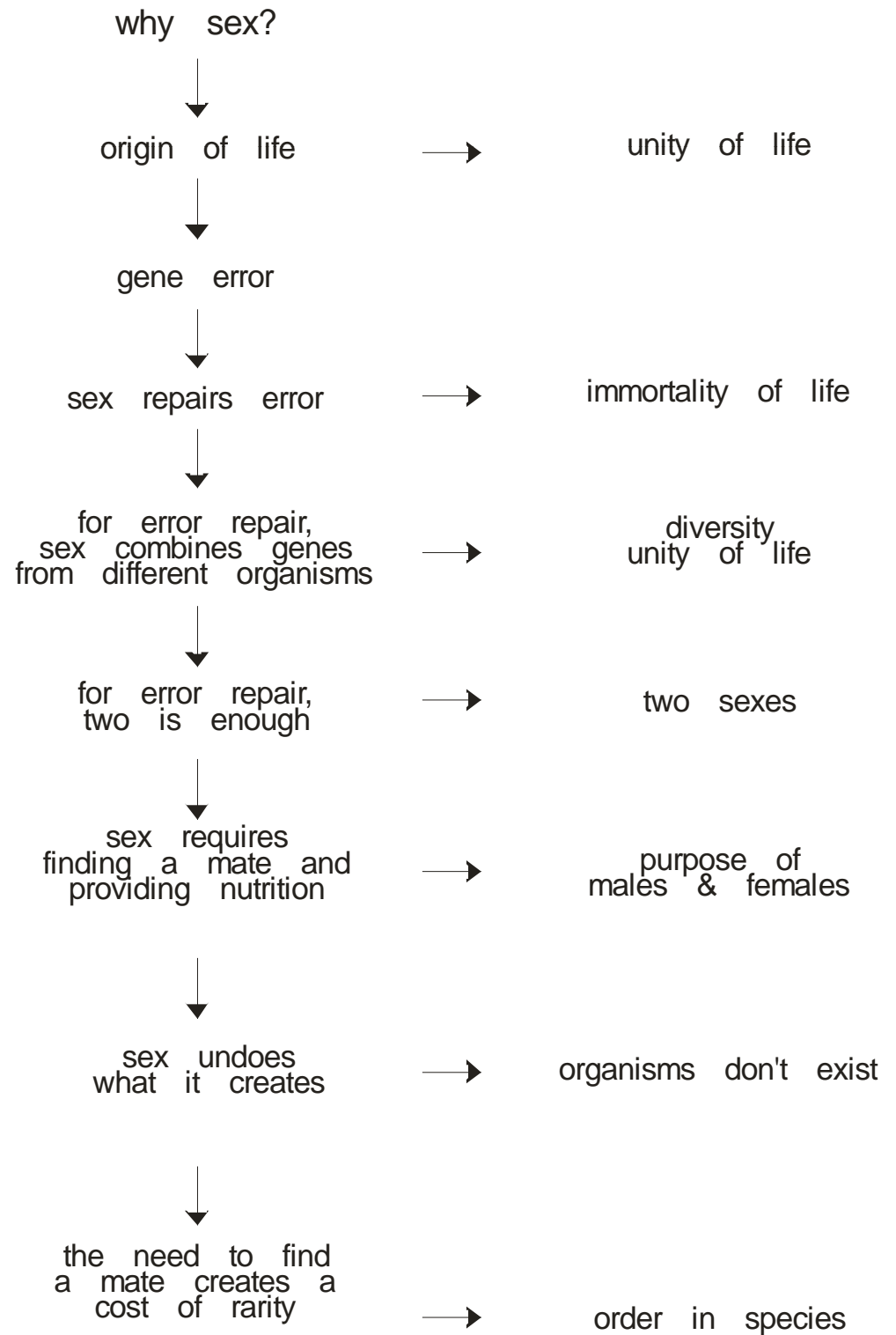
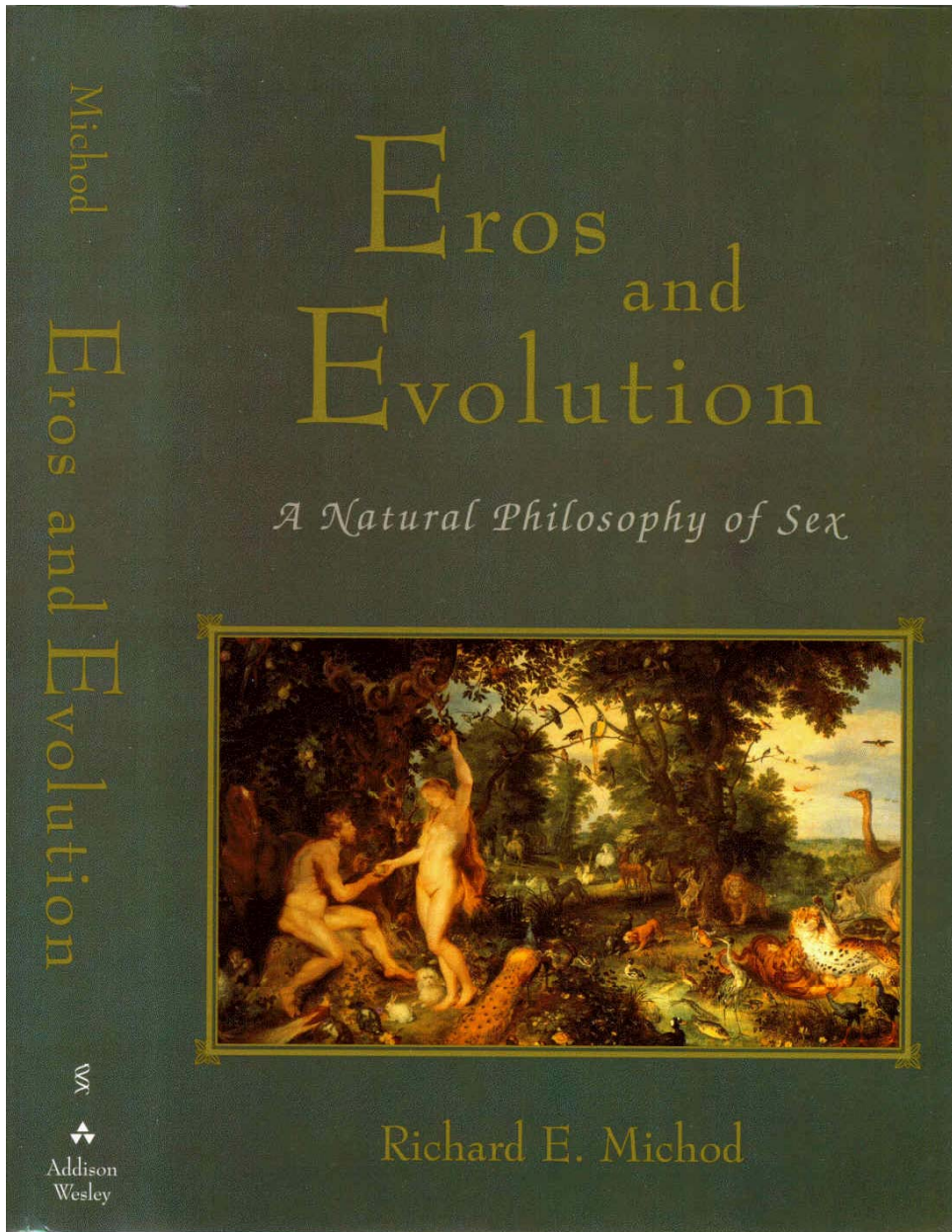


Plan of my lectures

- Cooperation and conflict in evolution
 - Monday
 - Molecules to societies
 - Multicellularity
 - Sunday
 - Teaching of biology (10:30am)
 - NSF high school teacher internship in our lab
 - Sex & immortality of life (4:30pm)

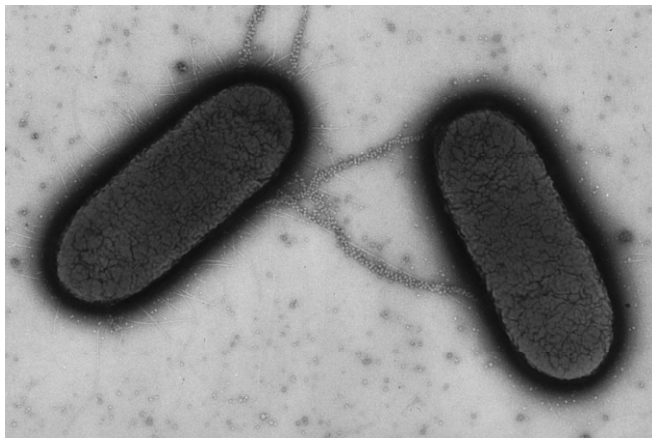


Plan of talk

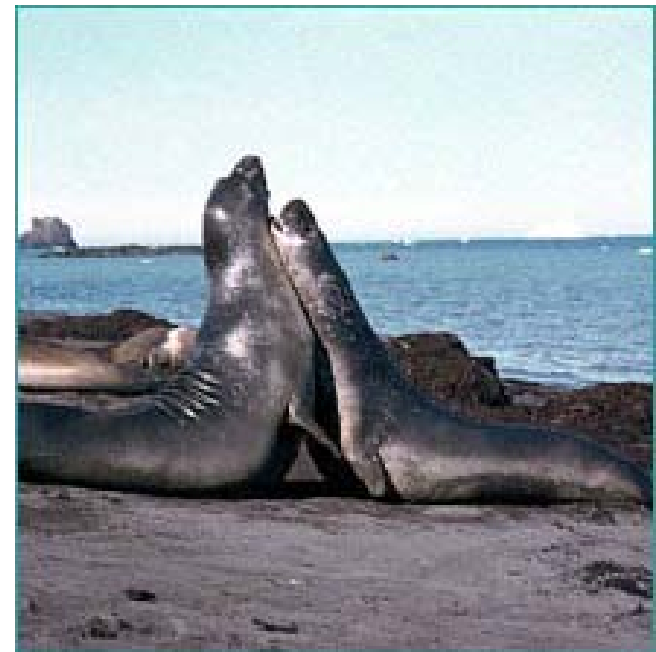
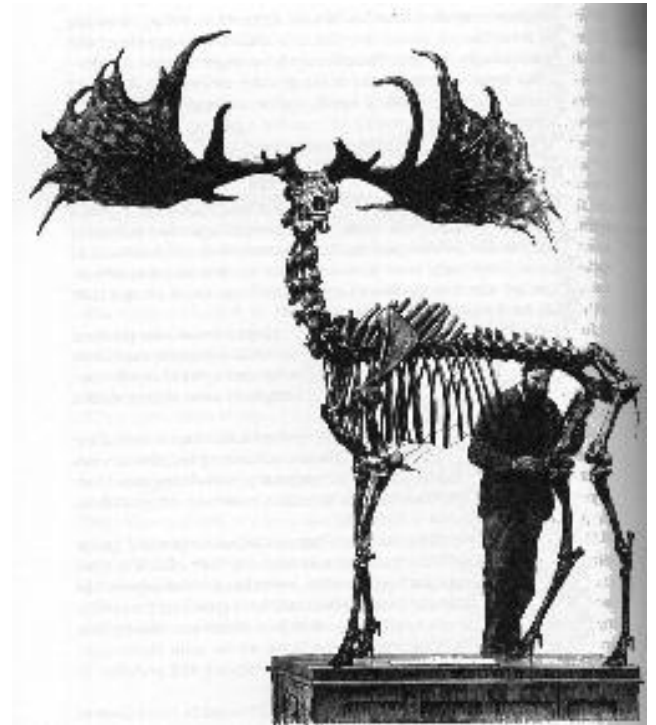
- Paradox of sex
- Variation
- Aging and DNA damage
- Origin of life
- DNA repair hypothesis
- Testing DNA repair hypothesis
 - Facultative sex
 - Sex in viruses
 - Sex in bacteria
 - Sex in multicellular eukaryotes
 - Sex in unicellular eukaryotes
- Sex as an ETI
- Sex and species
- Wrap up

What is Sex?

- Universal definition
 - Recombination
 - Outcrossing (mating)
- Mixing of genes
- Why sex?



Sex is costly

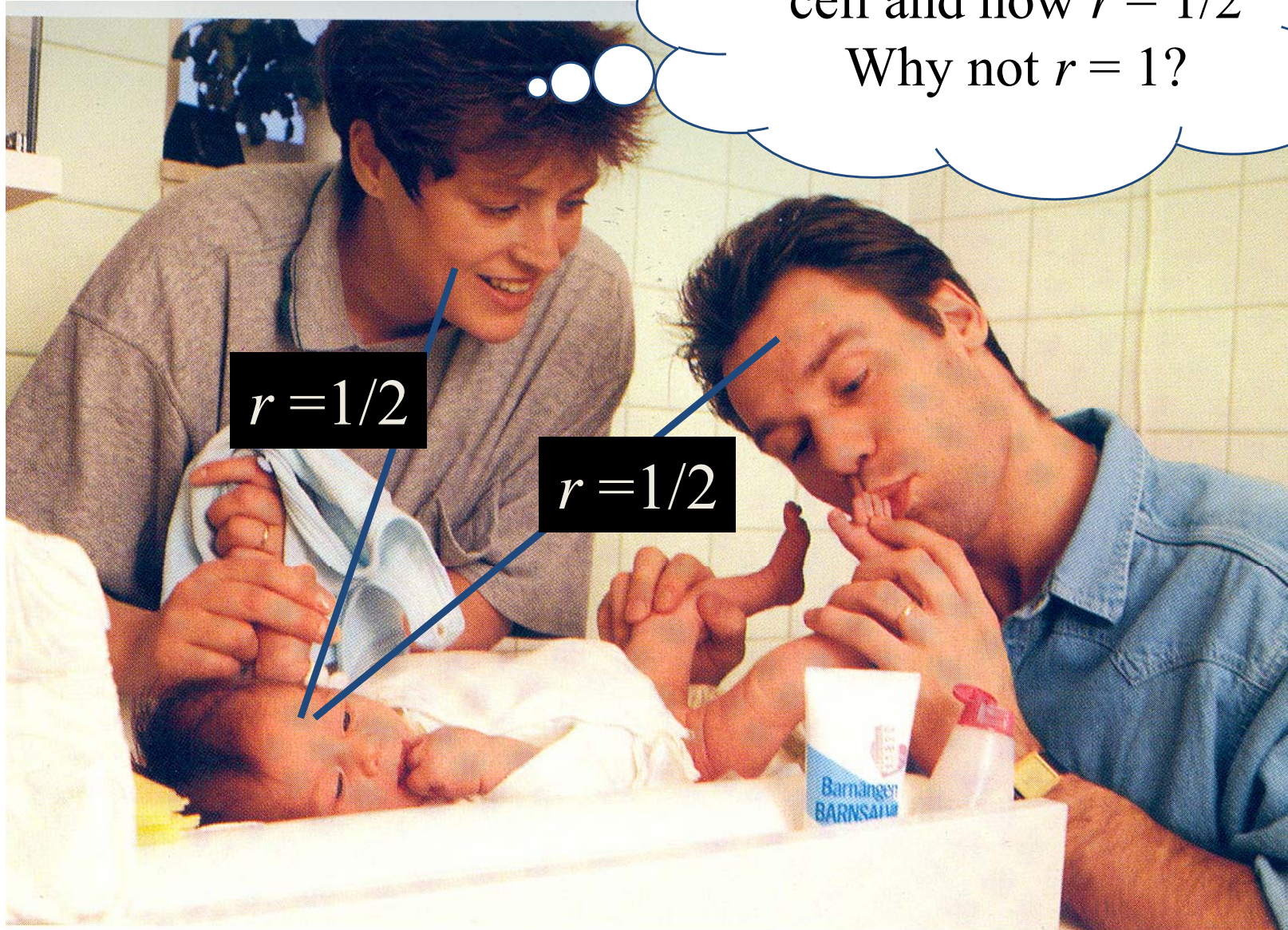


Parasites are a cost of sex

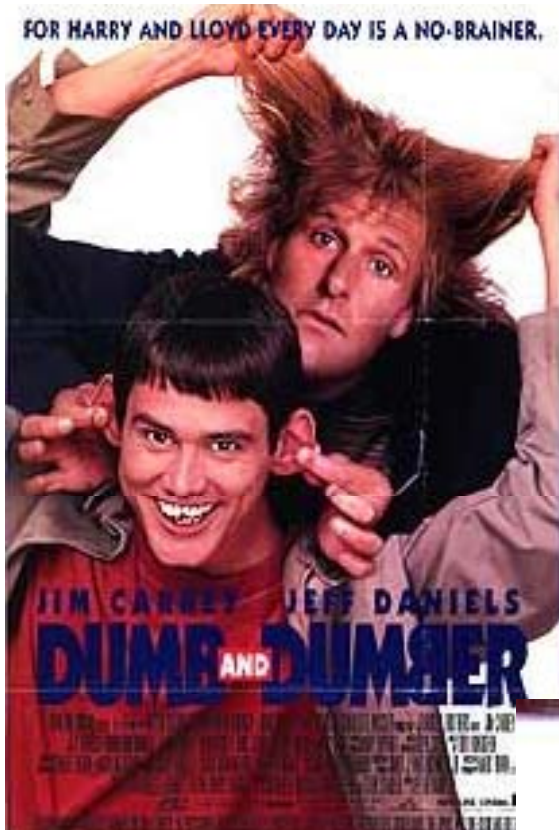
- Sexually Transmitted Diseases
 - Syphilis
 - Gonorrhea
 - Chlamydia
 - Genital herpes
 - Genital warts
 - Hepatitis B
 - AIDS
- Unfortunately, this makes perfect sense to the parasite

Genetic costs

He gave me just 1 cell and now $r = 1/2$
Why not $r = 1$?



Cost of males



Adults
time = t

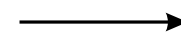
Eggs

Adults
time = $t+1$

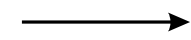
Asexual

♀ ♀

n



kn

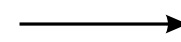


skn

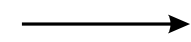
Sexual

♀ ♀

N



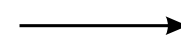
$\frac{1}{2}kN$



$\frac{1}{2}skN$

♂ ♂

N



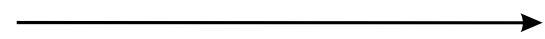
$\frac{1}{2}kN$



$\frac{1}{2}skN$

Frequency Asexual:

$$\frac{n}{2N+n}$$



$$\frac{n}{N+n}$$



Paradox of sex

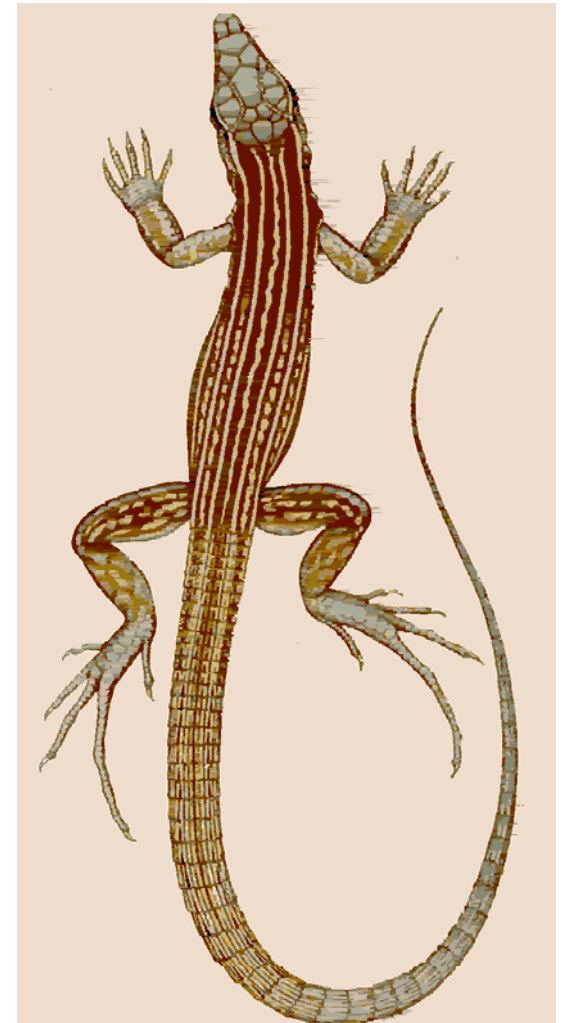
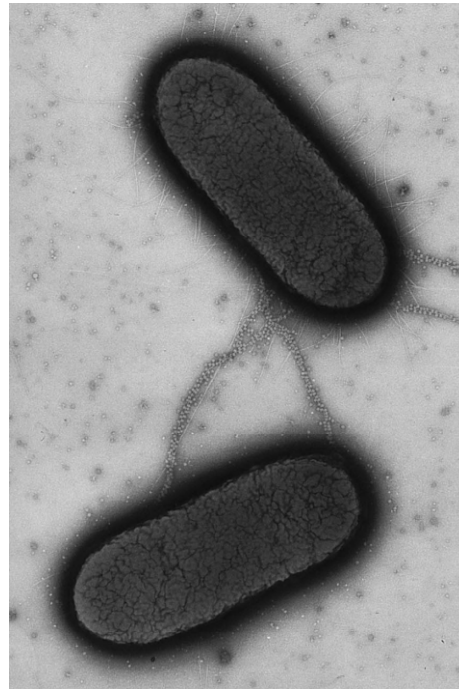
- Sex is costly
- Benefits are small or unclear
- Sex is common

Why is there sex?



Sex and Reproduction

- Reproduction without sex
- Sex without reproduction



Mouse Born Without Father

- Parthenogenesis
- Parthenogenesis does not occur in mammals because of genetic imprinting
- Meet Kaguya!

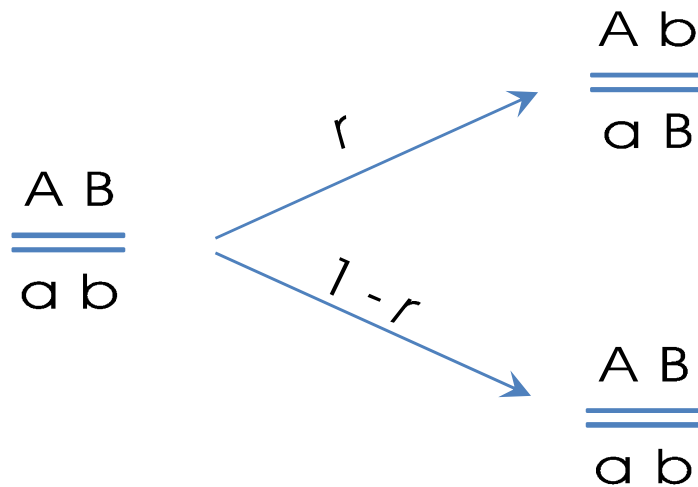


What are the benefits of sex?

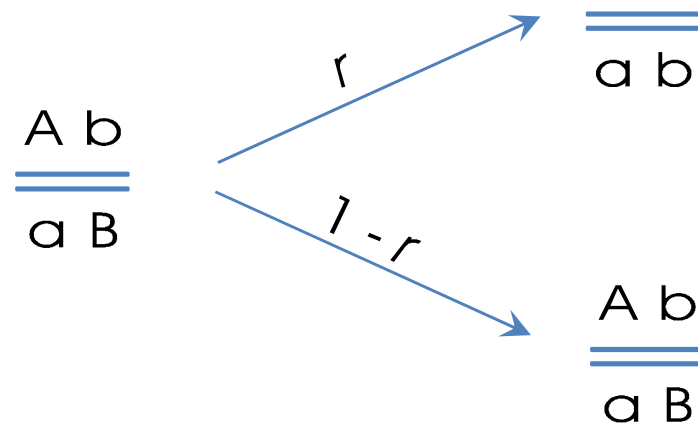
- Sex not necessary for reproduction
- Variation
- Rejuvenation
- Evolutionary biologists disagree
- The benefits are unclear
- Sex induced by stress



VARIATION



r is the probability of recombination



Variation

- Necessary for evolution
- Sex
 - Mixes
 - Reduces non-random associations between alleles at different loci
 - Paint bucket analogy
- Problems
 - Sex undoes what it creates
 - Cryptic recombination
 - What creates non-random associations
 - Need good genes associated with bad genes

Variation: Changing Environments

- Lottery model
 - lottery of life is the randomness of the environment
 - never know in what environment your offspring will end up
 - lottery ticket is your offspring--it's traits and genes
 - buy 100 tickets (= offspring)
 - "winning ticket" is that particular combination of traits (genes) most suited to the environment
- If entering one lottery,
 - it is better if the tickets have different numbers on them
 - sex = lottery tickets have different numbers
 - asex = lottery tickets all have the same number
- What if you are entering a 100 different lotteries?
 - then 100 tickets with same number may be just as good as 100 tickets with different numbers
 - not clear if sex is any better in this case

Variation

- Sibling competition
 - Sex is a good thing if your offspring enter the same lottery
 - Offspring must settle close to each other, so that they compete. Sex is useful then.
- Sex just mixes alleles at different loci
 - Sex undoes what it creates
 - An analogy: stirring a bucket of paint in which pigment has settled, after a while more stirring isn't useful

DNA DAMAGE AND AGING

Sex and Rejuvenation

- Babies are young
- How can two adults (old) produce babies (young)?
- Sex and rejuvenation
- Weismann (1886) dismissed idea: "Twice nothing cannot make one"
- Look to the workings of DNA

Aging

- General
 - impairment of function
 - inherent
 - progressive
- Specific
 - reduction of transcription
 - reduction of protein synthesis
 - reduction of cell viability
 - loss of tissue function
 - reduction in cell division rate

Evolution of aging

- Pleiotropic genes
 - beneficial effect early in life
 - deleterious effect late in life
- Genes with early benefits are favored by natural selection
 - Even if they have deleterious effects later in life
 - Early benefits are like compound interest in the bank
- DNA damage and DNA repair genes are likely causes of aging

Correlation of life span and DNA repair capacity

Hart and Setlow, 1974, PNAS
72:2169-2173.

unscheduled DNA synthesis
fibroblast cells

Fig. 5 of Hart and Setlow

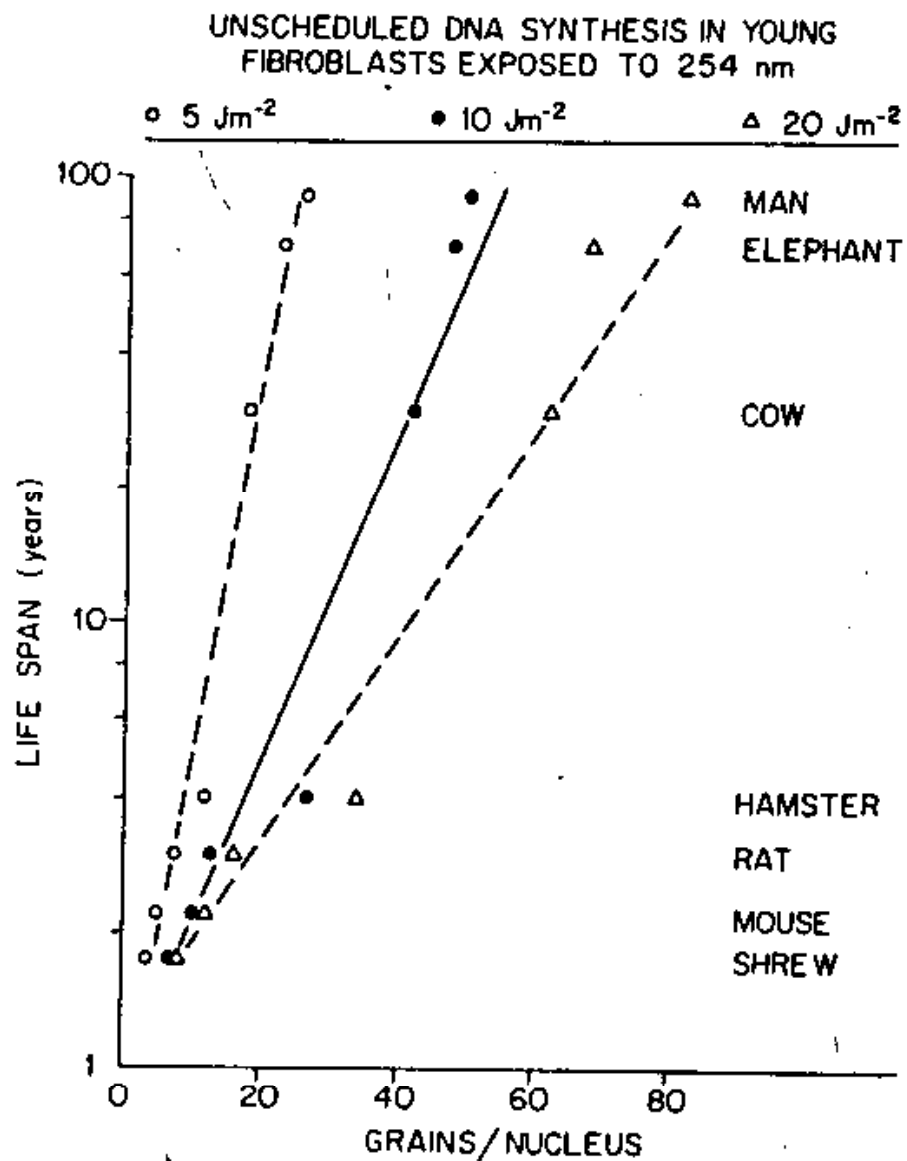


FIG. 5. A correlation between the amount of unscheduled DNA synthesis measured at 13 hr after exposure to several UV fluences and the estimated life-span of the species.

Aging in Paramecium

- Reproduction is asexual but sex occurs during conjugation
- In asexual culture
 - fission rate slows down and line dies out; fissions/day ---> 1 fission/day ---> death of cell line; max 200 divisions total
- Aging correlates with damage
 - mean size of DNA in macronucleus dec. with aging
 - mean size of DNA goes from 300 kb ---> 12 kb
- Sex, even selfing, rejuvenates the culture

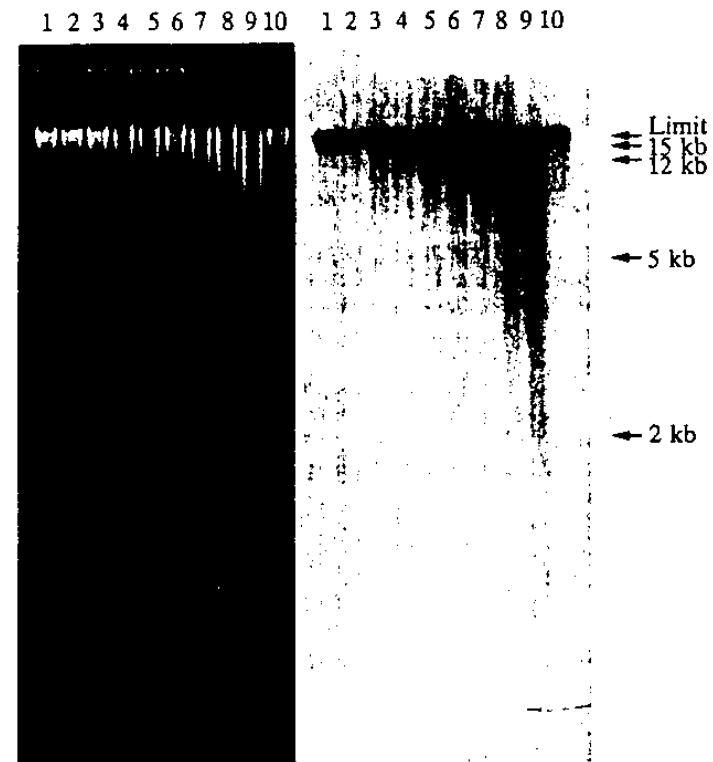


FIG. 2. Progressive breakage of aged DNA without loss of telomeric sequences. (A) Total genomic DNA from d48 cell line 3 at incremental points of aging resolved on a 1.0% agarose gel stained with ethidium bromide. Note that DNA greater than ≈ 20 kb will migrate as a compact band at the limit mobility (marked "limit"). Lanes and days postautogamy: 1, 4 days; 2, 7 days; 3, 17 days; 4, 23 days; 5, 30 days; 6, 37 days; 7, 45 days; 8, 60 days; 9, 66 days; 10, 4 days. (B) DNA transferred to nylon and probed with a ³²P 5'-end-labeled (C₄A₂)₄ *Paramecium* telomeric oligonucleotide.

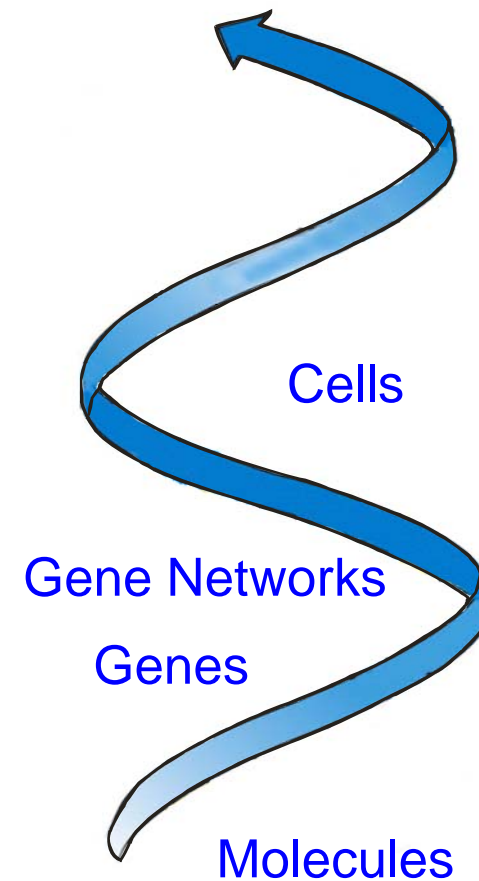
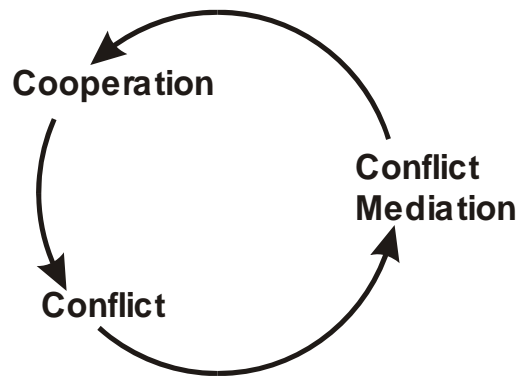
Aging

- Somatic line ages
- Germ line is immortal
- How is this possible?

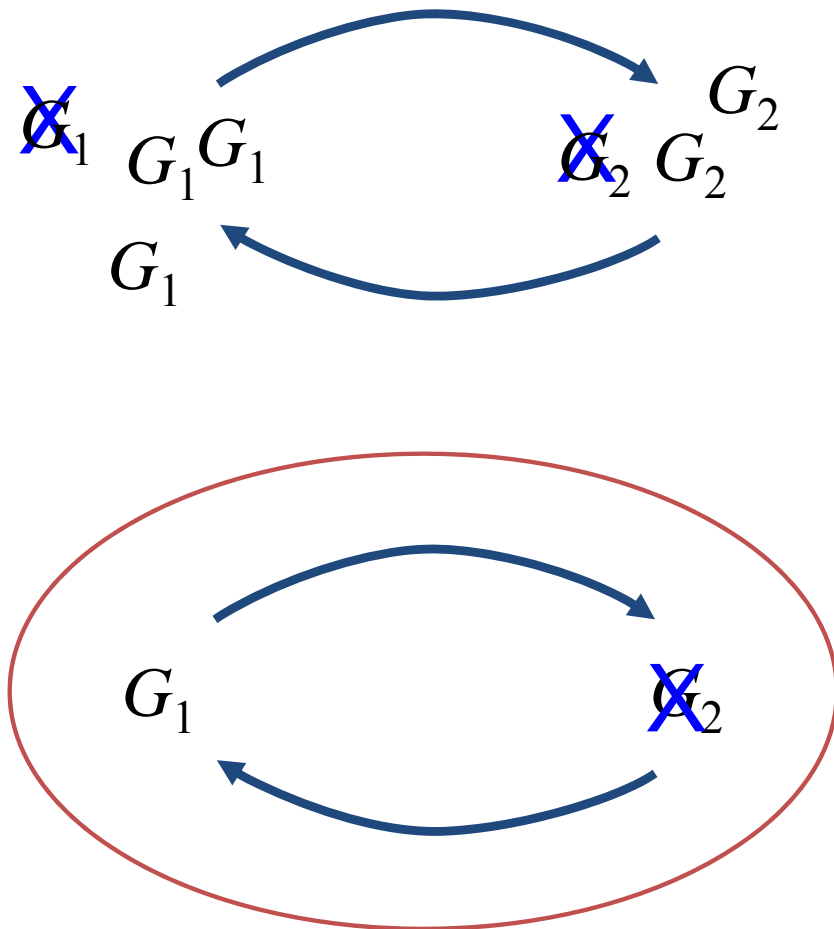
ORIGIN OF LIFE

The First Individuals Were...

- Molecular Replicators
- Cooperative Groups of Replicators
- The First Cell



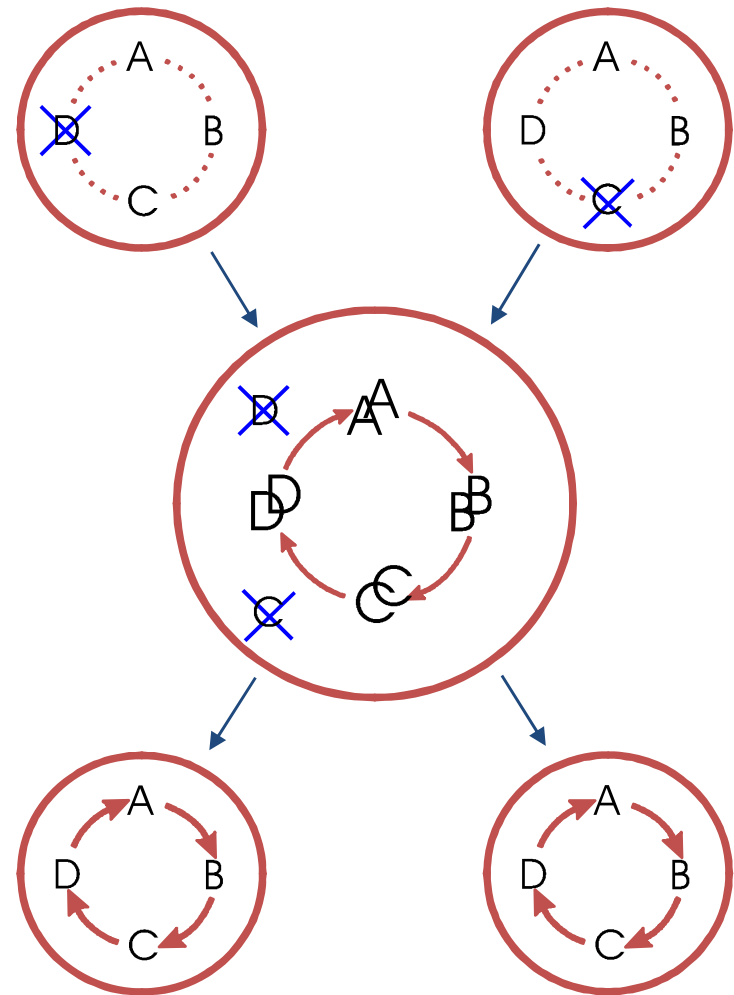
Sex in Cooperative Gene Networks



- Recall cooperative networks of genes
- Advantage of mixing and gene repair
- Living world born sexual
- Evolution of the cell
- Errors trapped
- Sex had to be reinvented

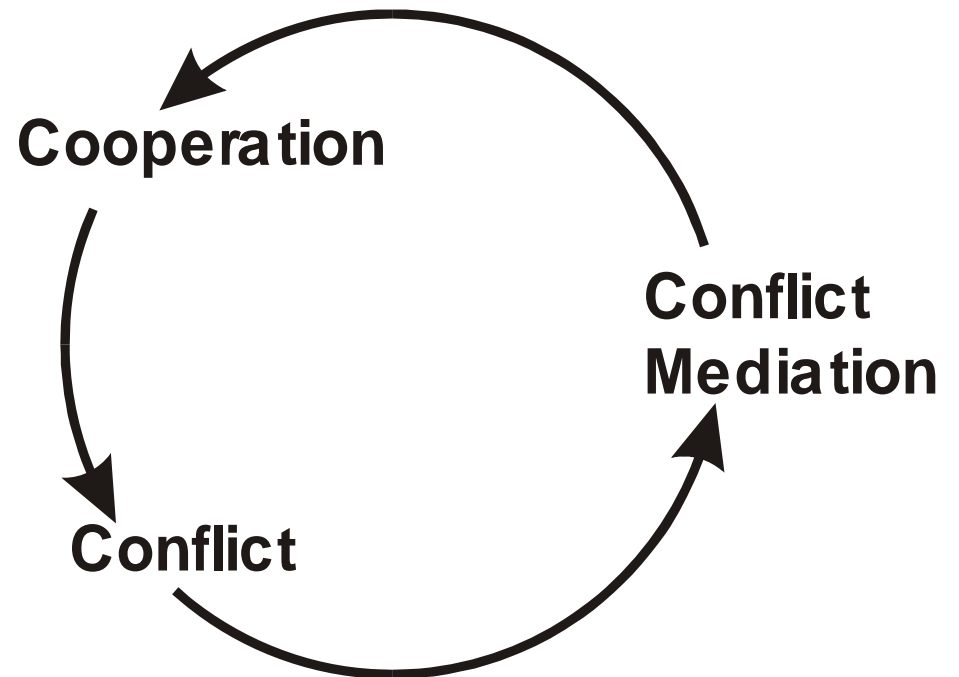
Sex Rejuvenates Life

- Sex repairs DNA damage
- Sex copes with deleterious mutation
 - Masking
 - Removal (repair)
- Healthy genes
 - in offspring
- Rejuvenation of life



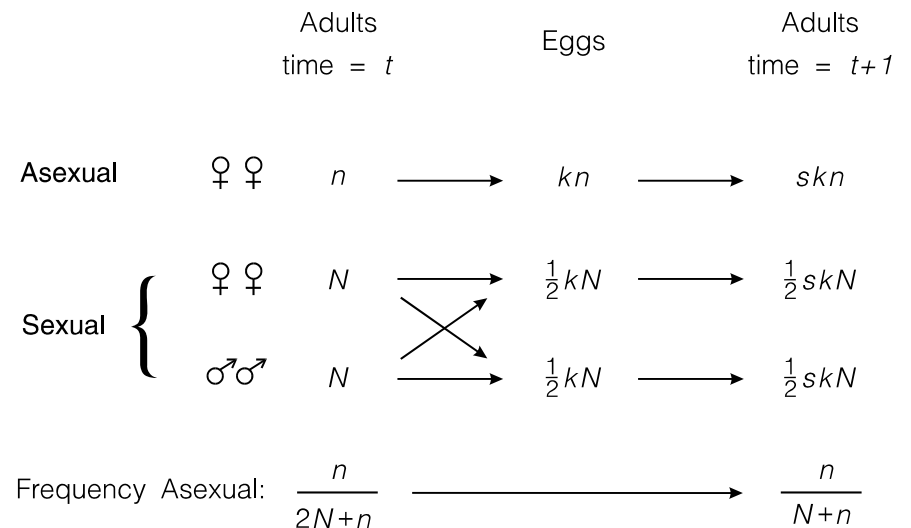
Sum Up: Origin of Life

- Single gene
 - Replication Error
- Cooperative gene networks
 - Sex came easy
 - Cheating
- Cell
 - Errors trapped
 - Sex reinvented



The Paradox of Sex Is That It Is Common But It Is Costly

- Sex is costly
 - Mating
 - Males
 - Meiosis
 - Infection
 - Rarity



- Sex is common
- What are the benefits of sex?

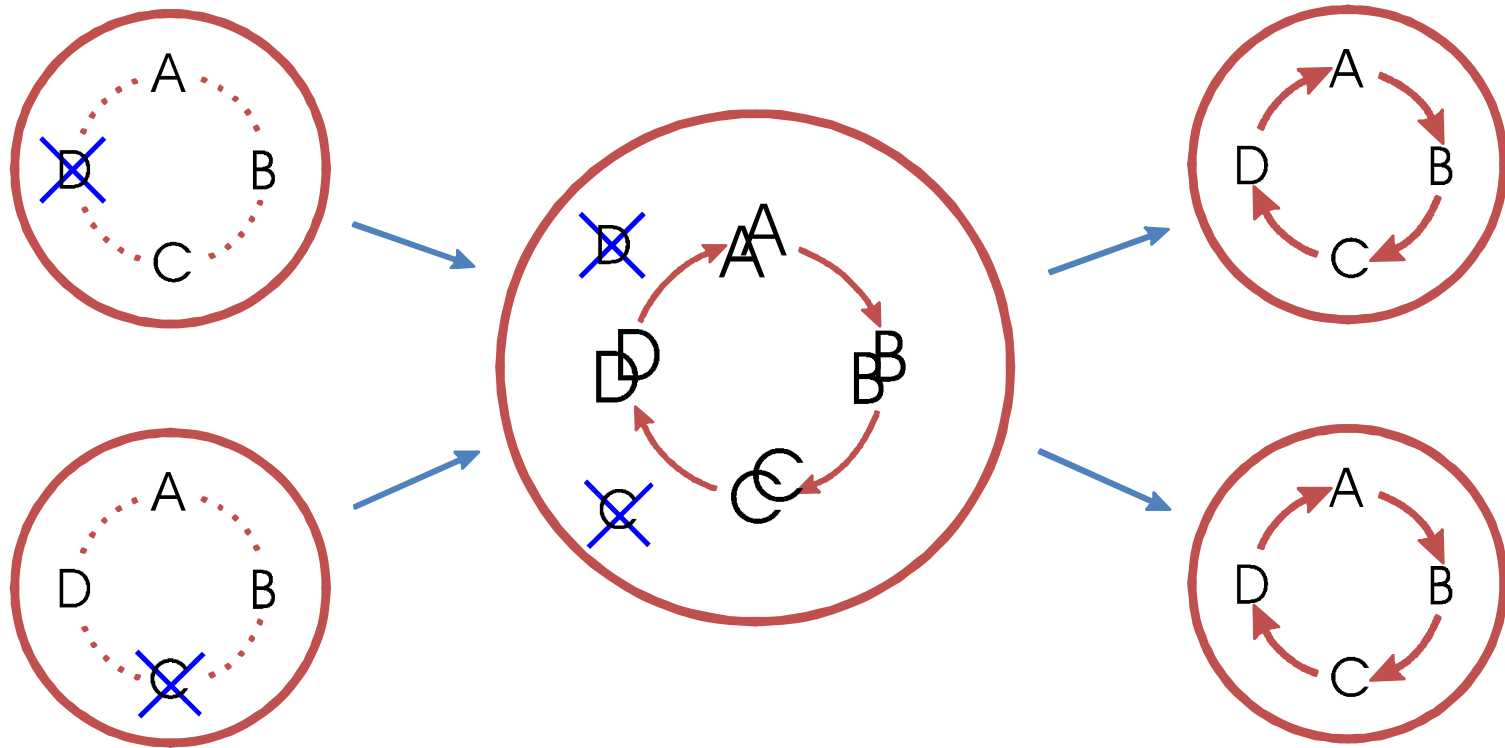
DNA REPAIR HYPOTHESIS

Individuality Traps Errors



Sex had to be reinvented

Origin of Sex for Error Repair



Sex as repair is a kind of cooperation

DNA repair hypothesis



- DNA is a complex and unstable molecule
- Maintaining the integrity of the information in DNA is a fundamental problem for life
- During homologous recombination, DNA repair occurs, so DNA repair could be the adaptive value of sex

Errors in Information Transfer

- mutation
 - replicated
 - not repaired
- damage
 - not replicated
 - repaired

Coping with Errors

- Avoidance
- Masking
- Selection
- Repair
 - must be able to recognize the error
 - must have a backup copy (spare part)

Repair and Recombination

- recombination affects fitness directly

~~recombination~~ → damage sensitive

~~redundancy~~ → damage sensitive

damage → increased recombination

~~non-rec repair~~ → inc damaged induced rec

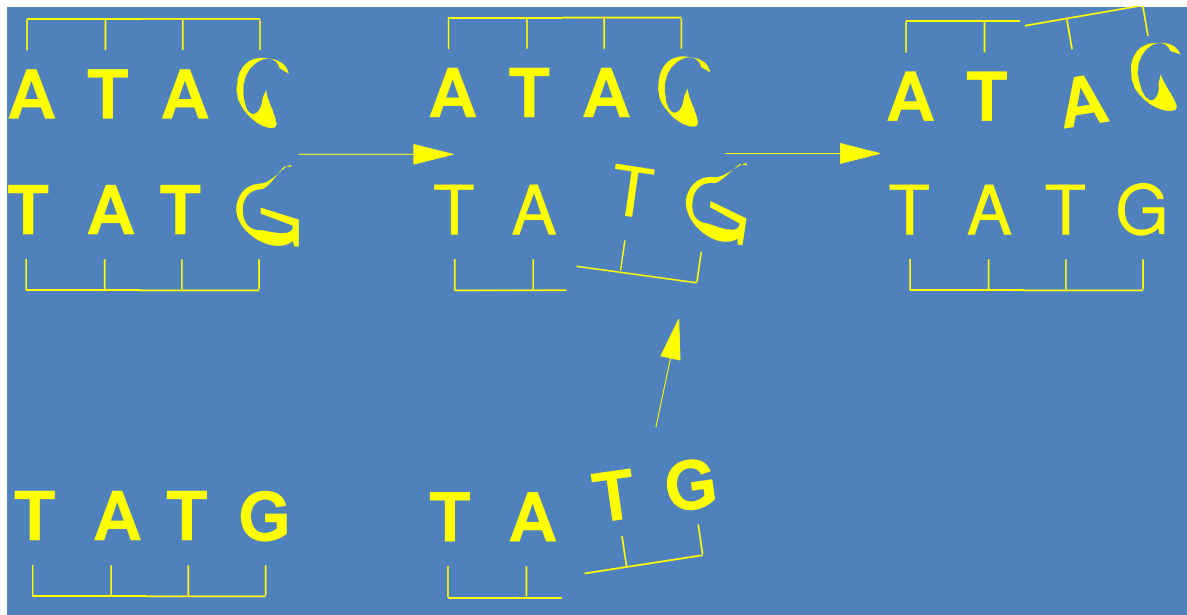
bacteria: rec & repair systems coupled

Benefits of Sex

- Controversial area

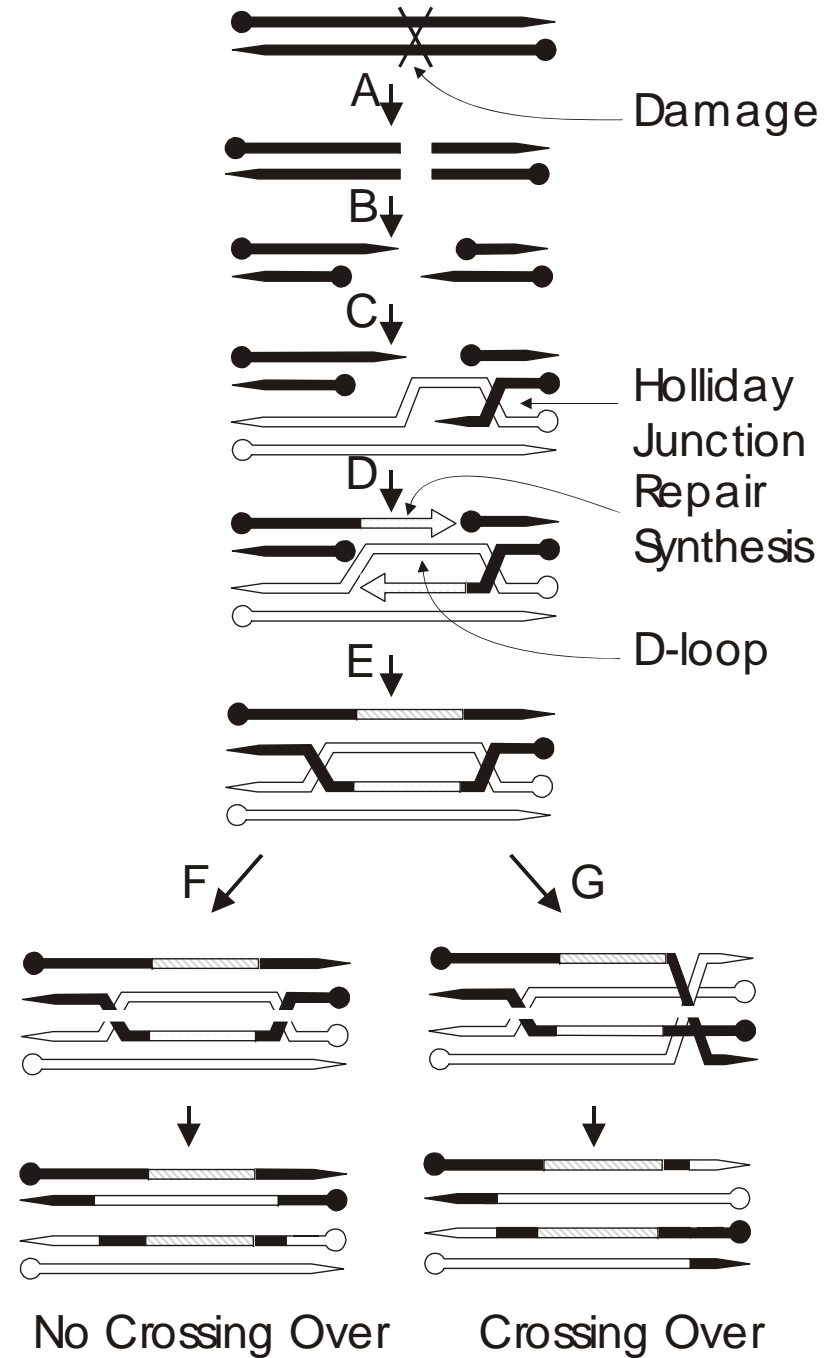
- Agreement

- Variation
- Recombination repairs DNA
- Sex induced by stress



Recombination & Repair

Double Strand Break Repair Model



Testing DNA repair hypothesis for sex

- Facultative sex
- Viruses
- Bacteria
- Eukaryotes
 - Multicellular
 - Unicellular

FACULTATIVE SEX

Facultative Sex and ETIs

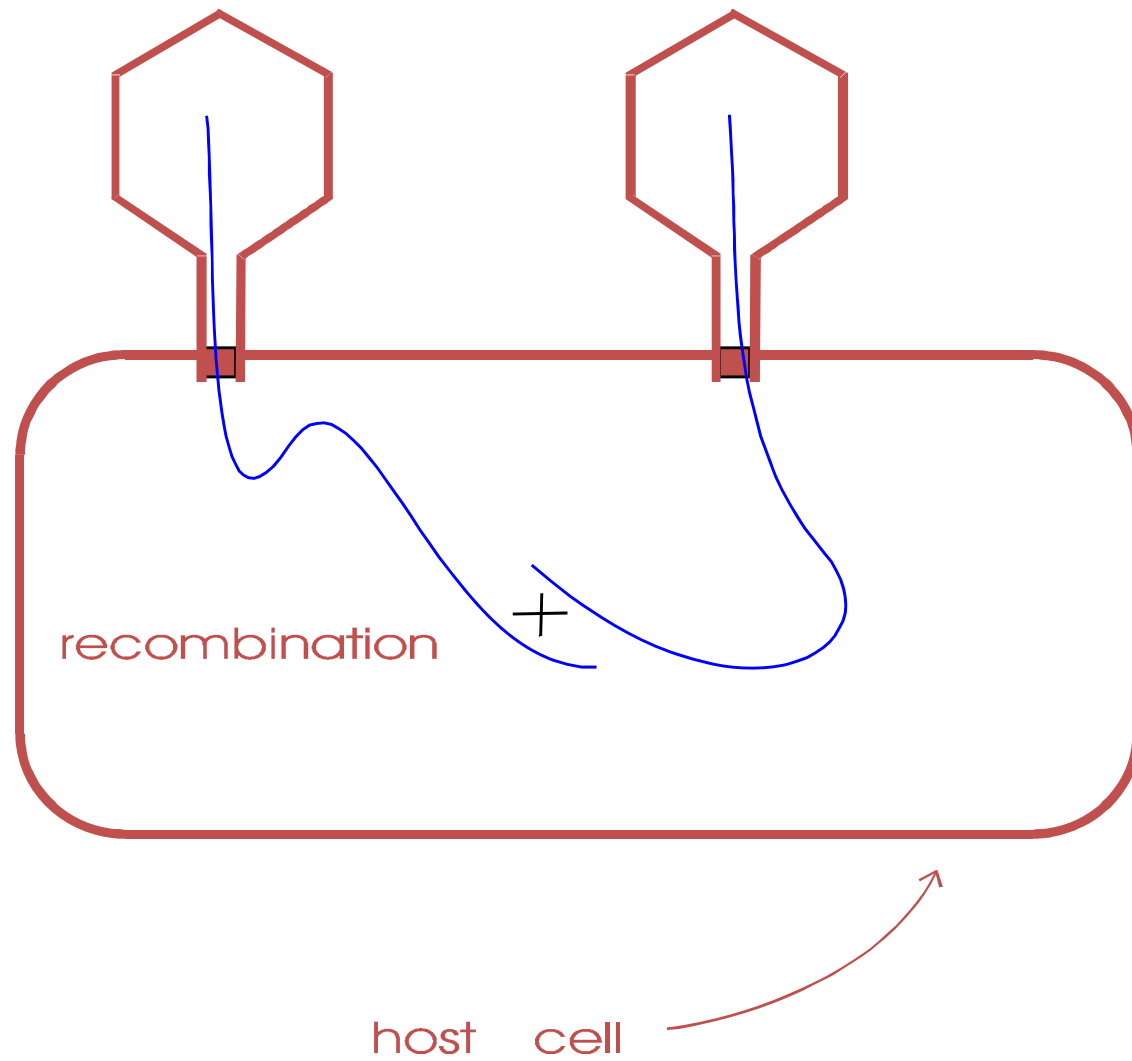
- Facultative sex is special
 - Facultative species are caught part way through the ETI
 - Sex is not necessary for reproduction
 - The transition to sex occurs in real time
 - The transition to sex occurs in response to stress
- For facultatively sexual species, what factors determine *which* mode is used, *when* and *why*?
- Balance Argument: if sex stage not beneficial, evolution would eliminate it

Why Stress and Sex?

- Life requires balance (redox balance)
- Stress upsets redox balance
- Stress creates oxidative compounds (= "ROS")
- ROS are damaging to DNA
- Sex repairs damages and copes with mutation
- Prediction: Primary signal for sex is ROS and ROS-induced DNA damage

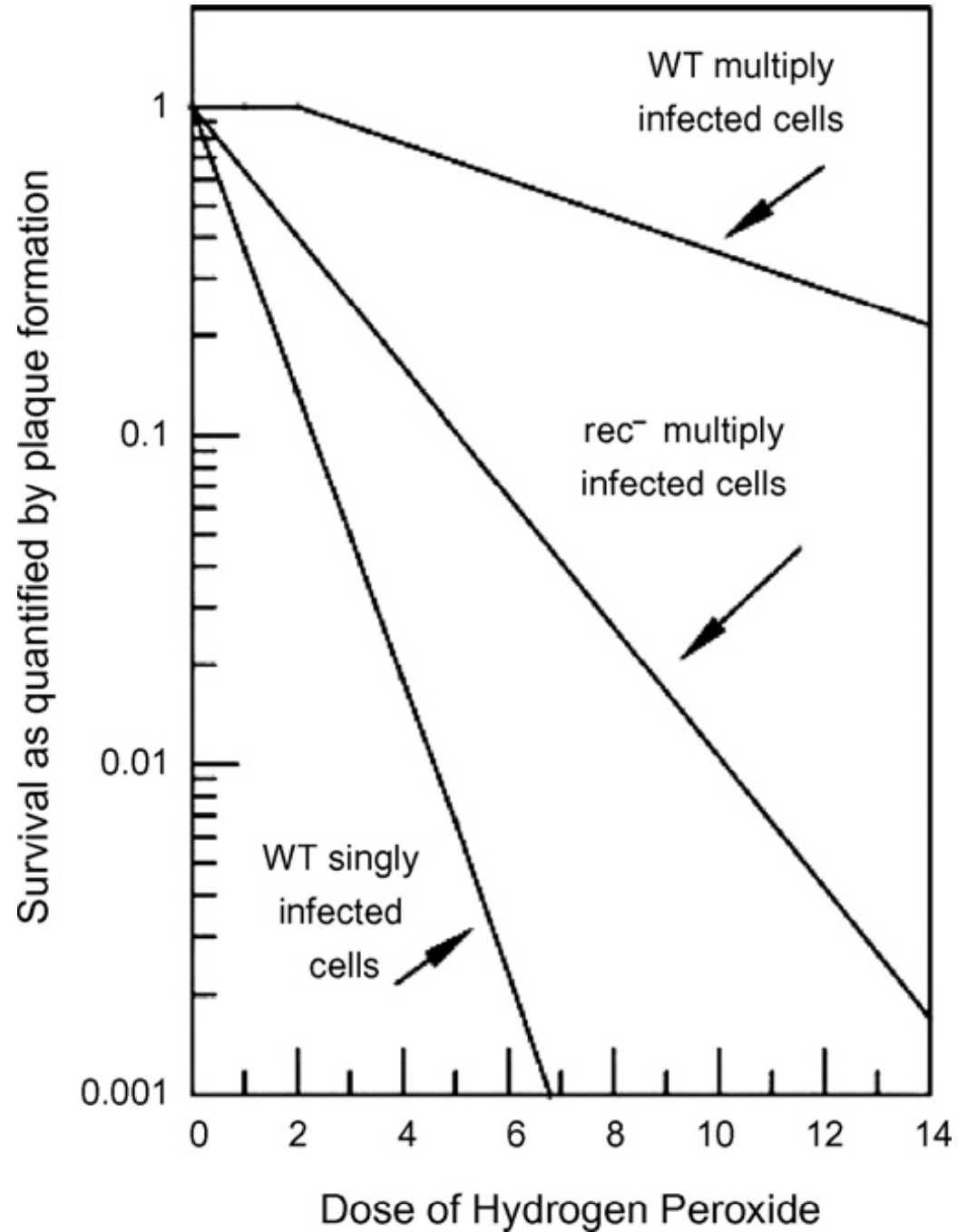
SEX IN VIRUSES

Virus Sex



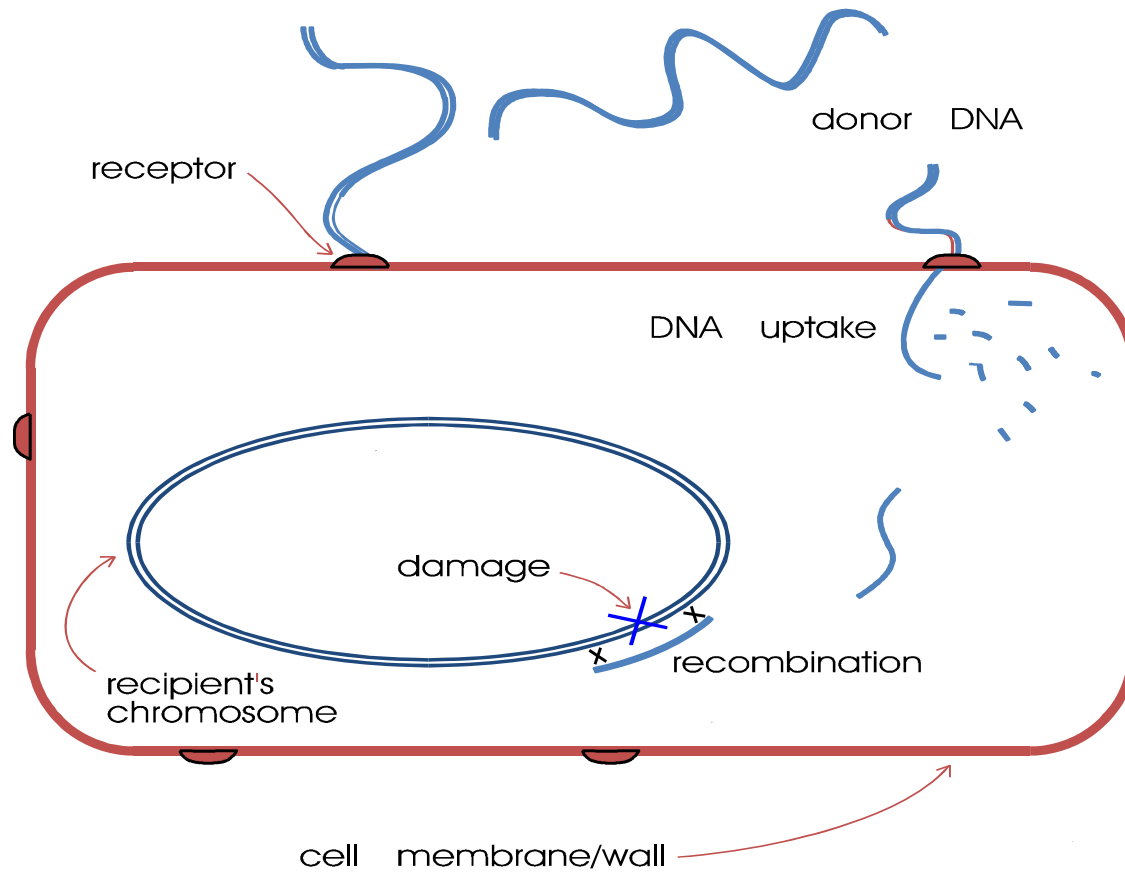
Sex repairs DNA damage in viruses

Fig. 1. Inactivation curves of plaque forming ability of cells singly infected and multiply infected by phage T4 versus dose of H₂O₂. Results are shown for multiple infection by wild-type (WT) phage and by tsL67 mutant phage defective in recombination (rec⁻).



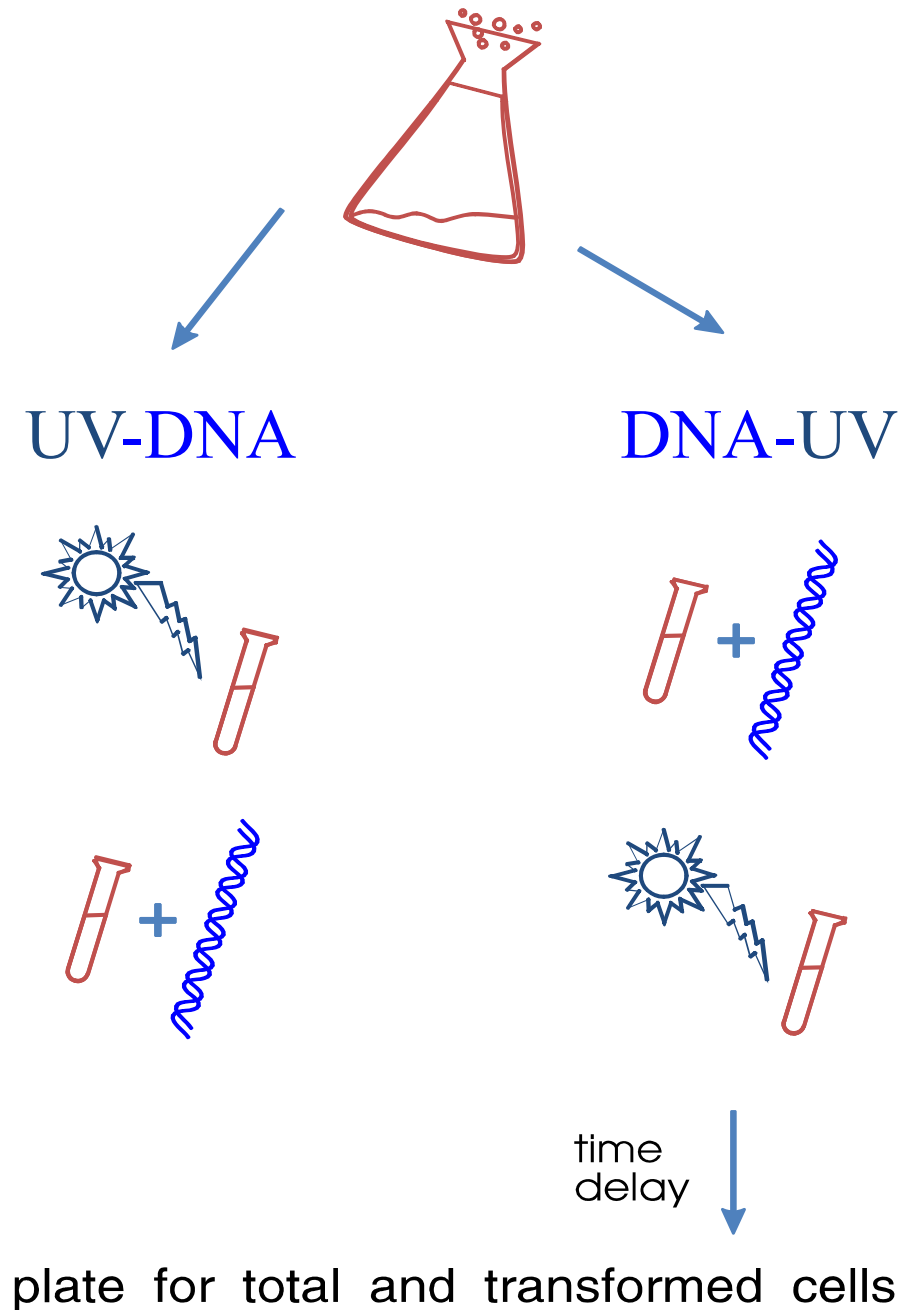
SEX IN BACTERIA

Bacteria sex

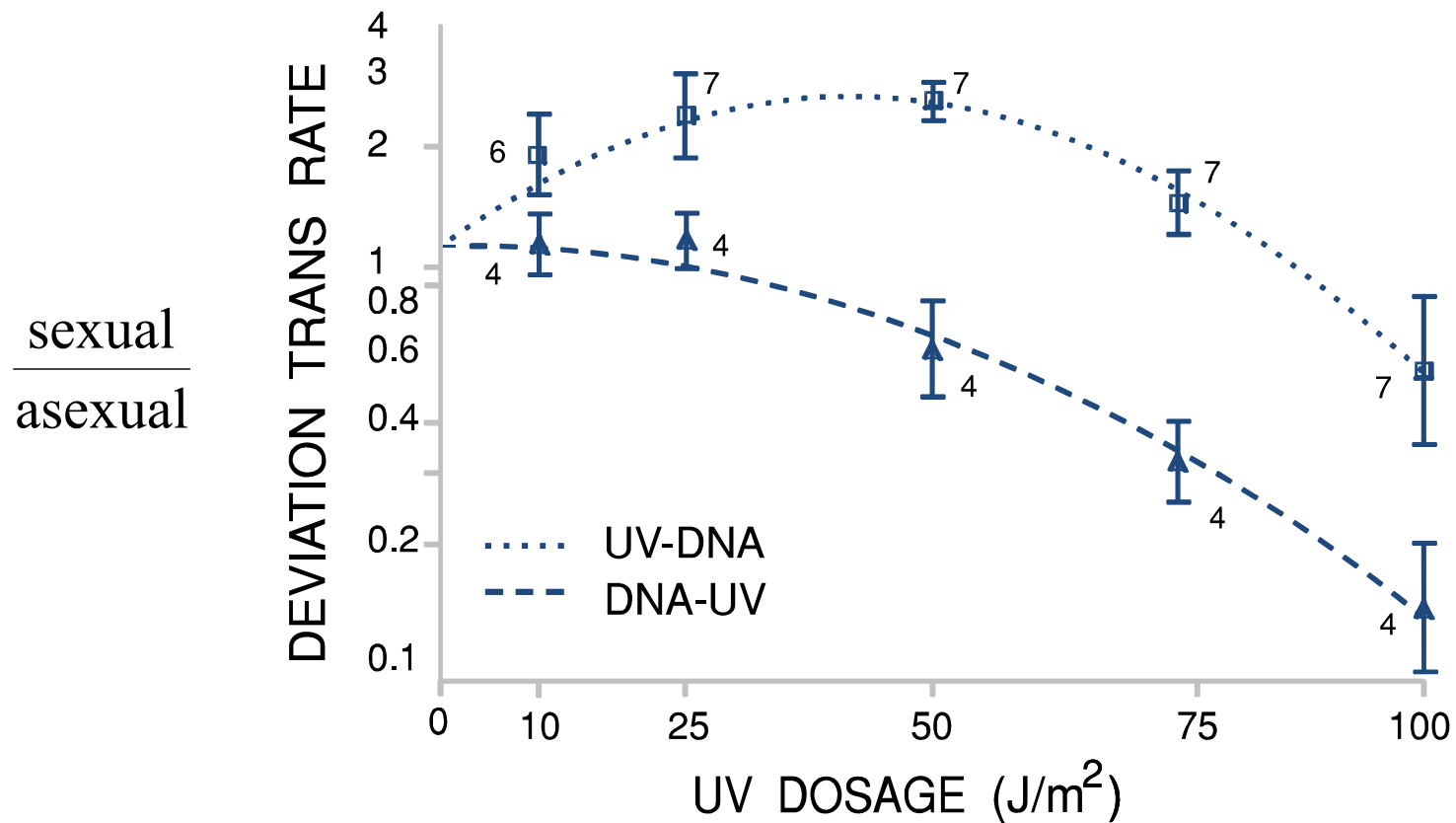


An experiment

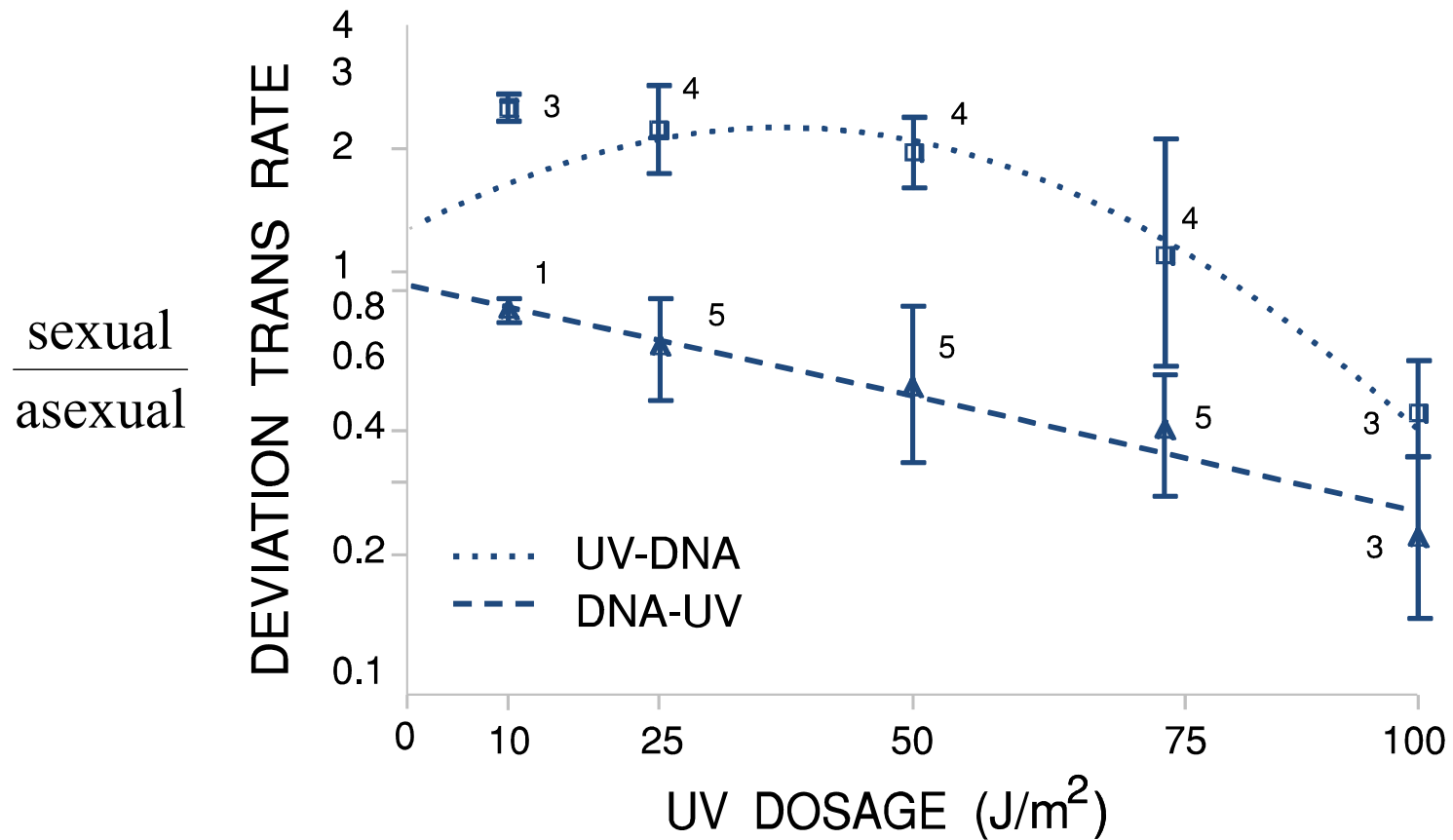
- Sex in bacteria
 - Not for reproduction
 - Transformation
 - Donor & recipient
- Protocol
- Experiments

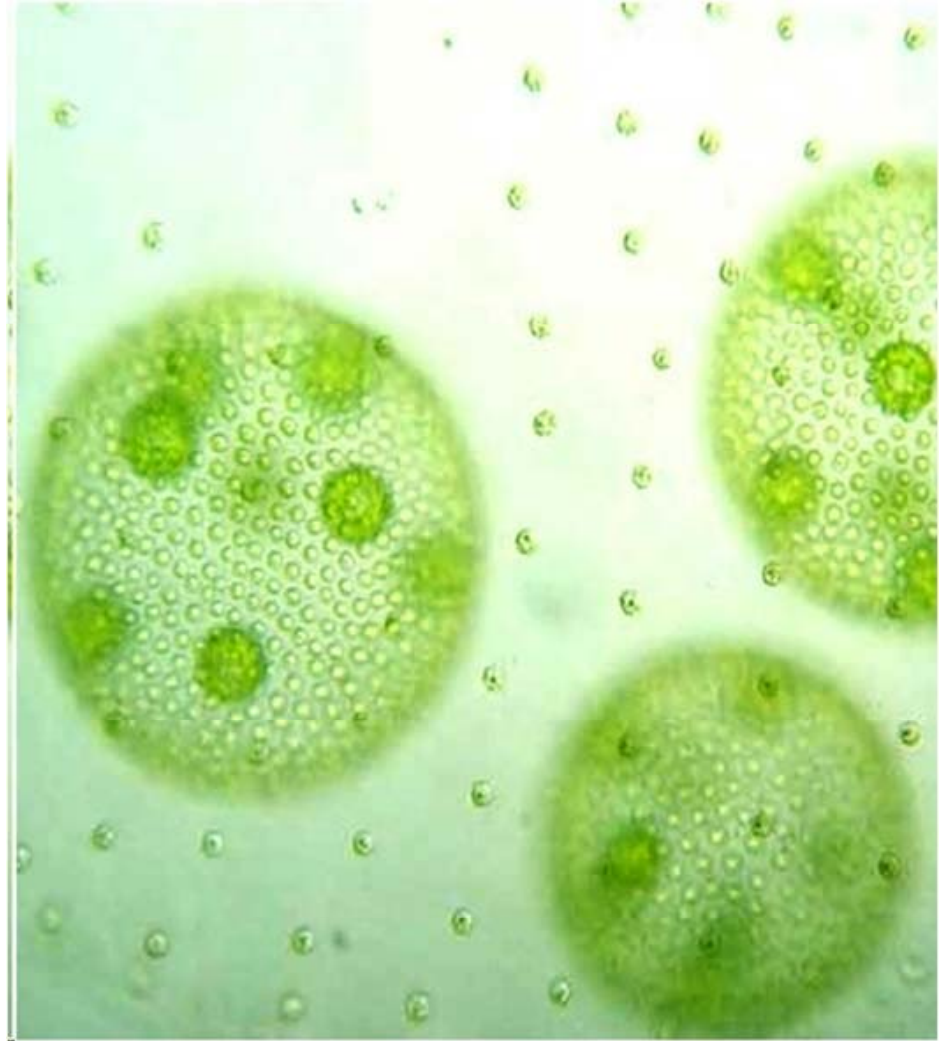
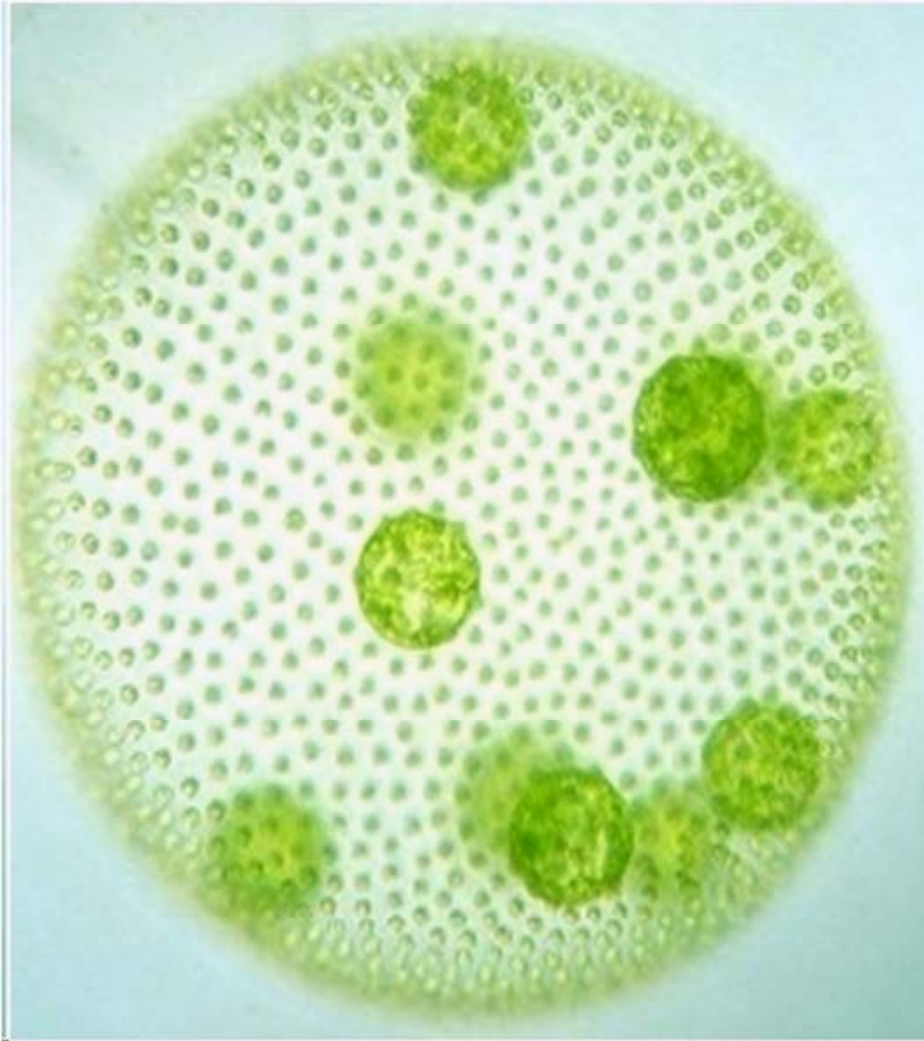


Sex is adaptive after damage, *Not* before



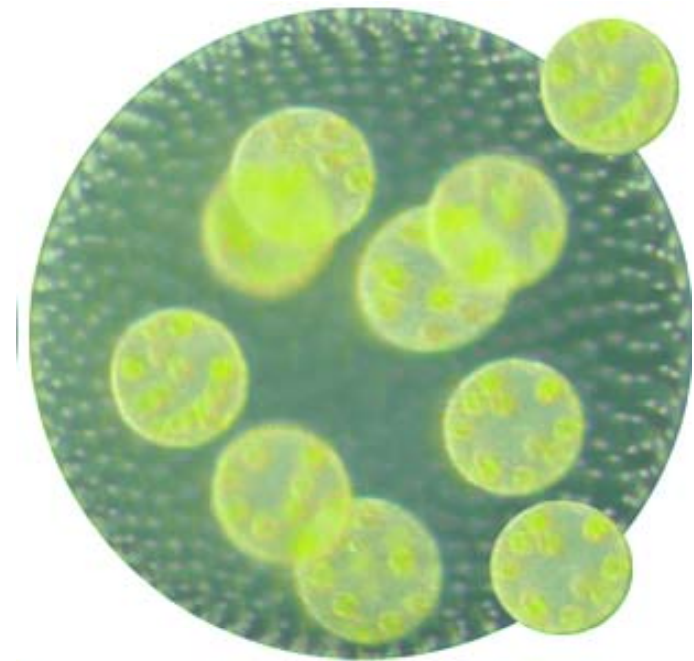
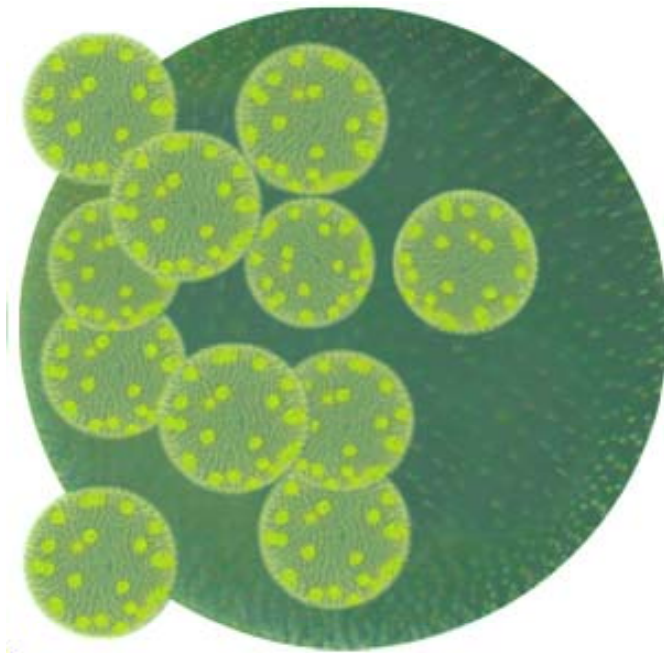
Is sex any good, if your partner isn't?



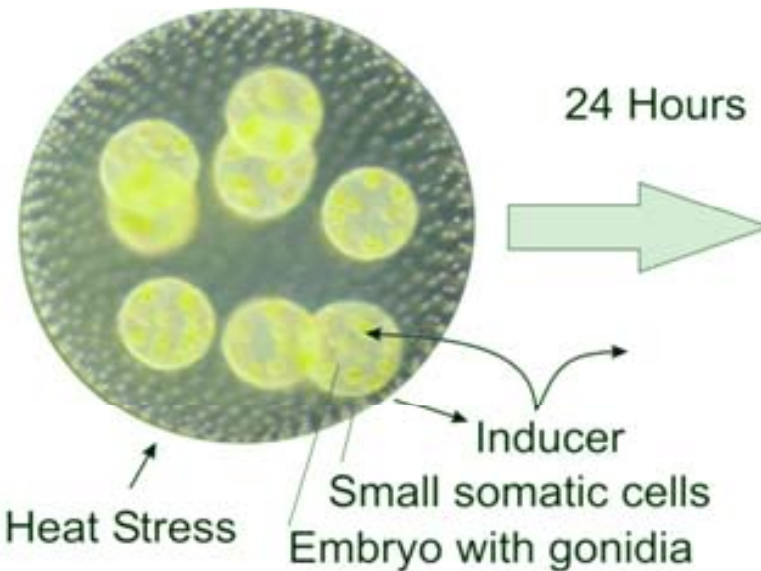


SEX IN A MULTICELLULAR EUKARYOTE

Sexual and Asexual Reproduction in *Volvox carteri*

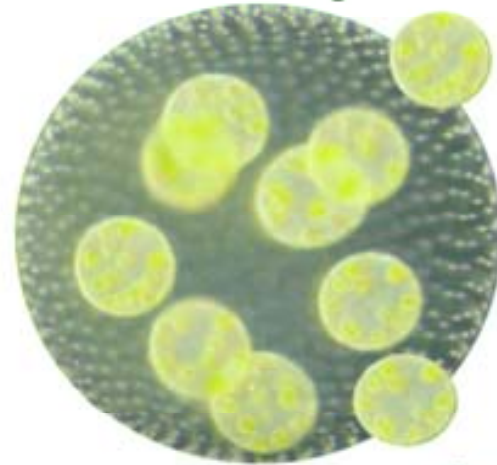


Asexual female with asexual embryos

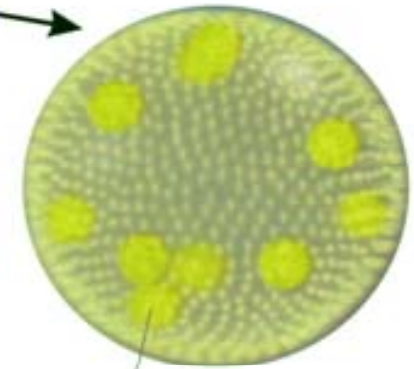


24 Hours

Asexual juveniles hatching

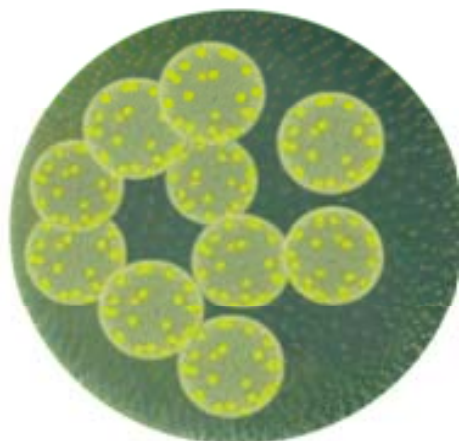


Asexual juvenile with gonidia



Gonidium

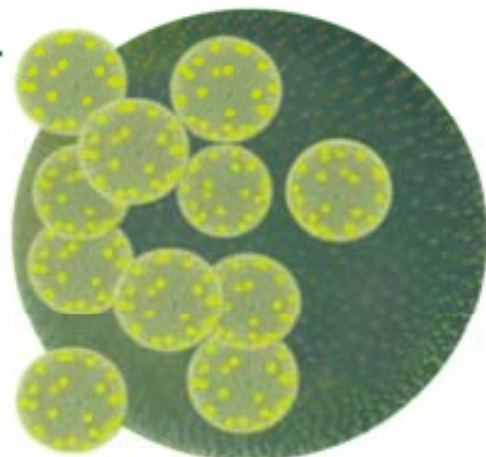
24 Hours



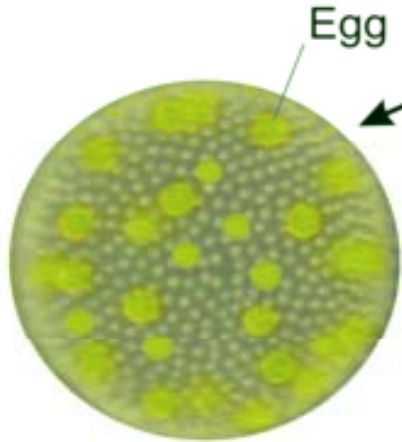
Asexual female with sexual embryos

24 Hours

Sexual juveniles hatching

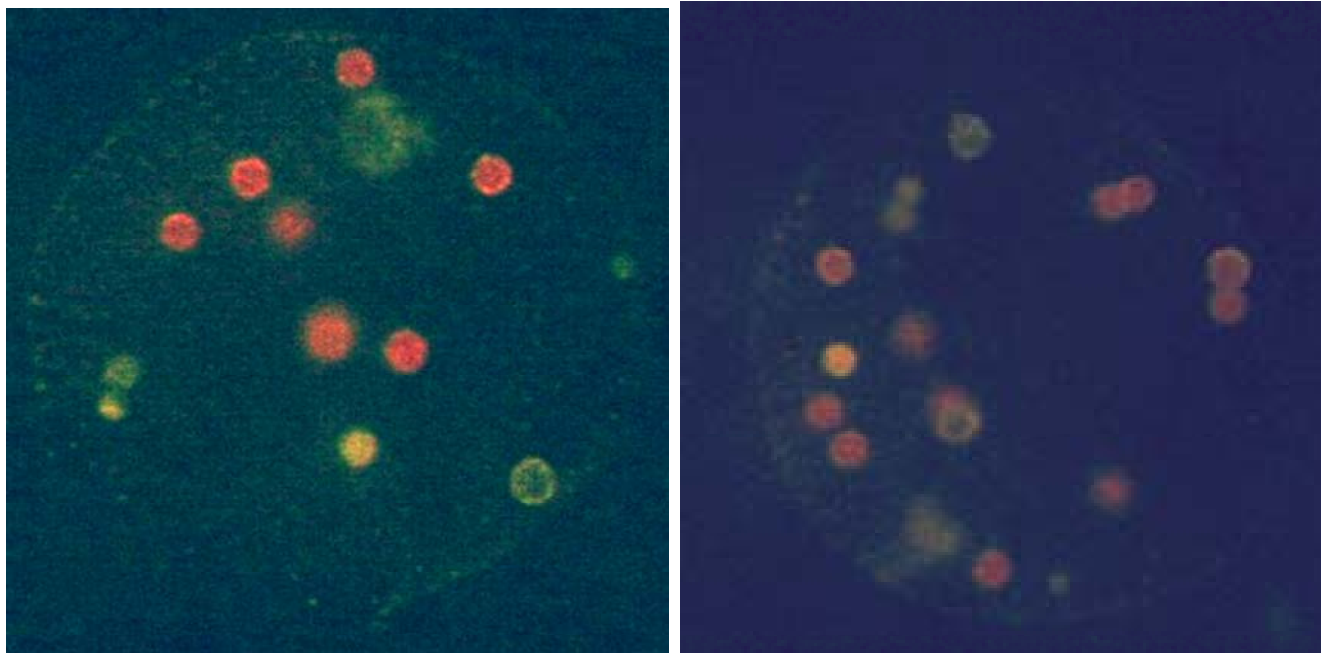


Sexual juvenile with eggs



Egg

Volvox Mom with Diploid Spores

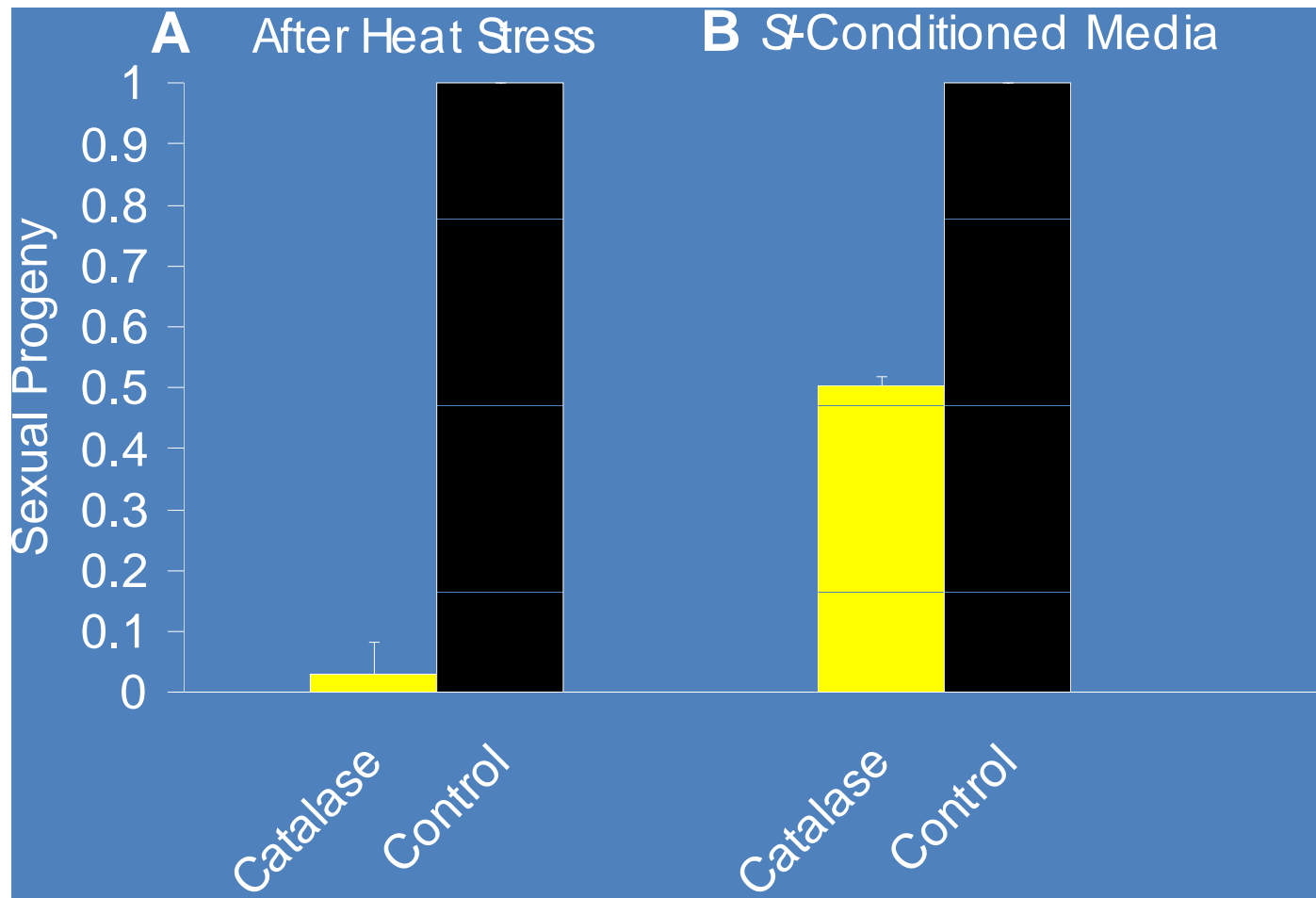


courtesy A. Nedelcu

Oxidative stress induces sex in *Volvox*



Anti-oxidants reduce sex induced by




Black is control, yellow treatment

Credit: A. Nedelcu

Difference between treatments → ROS turns on SI and other sex genes

Oxidative stress turns on the sexual inducer gene, *Sl*

After Heat Stress

- Cat			+ Cat		
1	2	3	1	2	3
					

Credit: A. Nedelcu

"Cat" = catalase an anti-oxidant

SI Acts as an oxidative stressor to partner

SI-conditioned media

- Cat
+ Cat



Heat Stress

- Cat
+ Cat

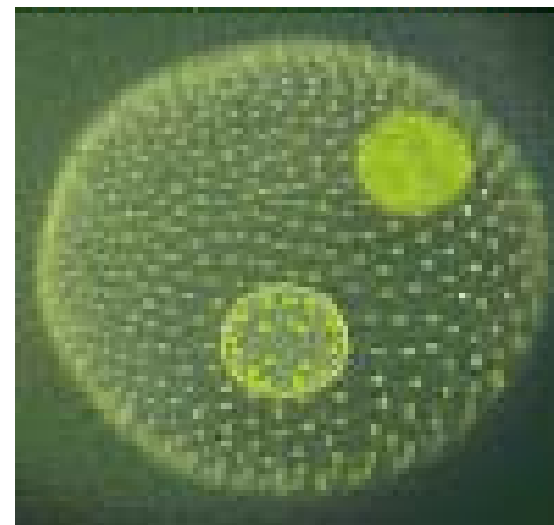
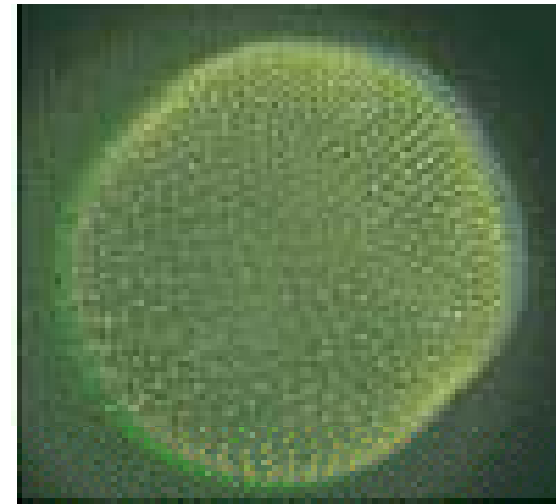
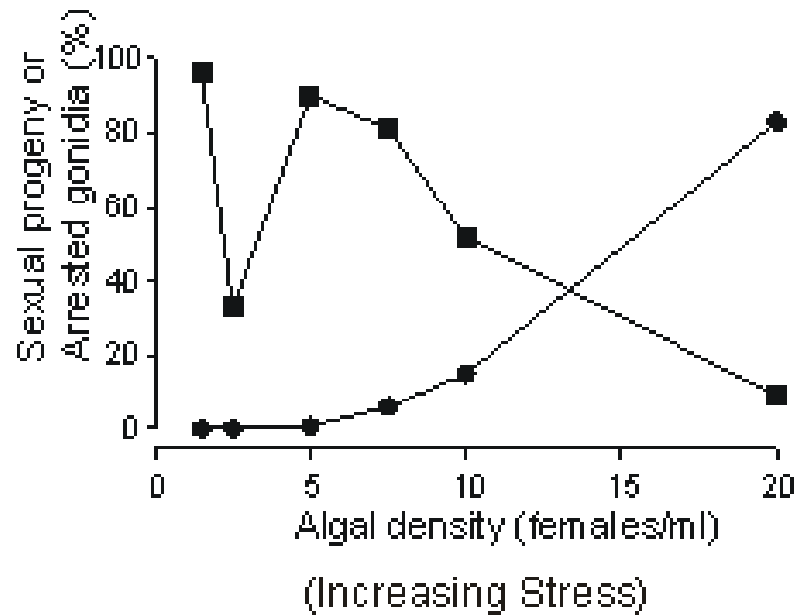


Clone B: gene known to be induced by wounding or during sex

Credit: A. Nedelcu

"Cat" = catalase an anti-oxidant

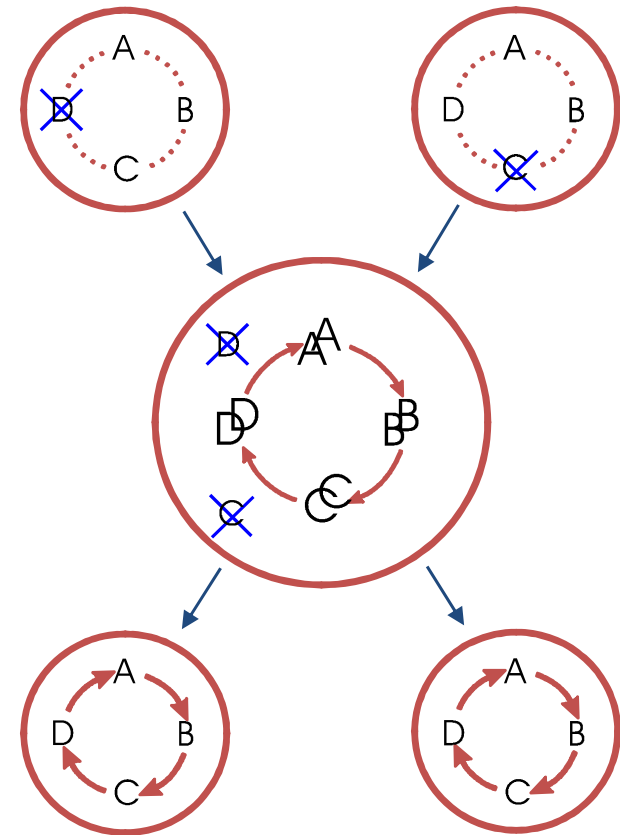
Sex, cell cycle arrest, programmed cell death as alternate strategies for coping with stress



Credit: A. Nedelcu

Sex: cooperation or manipulation?

- Sexual inducer acts via ROS & likely DNA damage
- Sexual inducer and wounding activate similar genes, similar to defense genes in plants
- Manipulate partner to having sex by stressing them
- Sex is selfish strategy to find template for DNA repair



Sexual Manipulation in *V. carteri*

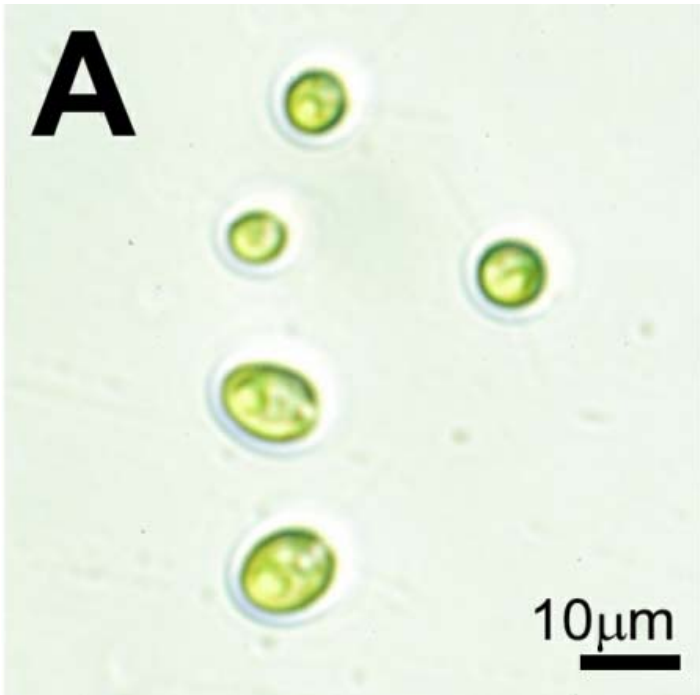
- Sexual inducer acts via DNA damage and ROS
- Sexual inducer and wounding activate similar genes, similar to defense genes in plants
- Manipulate partner to having sex by stressing and damaging them
- An SI-like protein exists in *C. reinhardtii* where it functions in stress responses (Nedelcu 2005)
- Sex is selfish

Cooperation and Conflict in Sex

- Stress is the Impetus for Sex
- Cooperative Sex
 - Partner may also be stressed, and "willing"
- Selfish Sex
 - Partner is not stressed, and "unwilling"
 - Sex competence must be induced in the partner

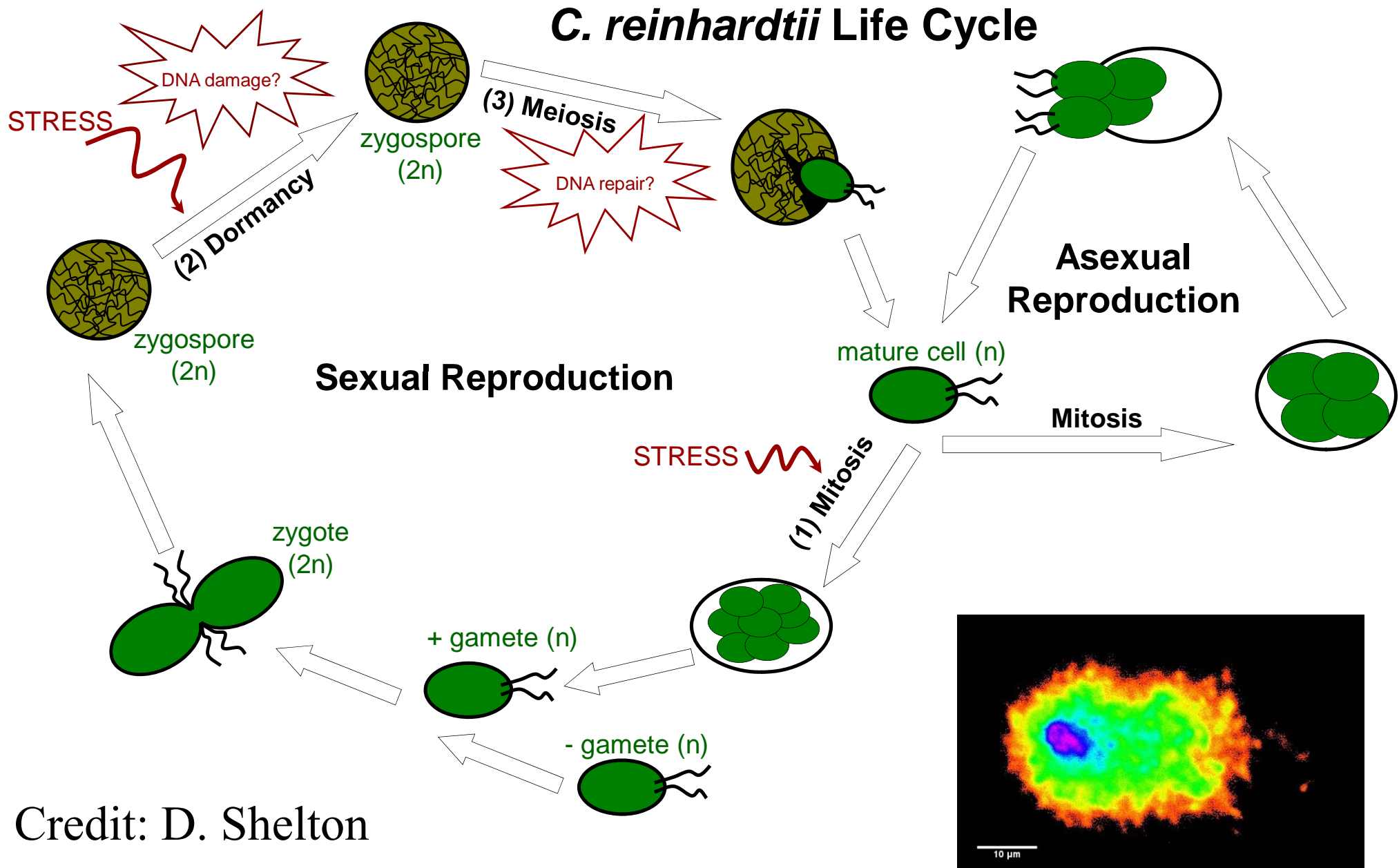
Sex is Selfish in *V. carteri*

- Sexual inducer acts via DNA damage and ROS
- Sexual inducer and wounding activate similar genes, similar to defense genes in plants
- Spontaneous males

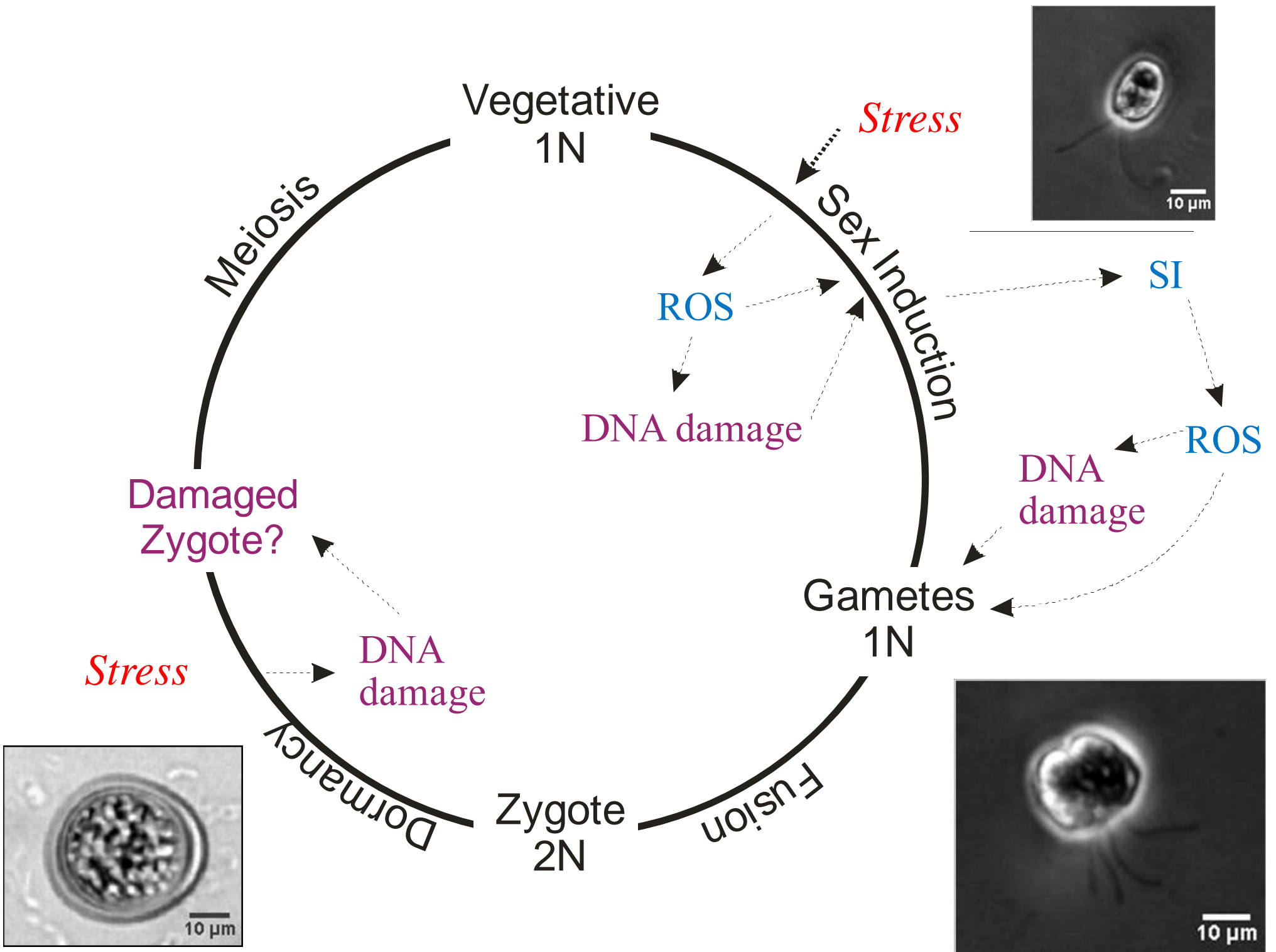


SEX IN A UNICELLULAR EUKARYOTE

Current work

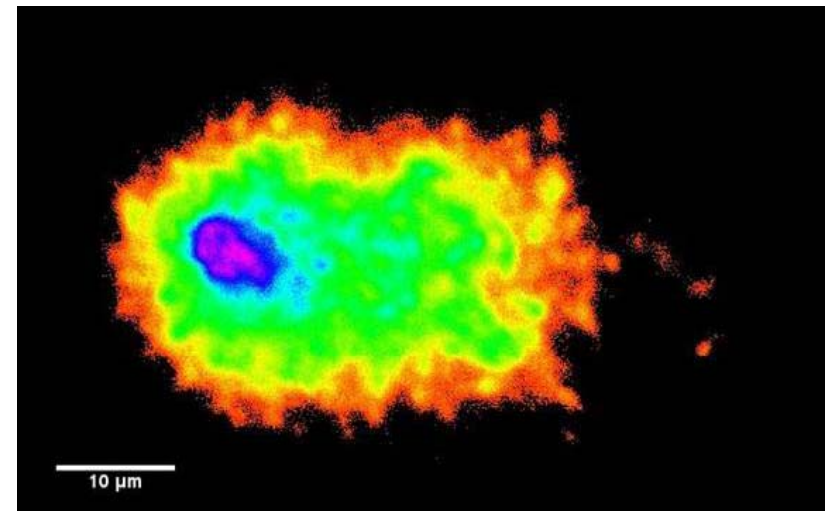


Credit: D. Shelton

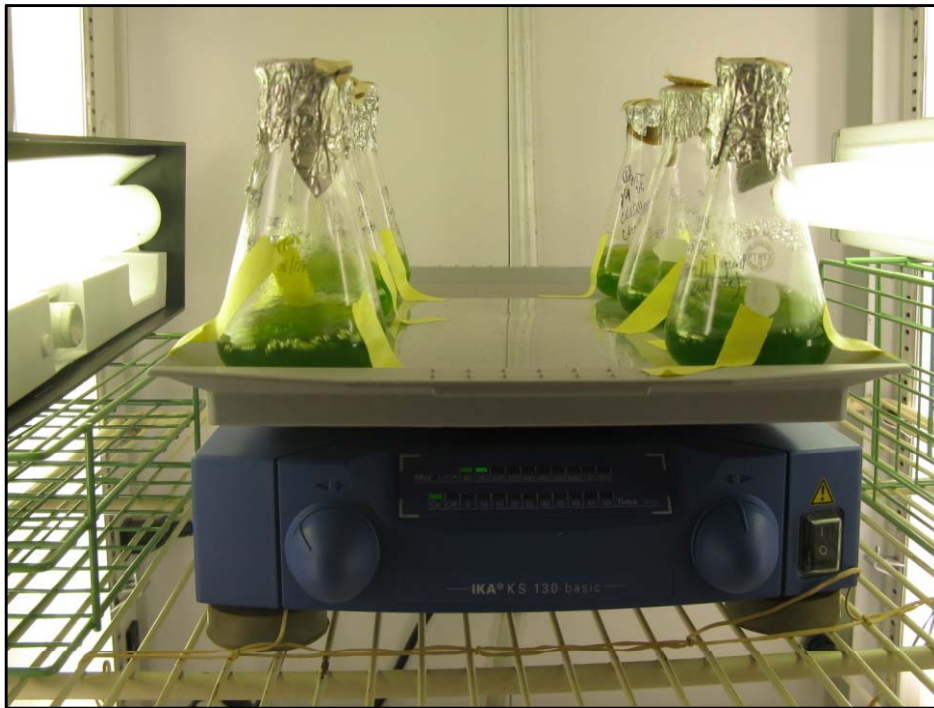


Comet Assay method for detecting DNA damage and repair

- Microscopically detect DNA damage at the level of a single cell
- Assay conditions must be optimized for the cellular characteristics of *C. reinhardtii*



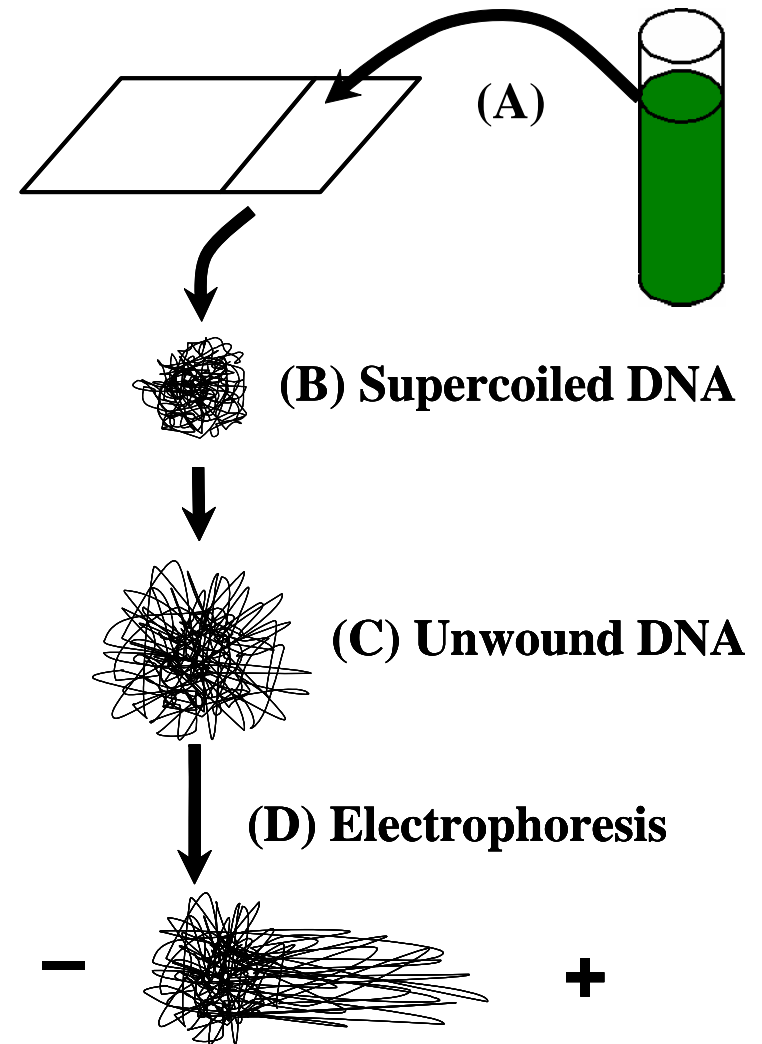
To demonstrate applicability of comet assay to *C. reinhardtii*



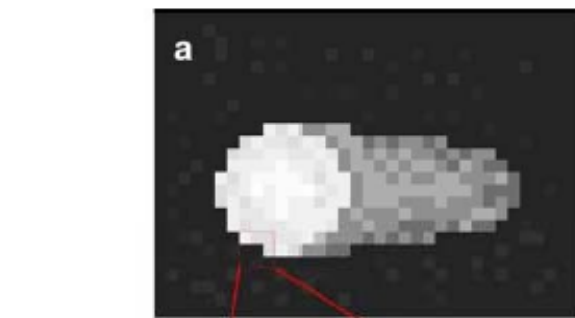
- Grow *C. reinhardtii*
- Expose cells to varying levels of hydrogen peroxide for 2 hr.
- Do comet assay protocol with modified conditions
- Image DNA from 30+ cells for each treatment
- Analyze comet metrics

Quantifying DNA damage using the Comet Assay

- Cells suspended in agarose on a microscope slide
- Cells are lysed, leaving a nucleoid suspended in agarose
- Electrophoresis pulls DNA into the "tail" proportionally to level of damage in DNA

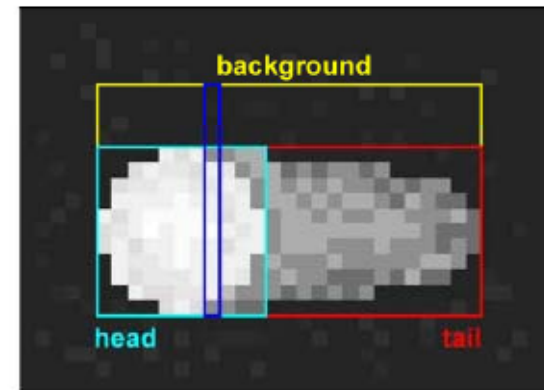
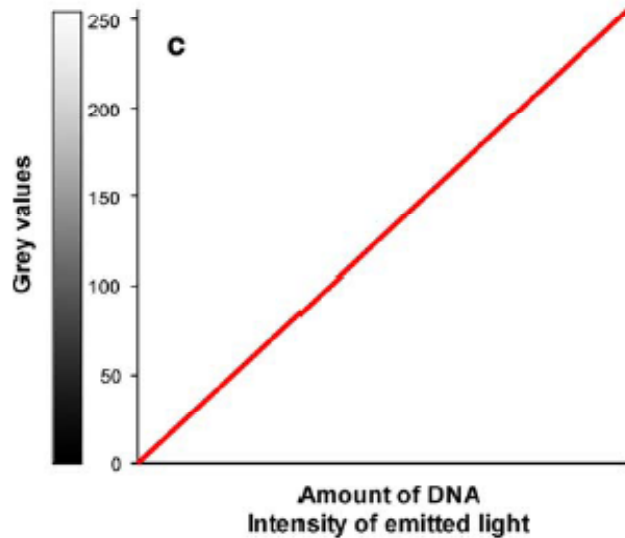


Comet parameters can be measured visually or by software



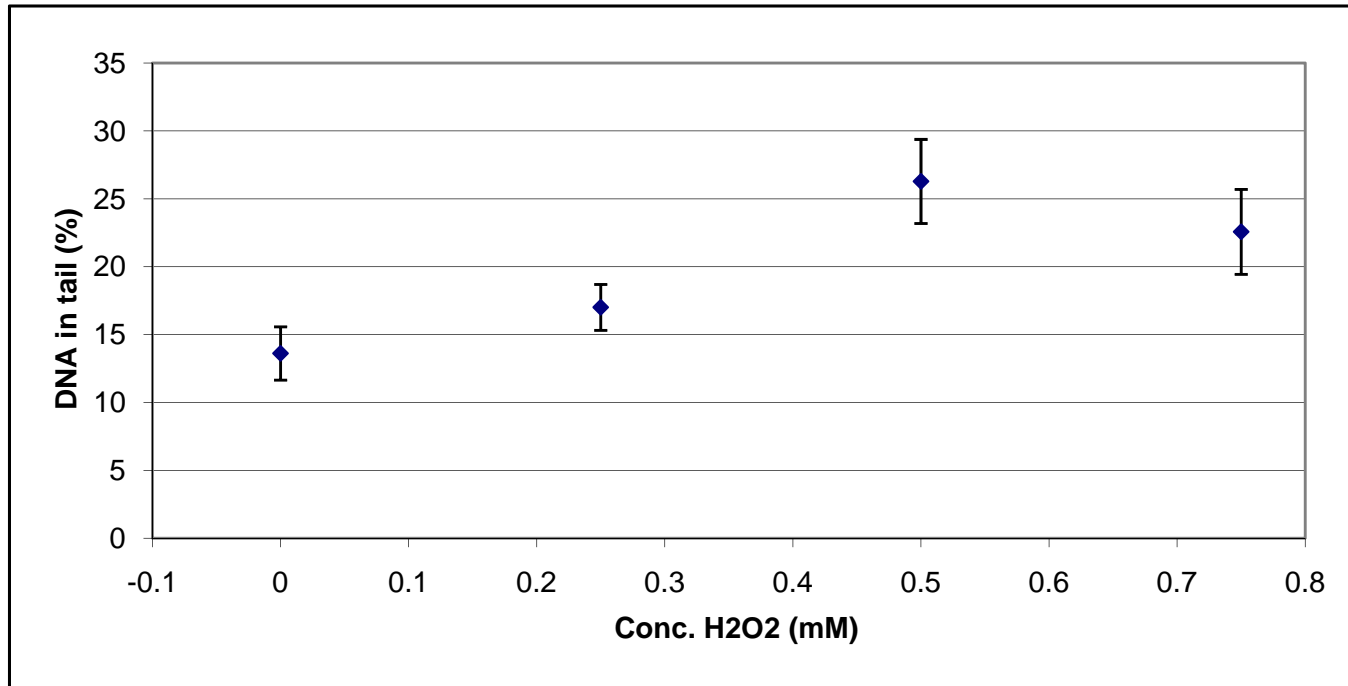
b

240	221	221
41	41	221
41	48	41



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
	Background																								
	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41
	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41
	41	51	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41
	46	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41
sum	169	174	164	164	164	164	164	169	164	169	164	169	164	169	164	164	169	164	164	179	164	179	164	169	164
	Head											Tail													
	41	41	41	41	240	221	240	141	141	171	171	46	41	41	41	41	41	41	41	41	41	41	41	41	41
	41	41	221	240	230	230	221	240	230	141	171	171	110	141	110	141	141	110	141	141	41	41	41	41	41
	41	221	230	230	240	240	230	230	240	230	141	171	141	171	141	171	141	141	110	141	110	141	141	41	41
	41	240	240	240	240	251	240	240	230	240	141	171	171	141	171	141	171	141	110	171	141	110	171	141	110
	240	221	240	251	251	251	251	240	221	240	240	141	171	171	141	171	141	141	141	171	141	141	141	171	110
	221	230	240	251	240	251	251	251	240	230	240	141	171	171	171	171	171	171	171	171	141	110	110	110	110
	221	240	221	240	240	251	240	240	240	240	141	171	171	171	141	141	141	171	141	141	141	141	110	141	110
	41	240	230	230	240	251	240	240	240	141	171	141	141	141	171	141	141	141	141	141	141	171	121	141	41
	41	240	221	230	230	240	240	240	230	141	141	171	141	141	110	110	110	141	141	110	171	110	110	41	41
	41	41	240	221	221	230	230	240	240	192	141	141	141	110	141	110	141	41	41	41	41	41	41	41	41
	41	46	41	41	221	240	221	141	141	110	110	41	41	41	41	41	41	41	41	41	41	41	41	41	41
sum	1010	1891	2185	2215	2593	2648	2694	2443	2398	2213	1877	1476	1439	1471	1379	1440	1349	1349	1310	1149	1210	1150	1062	929	658

C. reinhardtii show a dose-dependent response to a damaging agent



SEX AND SPECIES

Two Kinds of Order in Living World

- Design
 - Design results from natural selection
- Species
 - Distinct and discrete groupings in phenotypic and genotypic space
 - Gaps between

Darwin On Species

- Darwin's quotes
 - "why is not all nature in confusion instead of the species being, as we see, well defined"
 - "why are not all organic beings blended together in an inextricable chaos"
- Problem of missing links
- Missing links in habitat space
 - species are distinct with gaps between
 - Darwin's solution to missing links in space
 - intermediate niches are small
 - intermediate types will have small population size
 - intermediate types evolve more slowly and so go extinct
 - Darwin's solution to missing links in space leads to his second dilemma
- Missing links in time
 - "just in proportion as this process of extermination has acted on an enormous scale, so must the number of intermediate varieties, which have formerly existed, be truly enormous"
 - he appealed to the extreme imperfection of the fossil record

Species Problem Restated

- Infinite number of possible species/niches in world
- How are species/niches created?
- Two views:
 - niches exist in nature
 - the evolving species creates its niche
- Sex creates a cost of rarity
- Let N be species density, mating is $\propto N^2$ not N

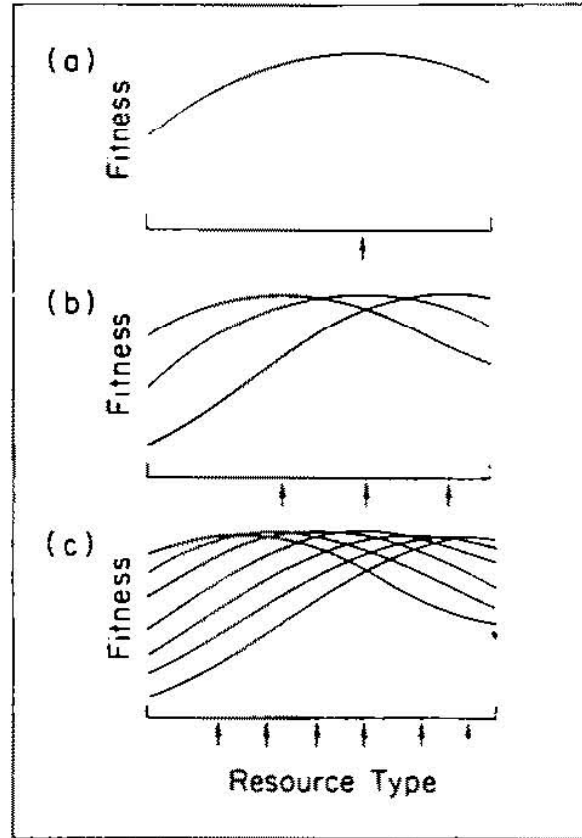


FIG. 1. Fitness (per capita rate of increase) along a resource grade for cases of (a) one species, (b) three species, and (c) six species. Horizontal axis indicates type of resource along this resource grade. Arrows indicate the resource type to which each species is optimally adapted and serves to distinguish the species. Each curve represents the fitness that each particular species would have for each type of resource. The fitness curves assume that the amount of resource is the same for each type of resource.

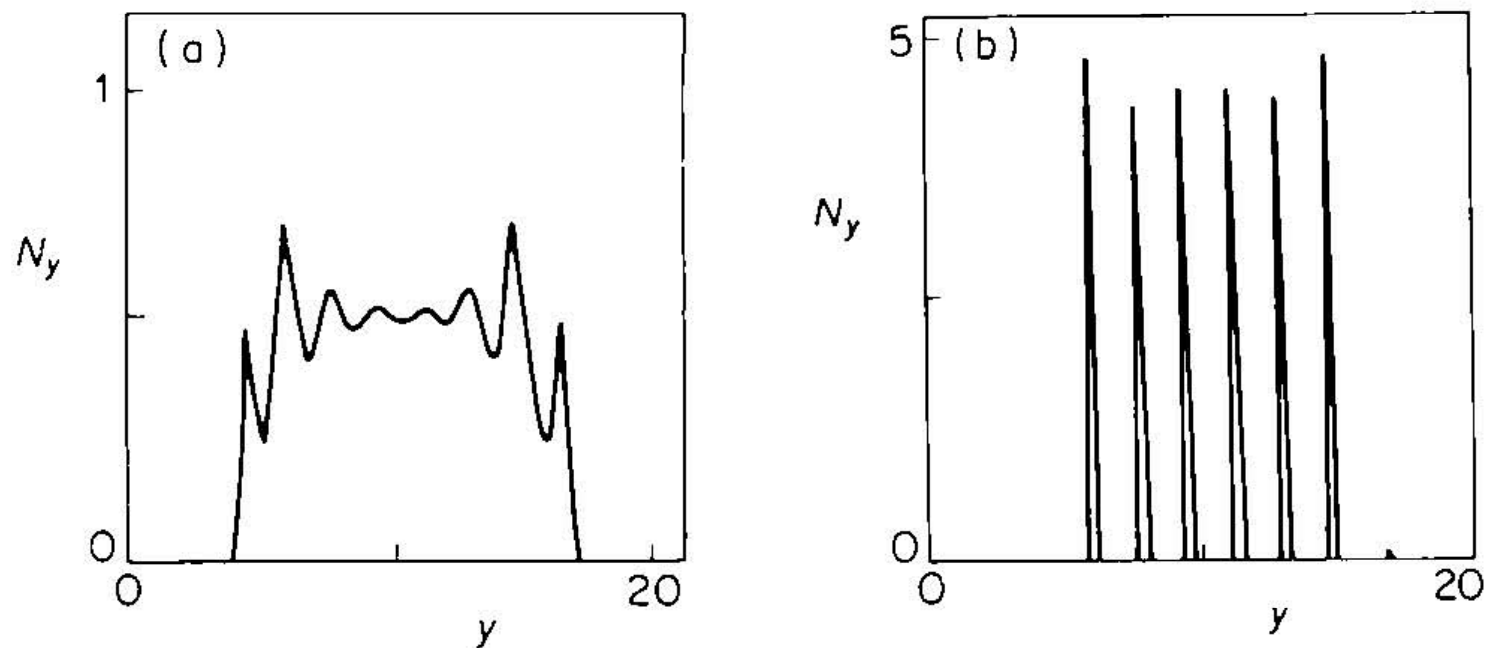


FIG. 2. Density N_y of type of organism labeled y (the labels correspond to the arrows in Fig. 1) along a resource grade, for (a) the case where the types are clone lines with no cost of rarity and (b) the case where the types are sexually reproducing species with a cost of rarity. Both distributions are the final, stable, result reached after long times. In both calculations, all types were assumed present initially. In both cases there is a continuous resource grade over the interval 0 to 20. Resource abundance is, in the absence of consumption by the types, taken to be trapezoidal in shape; the trapezoid is constant over the interval 3 to 17, and falls to zero at the points 0 and 20. The resource use is taken to be proportional to the fitnesses (see, e.g., Fig. 1).

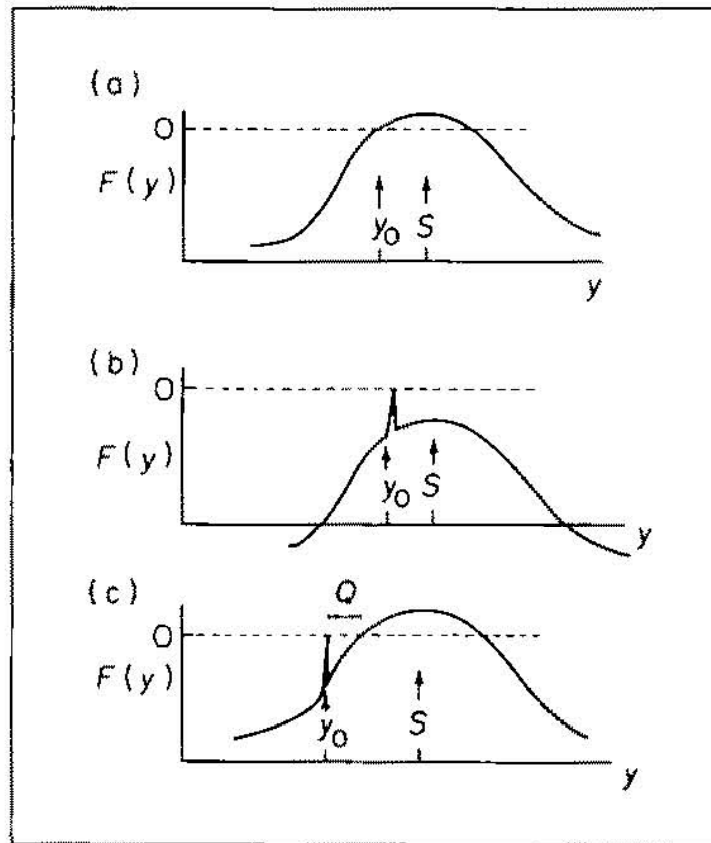


FIG. 3. Fitness $F(y)$ as a function of type of organism labeled y when utilizing a single resource labeled s for (a) the case where the types are clone lines with no cost of rarity, (b) and (c) cases in which the types are sexually reproducing species with a cost of rarity. Only one type of organism is assumed present, and its optimal adaptation is indicated by the arrow labeled y_0 . All other types (labeled y) are potential rare invaders. The spike on the curves (b) and (c) is the cost of rarity that is paid by all but the existent species. (c) describes poor adaptation of the existent species. The label Q indicates the gap between the existing species and the invaders with positive fitnesses (positive fitness implies that the species should be able to invade successfully).

**SEX AS AN EVOLUTIONARY
TRANSITION IN INDIVIDUALITY**

General Points

- With sex individuals don't have fitness, only mating pairs of individuals can reproduce
- The transition occurs in real time in facultative species

Differences with other ETIs

- Higher level unit, mating pair, does not participate in further transitions
- No pair-dependent heritability of mating pair fitness
- Thus, while the mating pair has fitness, this unit does not participate in ETIs the way the other units do (genes, cells, organisms...)

Stages involved in ETIs and sex

Stages

- Initiation
- Stabilization
- Integration
- Emergence
 - Fitness heritability of mating pair

Sex

- Impetus: stress
- Sexual inducer
- Facultative sex
- Obligate sex
- Emergence of fitness heritability of mating pair doesn't occur with sex

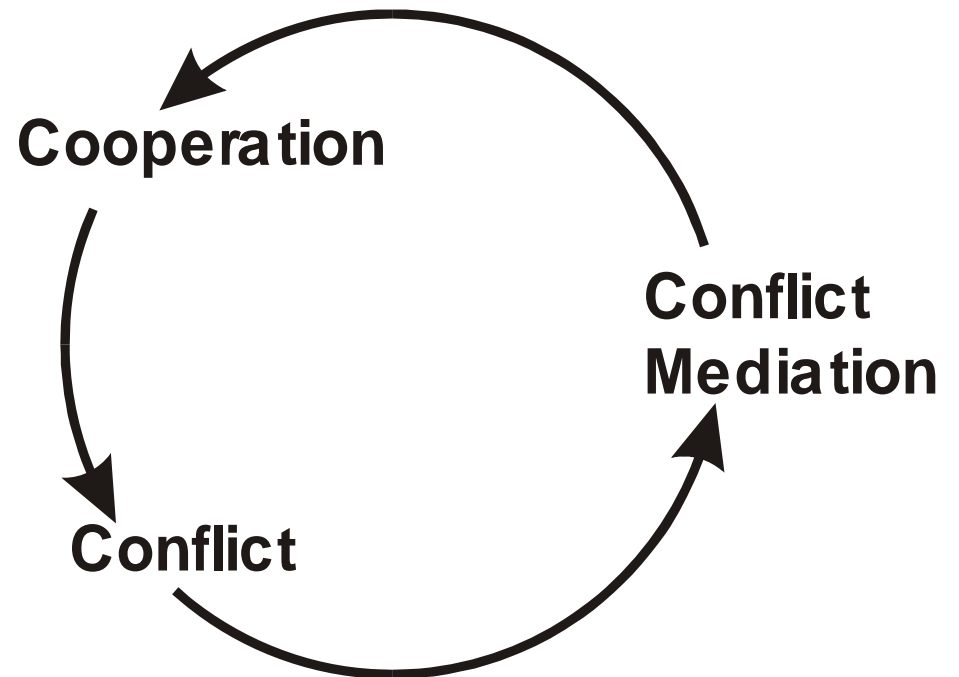
Conflict

- Stress
- Genetic error
 - Mutations
 - Damages
- Mediated through sex
- Sex introduces other conflicts
- Sex may be selfish or cooperative

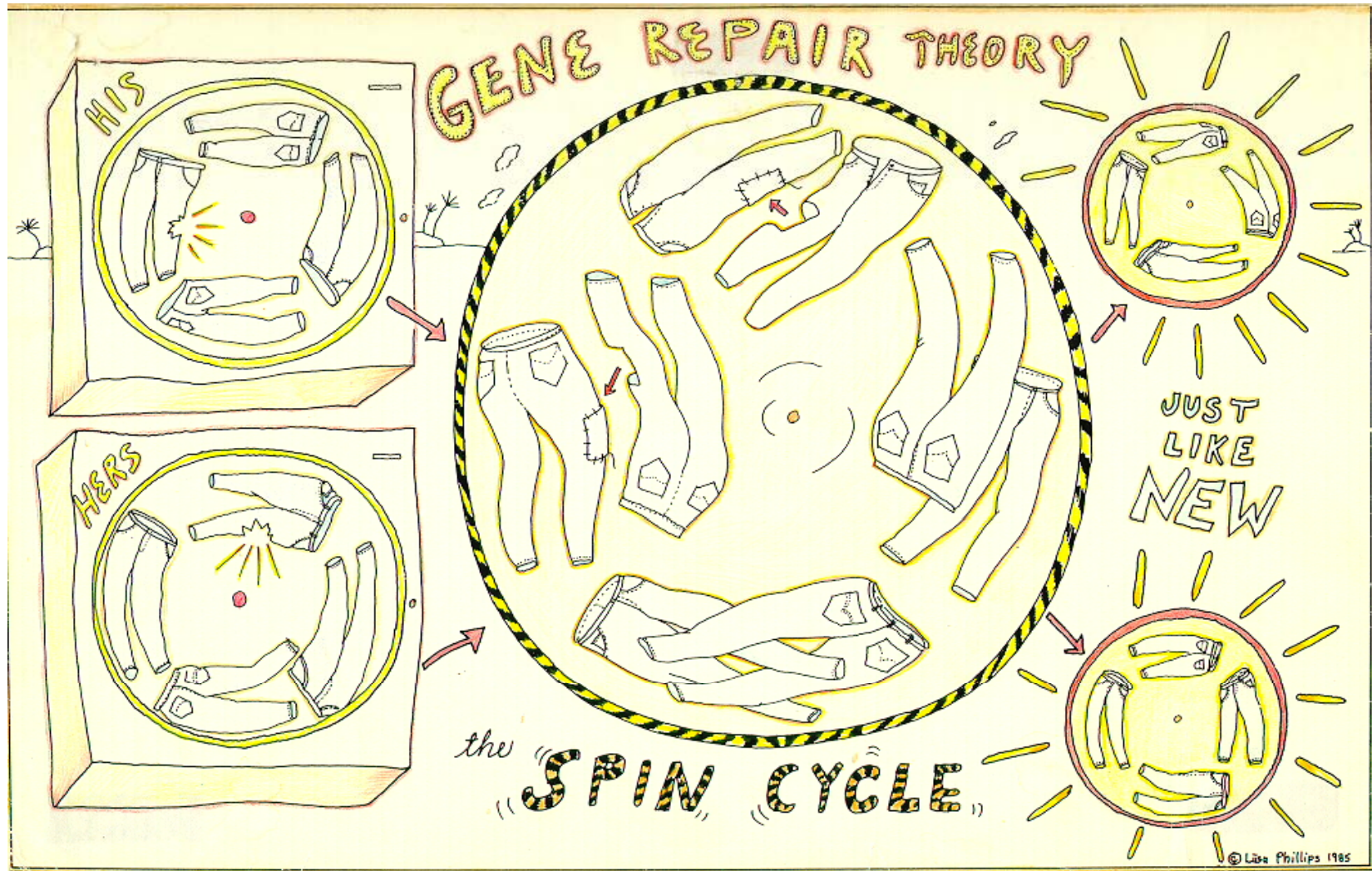
SUM UP EVOLUTION OF SEX

Sum Up: Sex

- Genetic Error
 - Error a fundamental problem for life
- Sex
 - Sex copes with error
 - Variation
- Immortality of life
- Sex introduces new conflicts
 - Manipulation
 - Genetic conflicts

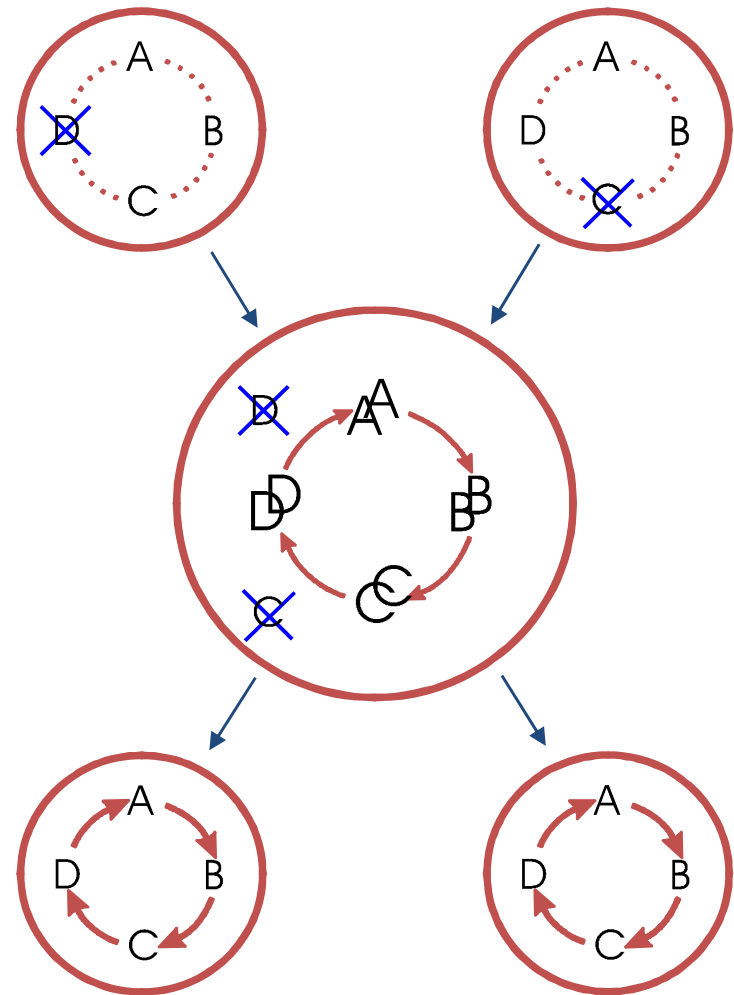


Sex the "The Spin Cycle" Keeps Genes Clean



Sex, Repair, Immortality

- Cell traps error
- Sex repairs error
- Keeps genes healthy
- Rejuvenates life
- Immortality



Sex and Individuality Are in Conflict

- Individuality
 - Requires closure
 - Mediates conflict
 - Facilitates adaptation
- Sex
 - Requires openness
 - Allows for conflict
 - Promises a better future
 - Variation for new environments
 - Coping with genetic error
 - Rejuvenates life
 - Immortality of life

Both are necessary for life

A sensual world because of sex



Immortality

- Uniquely biological concept
- Concerns not matter or substance but activity
- Cycle of life

- Weismann:

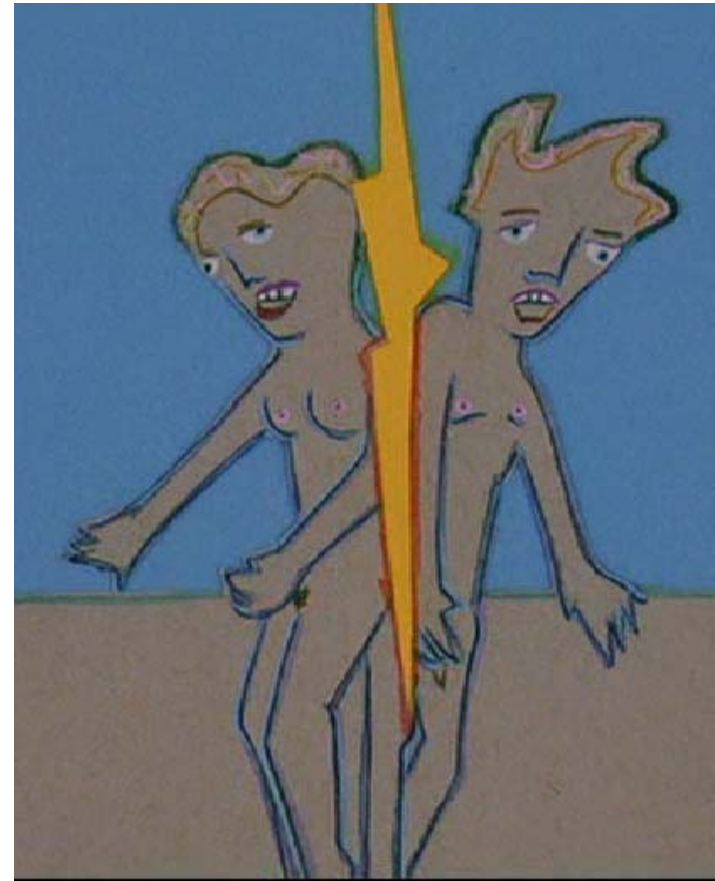
"And what is it, then, which is immortal? Clearly not the substance, but only a definite form of activity

...the cycle of life, i.e. of division, growth by assimilation and repeated division, should never end....

It is the only true immortality to be found in Nature-a pure biological conception, and one to be carefully distinguished from the eternity of dead, that is to say, unorganized, matter.."

Love is the Pursuit of the Whole

- Repair & rejuvenation through others...
- Love and desire for immortality in Plato's *The Symposium*
- Aristophanes story...



Credit: Hedwig and the Angry Inch

Plato on Love and Immortality

- "...It is in this way that everything mortal is preserved, not by remaining for ever the same, which is the prerogative of divinity, but by undergoing a process in which the *losses caused by age* are *repaired* by *new acquisition*, of a *similar kind*...it is in order to secure immortality that each individual is haunted by this *early desire and love*"

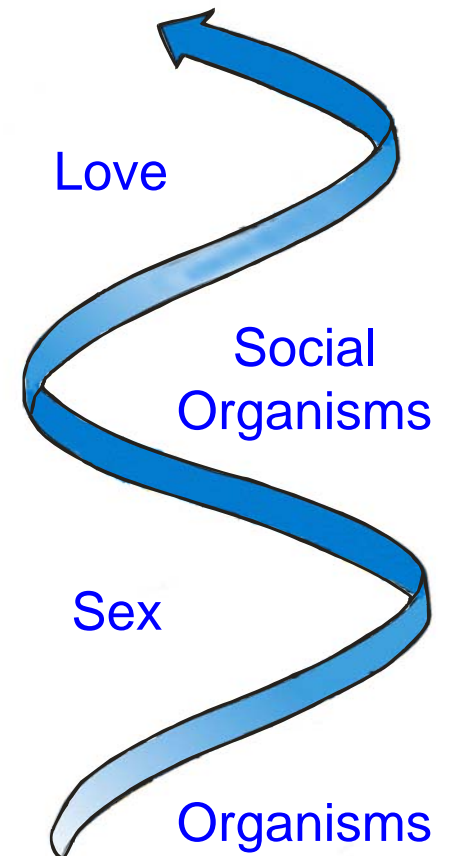
Genes in mate

Genetic Error

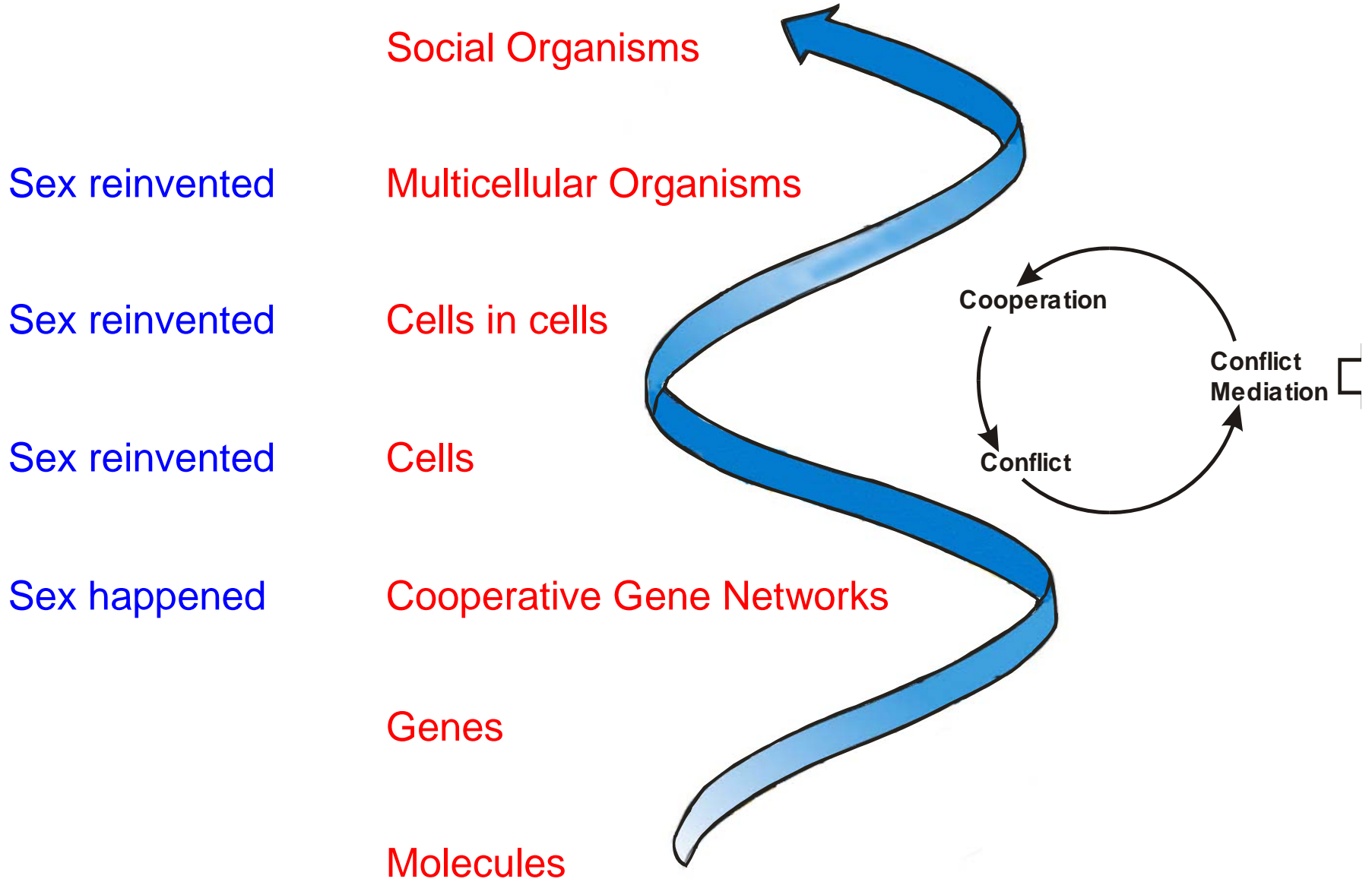
Partner from same species

On Human Nature

- Humans are social animals
- We evolved in small closely knit groups in which individual survival depended on group survival
- Cooperation was key
- If our genes are selfish, they have built us to be cooperative, social & trustworthy
- Cooperation provides meaning and fulfillment to our lives
- Sex and love keep us whole
- Cooperation feels good
- Enjoy!

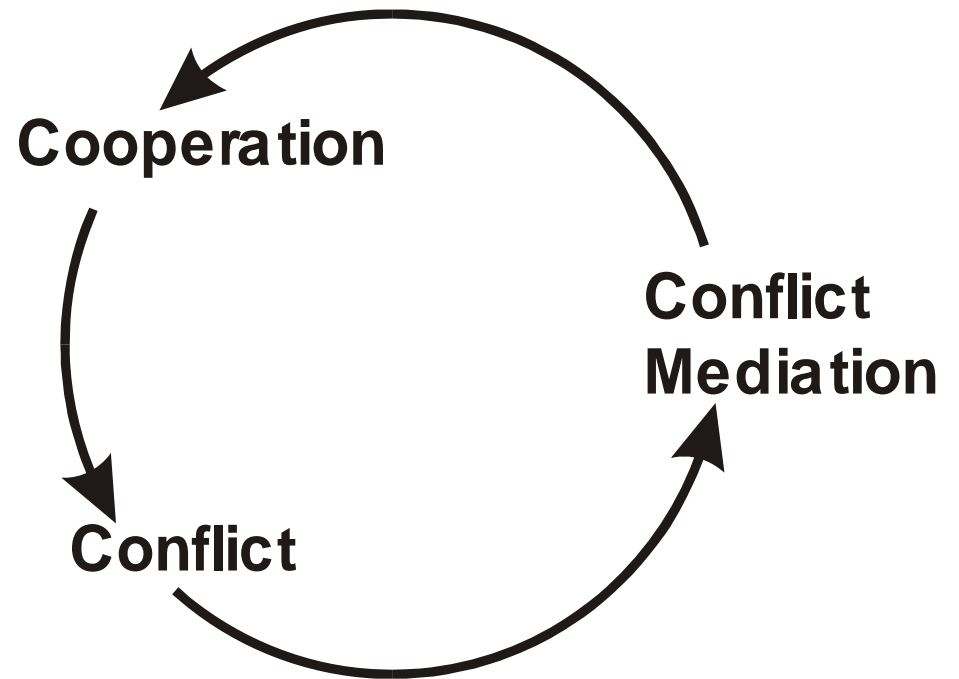


SUM UP ALL LECTURES

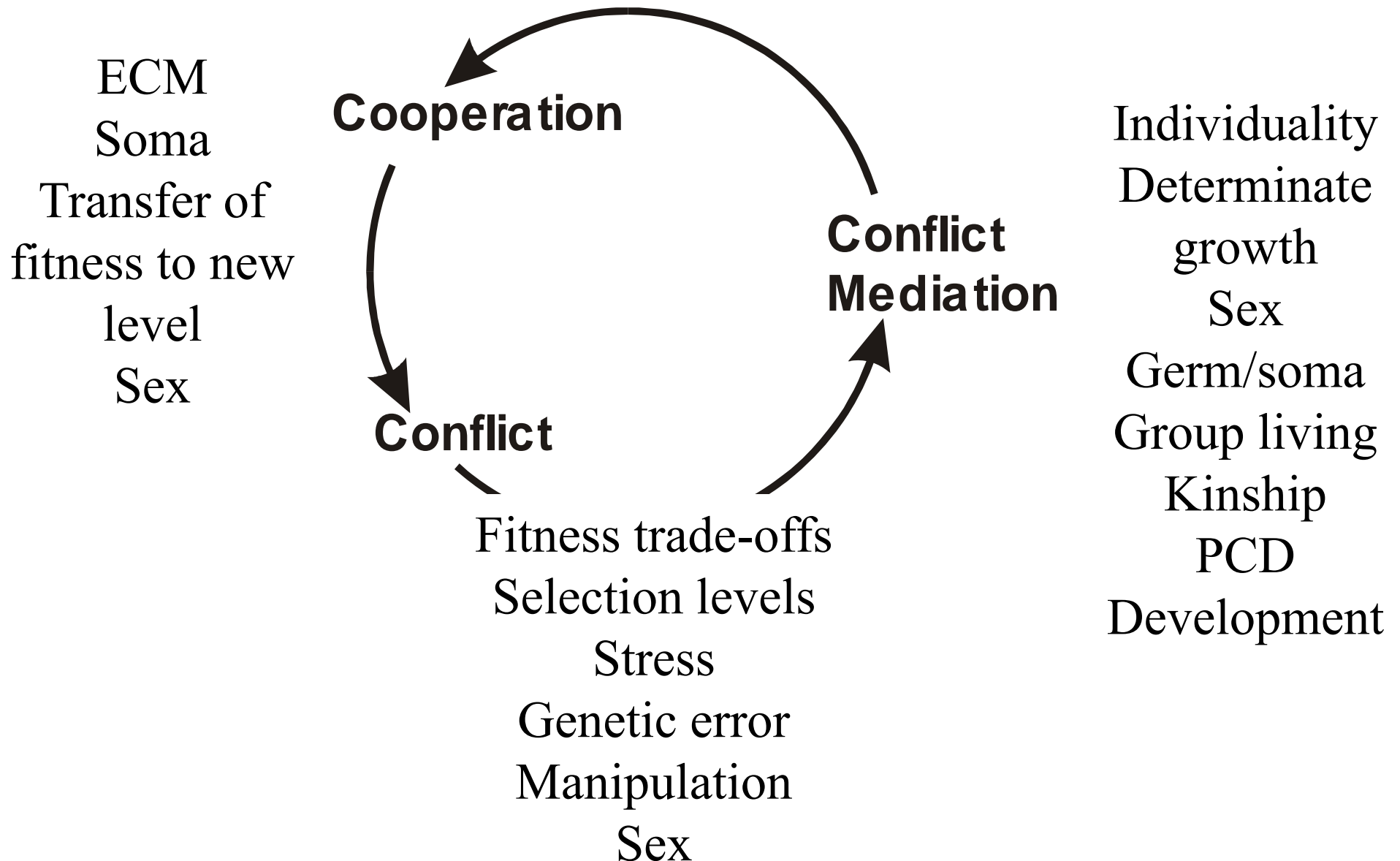


Theme of Lectures

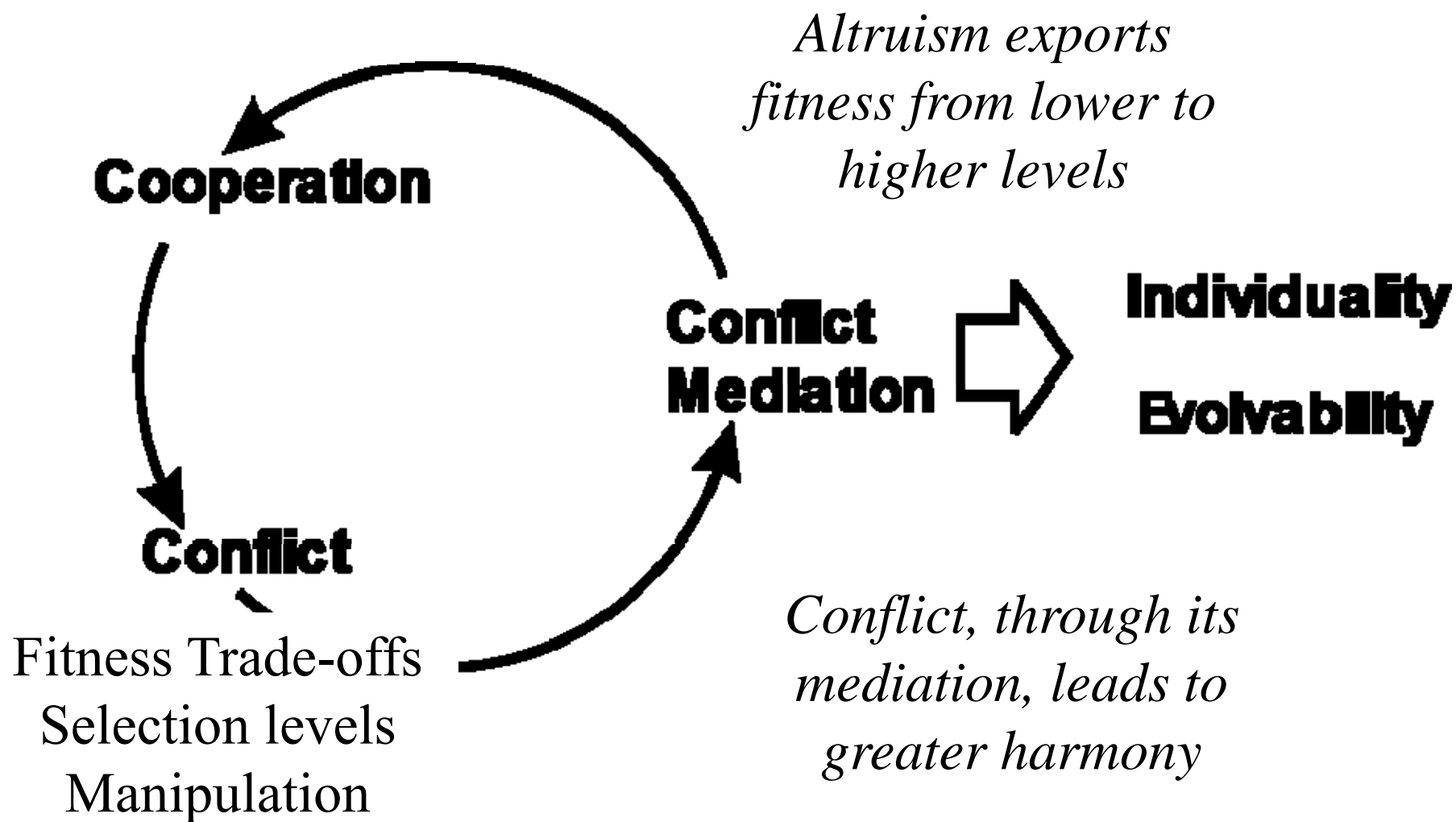
- *Basic properties of the living world emerge out of cooperation and conflict*
 - Cooperation and Sociality
 - Individuality
 - Hierarchical Structure
 - Sex
 - Immortality
- Teaching of biology



Kinds of cooperation and conflict



Cooperation and Conflict Cycle



THE END