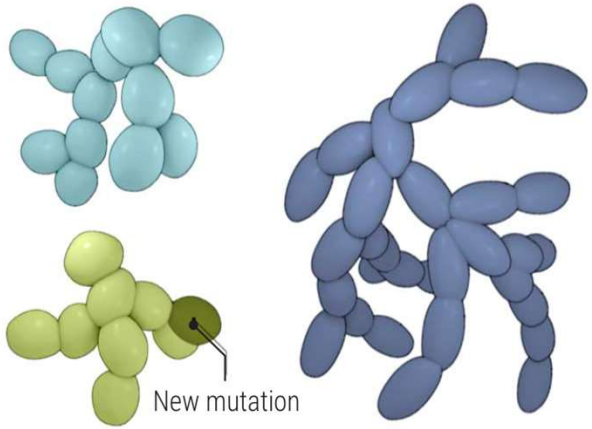
2 Multicellularity

A single mutation causes a reproducing yeast's daughter cells to stick together. Branching snowflake structures form.



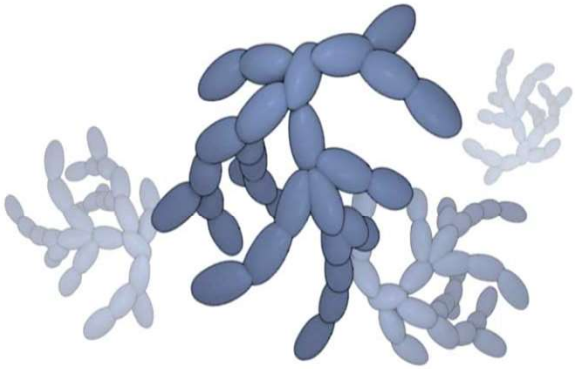
3 Differentiation

A few cells specialize to die early, releasing the cells at the tips of the snowflake to start new snowflakes.



4 Bottleneck

Each freed tip proliferates, and many varieties of multicellular snowflakes form.



5 Group-level selection

Some cell assemblages do better than others and thrive; others do not.

IF MULTICELLULARITY IS SO EASY, WHY DID IT TAKE SO LONG?

- TRADITIONALLY, RESEARCHERS HAVE BLAMED THE EARLY ATMOSPHERE'S LOW OXYGEN LEVELS: TO GET ENOUGH OXYGEN, ORGANISMS NEEDED THE HIGHEST POSSIBLE RATIO OF SURFACE TO VOLUME, WHICH FORCED THEM TO STAY SMALL. ONLY AFTER OXYGEN LEVELS ROSE ABOUT 1 BILLION YEARS AGO COULD LARGER, MULTICELLULAR ORGANISMS ARISE
- IN 2015, HOWEVER, NICHOLAS BUTTERFIELD (UNIVERSITY OF CAMBRIDGE, ENGLAND) PROPOSED THAT LOW OXYGEN LEVELS ACTUALLY FAVORED THE EVOLUTION OF MULTICELLULARITY IN ANCIENT MARINE ORGANISMS
- LARGER, MULTICELLULAR ORGANISMS—WITH MULTIPLE FLAGELLA—WERE BETTER AT SWEEPING WATER PAST THEIR CELL MEMBRANES TO HARVEST OXYGEN
- SCARCE NUTRIENTS IN THE ANCIENT SEAS WOULD HAVE HELPED DRIVE THE NEXT STEP, THE EVOLUTION OF SPECIALIZED CELL TYPES, BECAUSE MORE COMPLEX ORGANISMS CAN HARVEST FOOD MORE EFFICIENTLY

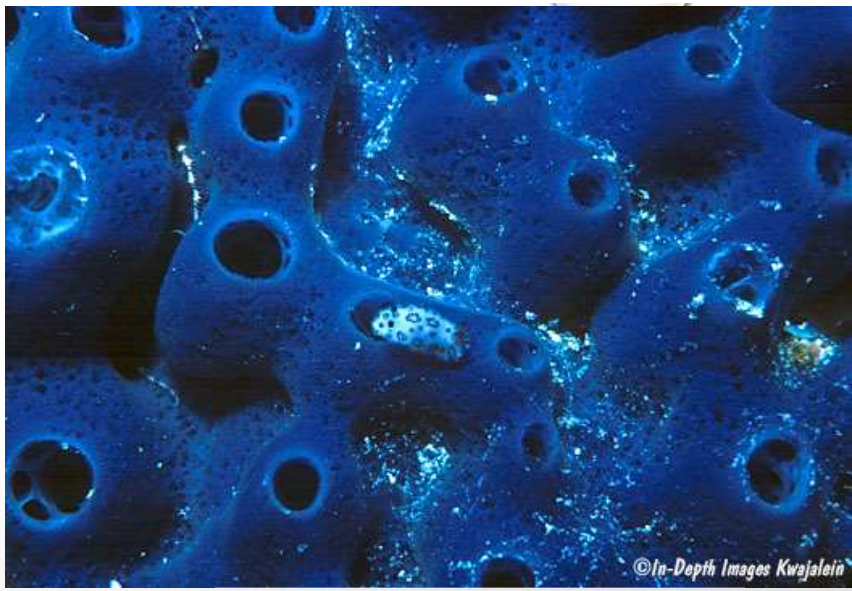
COMPLEX MULTICELLULARITY

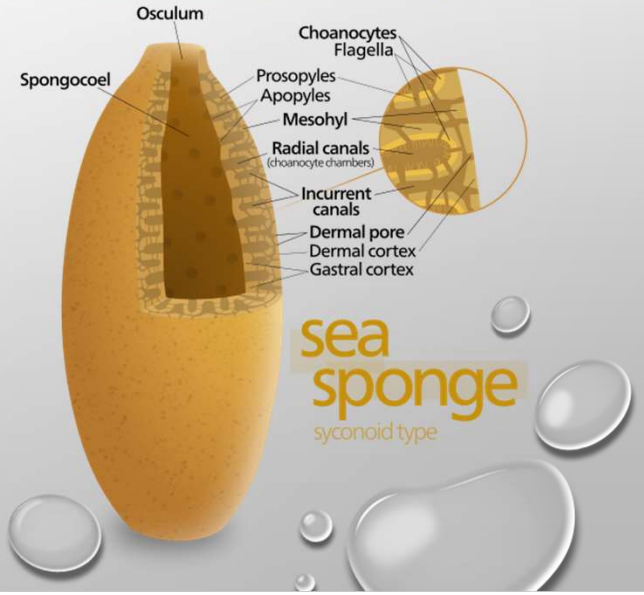
- ALTHOUGH THE TRANSITION TO SIMPLE MULTICELLULARITY MAY BE RELATIVELY EASY, WE DO NOT KNOW MUCH ABOUT THE EVOLUTION OF MULTICELLULAR COMPLEXITY
- WHILE SIMPLE MULTICELLULARITY AROSE MORE THAN 25 TIMES, COMPLEX MULTICELLULARITY HAS ONLY EVOLVED 6 SEPARATE TIMES: ANIMALS, FUNGI, GREEN ALGAE, BROWN ALGAE, RED ALGAE AND LAND PLANTS
- THE FUNDAMENTAL FEATURE OF EUKARYOTES, THEIR DYNAMIC CYTOSKELETAL AND MEMBRANE SYSTEMS, ALLOWS COMPLEX PATTERNS AND MORPOHOLOGIES
- COMPLEX MULTICELLULAR ORGANISMS SHOW NOT ONLY EVIDENCE OF CELL-CELL ADHESION AND INTERACTION, BUT ALSO INTER-CELLULAR COMMUNICATION AND, COMMONLY, TISSUE DIFFERENTIATION
- GENERATING THE DIVERSITY OF FORM AND FUNCTION SEEN IN EUKARYOTIC CELLS REQUIRES SPECIAL MECHANISMS — NAMELY, SOPHISTICATED MEANS OF GENETIC REGULATION AND AN EXPANDED REPERTOIRE OF SYSTEMS TO CONTROL GENE EXPRESSION

- THESE KINDS OF REGULATORY MECHANISMS ARE THOUGHT TO HAVE GIVEN EUKARYOTES A LEG UP IN EVOLVING INTO COMPLEX MULTICELLULAR ORGANISMS
- THE COOPTING OF EXISTING FUNCTIONS TO NOVEL ROLES AND SUBSEQUENT EXPANSIONS WOULD HAVE INCREASED THE REPERTOIRE OF AVAILABLE REGULATORY MECHANISMS

- **CASE IN POINT:**
- IN EUKARYOTES, DNA IN CELLS IS WRAPPED TIGHTLY AROUND PROTEINS CALLED HISTONES, WHICH, IN TURN, ARE PACKED TOGETHER INTO CHROMATIN
- MODIFICATIONS TO THE HISTONE PROTEINS REGULATE GENE EXPRESSION DURING DEVELOPMENT IN ALL ANIMALS, INCLUDING THE MOST ANCIENT — SPONGES

- BY ANALYZING HISTONE MODIFICATIONS IN A MORPHOLOGICALLY-SIMPLE, EARLY BRANCHING ANIMAL, THE SPONGE *AMPHIMEDON QUEENSLANDICA*, IT WAS SHOWN THAT THE REGULATORY LANDSCAPE USED BY COMPLEX ANIMALS WAS ALREADY IN PLACE AT THE DAWN OF ANIMAL MULTICELLULARITY
- THIS INCLUDES DNA SEQUENCES THAT ACT TO ENHANCE GENE TRANSCRIPTION, CHROMATIN STRUCTURE REFRACTIVE TO TRANSCRIPTION, AND TRANSCRIPTIONAL UNITS MARKED BY SEQUENCES THAT PROMOTE GENE ACTIVATION THAT VARY WITH LEVELS OF DEVELOPMENTAL REGULATION
- THESE RESULTS SUGGEST THAT THE REGULATORY FOUNDATION FOR SPATIOTEMPORAL GENE EXPRESSION EVOLVED PRIOR TO THE DIVERGENCE OF SPONGES AND METAZOANS, AND WAS NECESSARY FOR THE EVOLUTION OF ANIMAL MULTICELLULARITY





AN EVOLUTIONARY RATCHET

- ONCE ORGANISMS HAD CROSSED THE THRESHOLD TO MULTICELLULARITY, THEY RARELY TURNED BACK
- THE NUMBER OF TYPES OF CELLS AND ORGANS CONTINUED TO GROW, AND THEY DEVELOPED EVER-MORE-SOPHISTICATED WAYS TO COORDINATE THEIR ACTIVITIES
- THIS DROVE EVOLUTION TOWARDS THE MORE SOPHISTICATED GENE REGULATION NEEDED FOR MULTICELLULARITY
- A RATCHETING EFFECT TOOK OVER, DRIVING AN INEXORABLE INCREASE IN COMPLEXITY → THE MORE SPECIALIZED AND DEPENDENT ON ONE ANOTHER THE CELLS OF COMPLEX ORGANISMS BECAME, THE HARDER IT WAS TO REVERT TO A SINGLE-CELL LIFESTYLE

GENETIC CONFLICTS IN MULTICELLULARITY

- THE ADVANTAGES OF MULTICELLULARITY DEPEND UPON COOPERATION AMONG CELLS, BUT COOPERATION INVITES CHEATING
- KIN SELECTION THEORY PREDICTS THAT COOPERATION AMONG CELL LINEAGES WILL BE FAVORED WHEN THERE IS GENETIC RELATEDNESS
- RECENT DESCENT OF ALL CELLS BY CLONAL DEVELOPMENT FROM AN ANCESTRAL UNICELL PROVIDES THE GREATEST ASSURANCE OF HIGH RELATEDNESS (THINK FERTILIZED EGG)
- SELECTION CAN THEN FAVOR GENES THAT RESULT IN SOME CELLS OF THE ORGANISM CEASING DIVISION (OR DYING) TO ENHANCE SURVIVAL AND REPRODUCTION OF THE REMAINING CELLS THAT CONSTITUTE THE ORGANISM

CANCERS: A FAILURE OF MULTICELLULARITY

- WHEN AN ORGANISM MAKES THE LEAP TO MULTICELLULARITY, IT MUST EVOLVE GENE REGULATORY NETWORKS TO ENSURE ITS CELLS STOP DIVIDING AT THE APPROPRIATE TIME AND FUNCTION IN STEP WITH THEIR NEIGHBORS
- CANCERS CONSTITUTE THE CLEAREST EVIDENCE FOR ROGUE CELL LINEAGES IN CLONAL DEVELOPERS
- IN CANCER, MUTATIONS THAT CRIPPLE THE NETWORKS CAUSE THOSE CONSTRAINTS TO BREAK DOWN
- CANCERS SEEM TO UNDO THE MOLECULAR CONSTRAINTS AND CONTROLS THAT EVOLVED TO ENABLE MULTICELLULAR LIFE

A TANTALIZING NOTION

- **CANCEROUS CELLS REWIND THE EVOLUTIONARY CLOCK AND REVERT TO ACTING LIKE UNICELLULAR LIFE**
- RECENTLY, DAVID GOODE (MACCALLUM CANCER CENTRE, MELBOURNE, AUSTRALIA) AND COLLEAGUES HAVE FOUND EVIDENCE TO SUPPORT THAT IDEA
- THEY EXAMINED GENE EXPRESSION IN SEVEN TYPES OF SOLID TUMORS—INCLUDING BREAST, STOMACH, AND LIVER CANCERS—AND TRACED THE ANCESTRY OF THE ACTIVE GENES THEY FOUND
- GENES THAT DATE ALL THE WAY BACK TO EARLY SINGLE-CELLED EUKARYOTIC ORGANISMS WERE UP-REGULATED
- IN CONTRAST, GENES UNIQUE TO MANY-CELLED ANIMALS WERE INACTIVATED