

Source: [KBBiologyMasterIndex](#)

## 1 | Overview of Human Diseases

A lecture by the Legendary Dr. Paul Hauser. Slides are here

#flo #disorganized

**Disease** is an abnormal condition that causes impairment in/loss of function of an organism (a.k.a. decreased fitness) that is not due to immediate external injury.

- What causes human disease?
  - Infectious agents
  - Deficiency disorders
  - Heritable factors
  - Physiological disorders (immunodeficiency, autoimmune disorders, allergies, etc.)

### 1.1 | Congenital vs. Acquired disease

Congenital diseases => diseases present at birth due to DNA abnormalities / pregnancy pathological issues

Acquired diseases => diseases that begin during lifetime, including...

- Microorganism invasion => “infectious diseases”
- Autoimmune reaction
- Nutrient deficiency
- Mechanical wear
- Ingestion of noxious chemicals

**Infectious diseases actually smaller on the causes of death in the US**

- Heart disease => wear + deficiency
- Cancer => heritable + DNA
- Unintentional injuries => not a disease
- Chronic respiratory disease => wear
- Stroke => not a disease
- Alzheimer disease => wear
- Diabetes => autoimmune, nutrient, wear
- Influenza <= here, finally, an infectious disease.

### 1.2 | Disease causing agents

- **Protozoan** => single-celled eukaryotes
- **Fungal** => single/multi-celled eukaryotes
- **Bacteria** => single-celled prokaryotes
- **Viral** => acellular parasitic infectious agent
- **Helminthus** => multicellular worms
- **Prions** => acellular misfolded proteins
- **Viroids** => infectious nucleic acids w/o protein coat to make virus

## 1.3 | Pathogenicity + Virulence

**Pathogenicity** => relative capacity to cause disease

- Non-pathogenic agents => no disease
- Primary pathogens => yes disease
- Opportunistic pathogens => yes disease only when it can, for instance, in immunocompromised individuals

**Virulence** => numerical measures for pathogenicity

- Measured experimentally with LD<sub>50</sub> + ED<sub>50</sub>
- 

## 1.4 | Overview of various diseases

This video

### 1.4.1 | Protozoan

- **Protozoan factors** => direction pathogenesis leading to tissue damage
- **Host-mediated factors** => immune evasion + escape mechanisms + immunosuppression

Adaptable!!

### 1.4.2 | Fungal

- **Fungal factors** => many shapes and very adaptable, could produce specialized enzymes to take root in body
- **Host-mediated factors** => cause immunocompromise, acquired through inhalation, etc.

### 1.4.3 | Bacteria

- **Bacterial-induced toxicity** => produces toxins + has hard capsule cell
- **Host-mediated factors** => may develop host resistance, could compete for resources, and could be grown intracellularly

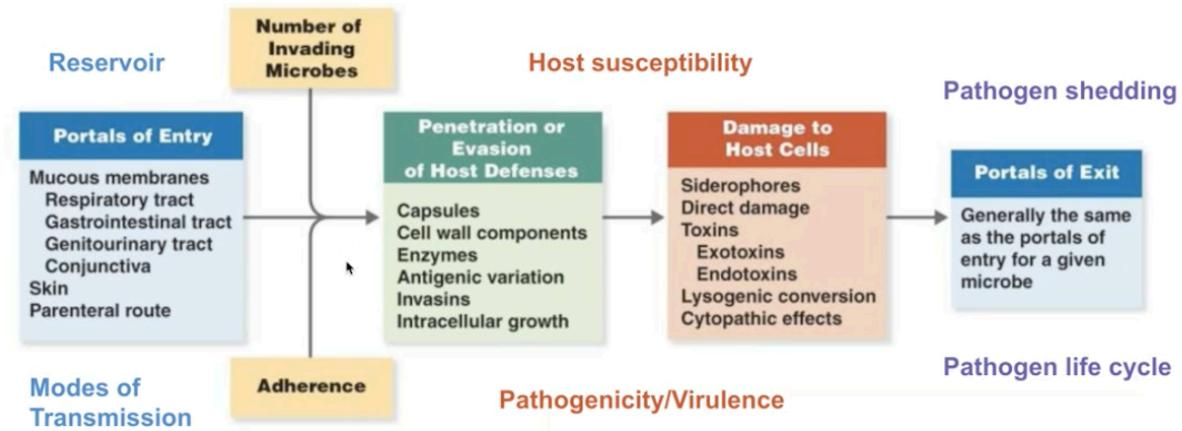


Figure 1: Screen Shot 2020-10-12 at 3.08.53 PM.png

## 1.5 | Bacteria causing diseases

### Biofilm formation

- Communities of bacteria could work together by adhering and exchanging information
- Bacterial could perform quorum sensing => exchange of information with each other + recognize various members of their group

### 1.5.1 | Fighting bacterial infections

**Antibiotics** => drugs with selective toxicity for specific bacterial types

Act by...

- Disrupting membrane + cell wall integrity
- Selectively target + impair bacterial ribosomes
- Block bacterial DNA replication/transcription
- Inhibit bacterial metabolism

## 1.6 | Viruses causing diseases

### Viruses: acellular macromolecular assemblies

- Contain protein coat called capsid
- DNA or RNA, but not both
- Are obligate parasites that could only replicate within host
- Assembled and mature viral particles => virions, which contain...
  - Capsid
  - Genetic material

- Occasionally outside lipid layer

=> Viruses exist on the nanometre scale, but they are difference in shape and size

### 1.6.1 | Structure of viruses

- All contain
  - Capsid => structural protein coat
  - Genome => RNA/DNA; but not both
- Some contain
  - Membraneous-enclosed capsid => envelope
  - Externally-facing host-cell fusion proteins => spikes
  - Viral genome replication enzymes => polymerases
  - Other proteins for fun => enzymes, motor proteins, transcription factors, host-cell interacting proteins, etc.

### 1.6.2 | Two types of virus

- Prokaryotic-infecting viruses
  - Variety of shapes
  - Complex and prolate shapes
  - Has, sometimes complex shapes! a la this image
- Eukaryotic-infecting viruses
  - Much more “boring” in terms of shape
  - Icosahedral/spherical outside
  - Enveloped constructions => envelope protein layer outside, spherical inside
  - Helical/Cylindrical/Bullet shapes, too!
  - Often single patterns assemble together to create symmetric shape that creates the whole of the virus

### 1.6.3 | Viral Life Cycle

1. Attachment => protein contact between virus and host
2. Viral entry/Uncoating => shedding the protein layer
3. Biosynthesis => make baby viruses
  1. Genome Replication: transcribe DNA/RNA
  2. Genome Expression: read DNA/RNA to make proteins
4. Viral genome integration => retrovirus only
5. Assembly => put it all together
6. Viral Exit => mature virions leave

#### Viral Entry Option 1: Direct Injection/insertion

- Insert genome through the bi-layer
- Leave the rest behind
- Tada!

#### Option 2: Endocytosis

- Trick the host cell into introducing the virus as food
- Endocytosis!
- Bam

### Option 3: Fusion

- Virus fuse with cell membrane
- Shed the protein coat once in
- Shazam!

**All of these involve attachment first, which usually takes two steps.**

This process causes the organism-specific response to viruses:

1. Attachment: adhere roughly to random sugar proteins
2. Binding: roll over slowly, and bind to the entry receptor it needs

### Uncoating

- Virus triggers *early endosome*
  - Causes pH dependent protein denaturation
  - Causing the capsid to fall apart
  - Triggering *late endosome* => releasing genome

**Viral Replication** Key questions:

- **How are viral mRNAs produced from the viral genome?** => virus will hijack the ribosomes in the host cells. So, it is more important to ask how the mRNAs are produced to tell ribosomes what to do
- **What serves as the template for viral genome replication** => replication will need a polymerase; but the source and mechanism is dependent on viral genome structure/composition

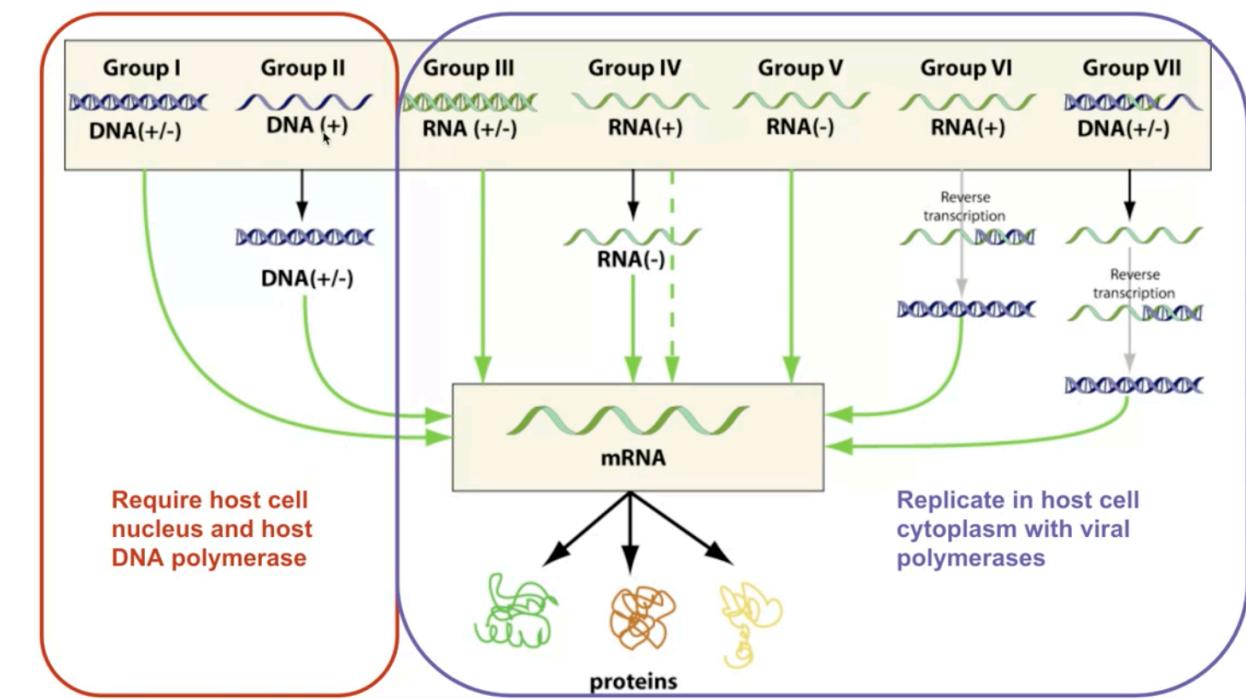


Figure 2: Screen Shot 2020-10-12 at 11.04.53 PM.png

## DNA Viruses

How are viral mRNAs produced from the viral genome?

- Viral DNA enters, through RNA polymerase II in the host cell, mRNA is produced
- mRNAs then read by ribosomes, and there we go

What serves as the templates for viral genome replication?

- Viral DNA serves as template for host cell DNA polymerase
- Viral genome copied repeatedly
- Virus, then, **will be replicated within the nucleus** due to it needing the polymerase to copy DNA

Except! Poxviridae carry their own polymerase, so they replicate in the cytoplasm.

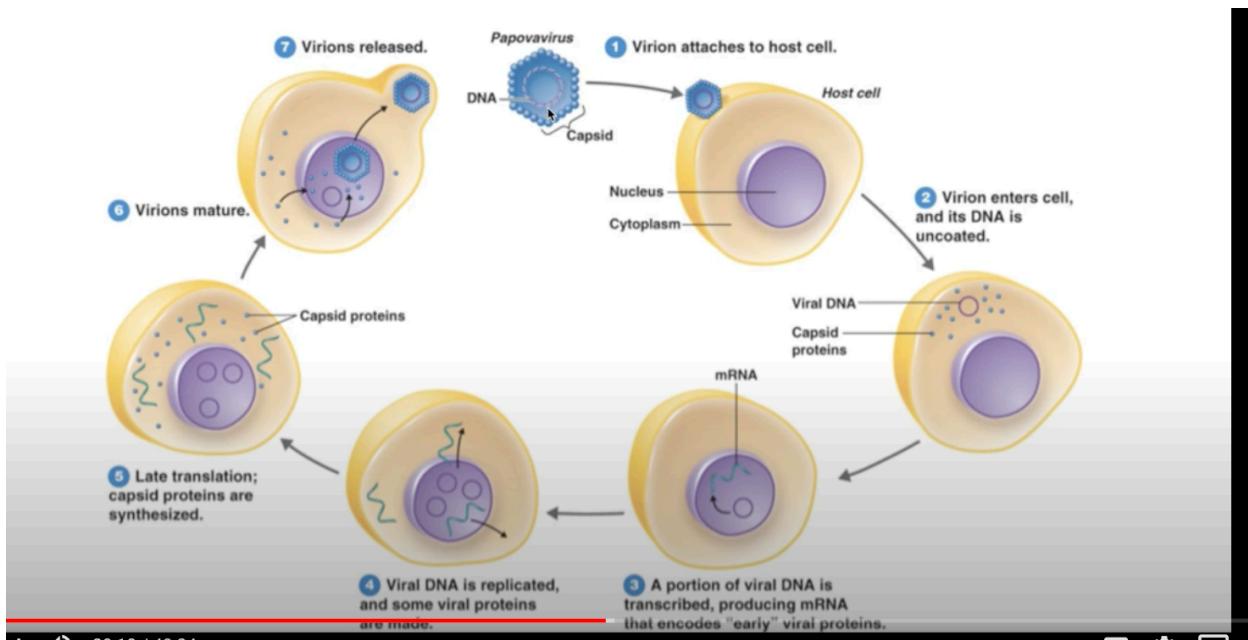


Figure 3: Screen Shot 2020-10-12 at 11.09.46 PM.png

## RNA Viruses

*How are viral mRNAs produced from the viral genome?*

- +Strand: reproducible RNA => could be directly translated by the ribosomes
- -Strand RNA: useless template RNA (less easy to be detected)
  - Need to be processed by RDRP (RNA-dependent RNA Polymerase)
  - Once entered the cell, RDRP goes to work copying -Strand RNA to +Strand RNA
- double-stranded RNA virus => (+, a.k.a. sense)
  - +-stranded RNA => same idea as above
  - • strand RNA => virus comes with RDRP that converts -ssRNA to +ssRNA. Then, same idea as above.

*What serves as the templates for viral genome replication?*

- RNA viruses do not need host-cell polymerase to copy RNA
- They come with polymerase that...
  - with dsRNA; takes +ssRNA and makes -ssRNA; combining the two to produce dsRNA
  - with +ssRNA, takes +ssRNA and makes temporary -ssRNA which makes more +ssRNA
  - with -ssRNA, takes -ssRNA, and makes temporary +ssRNA, which makes -ssRNA

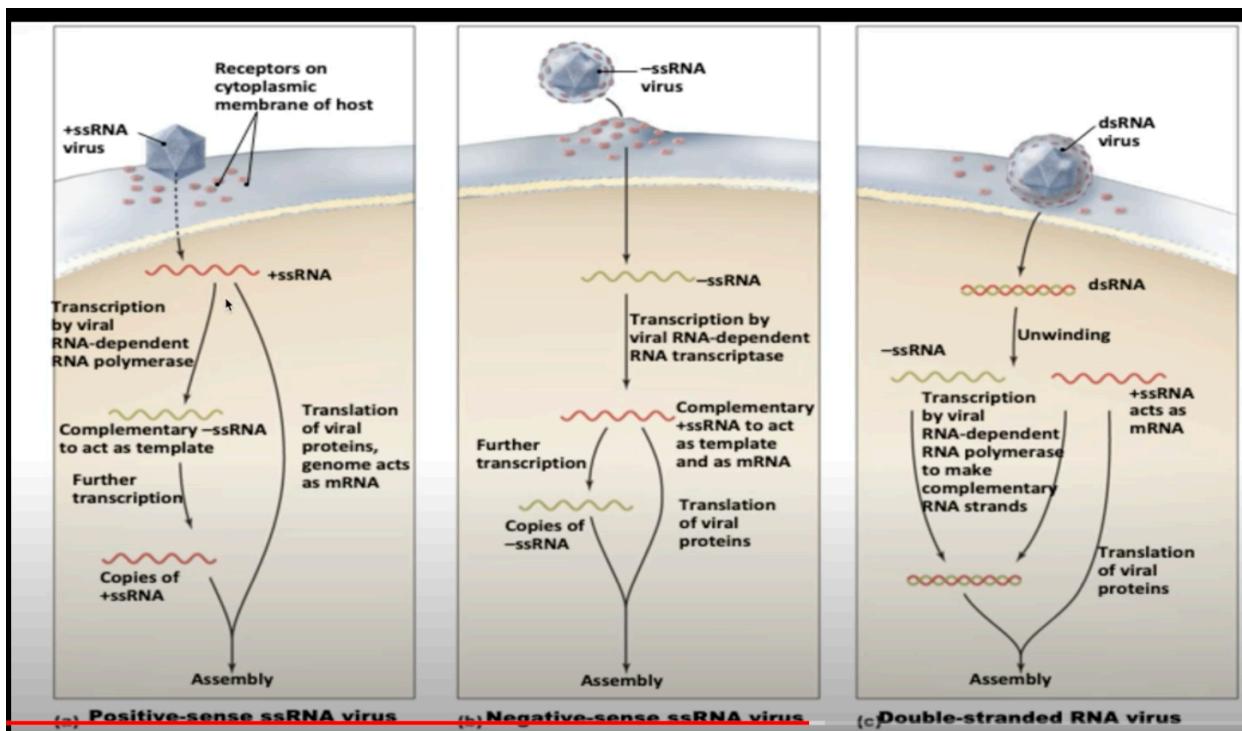


Figure 4: Screen Shot 2020-10-12 at 11.14.30 PM.png

**Packaging** Does not require ATP. Just sealed in.

### Viral Exis Lysis

Replicate so much that the membrane burst.

### Budding

Trigger...

- Trigger exocytosis
- Meanwhile, send virus's own spikes to the membrane
- On exit by exocytosis, steal a part of the newly-spikey membrane with it to serve as new casing

### 1.6.4 | Viral Genetic Shift + Viral Genetic Drift

**Shift** => whole segments of genome exchange abruptly as two flu viruses infect the same cell to create a new strand.

**Drift** => single/groups of nucleotides flip slowly over time.

The former is an environment-dependent process, where the latter is able to be modeled as it is due to transcription mistake.

### 1.6.5 | Retroviruses + How to Stop Them

**Viruses that have the ability to intergrate into the chromosomes of the host cell**

## Early Events

- Viruses is uncoated, and uses an enzyme called reverse transcriptase to turn ssRNA to cDNA, and finally into dsDNA
- Then, the enzyme integrase threads the viral dsDNA into the cell's nucleus
- HIV protease cuts HIV polyproteins into individual parts ready for budding

## Late Events

- Proviral region is transcribed slowly whenever ribosome comes across it by the host DNA polymerase II to make viral proteins + replicate the viral genome
- Components are later exported, assembled, and slowly released through budding

To make this happen, the virus needs...

- **Reverse Transcriptase**
  - Transcript RNA to double-stranded RNA
  - Take double-stranded RNA to turn into DNA
- **Integrase**
  - Force insert the DNA into the genome of the host cell

And because of the fact that viral DNA is now in cellular DNA, these viruses' DNAs are hard to get rid of.

And this is why we can't cure HIV.

Virus, in this case, spread through cell duplication

- Proviral region on the DNA, every time the ribosome comes across it, makes a new viron
- These components are then assembled, sent, etc. as usual
- Because of the fact that the ribosome needs to, well, come across the bit of DNA for this to work, the viroids are made slowly by "trickling out."

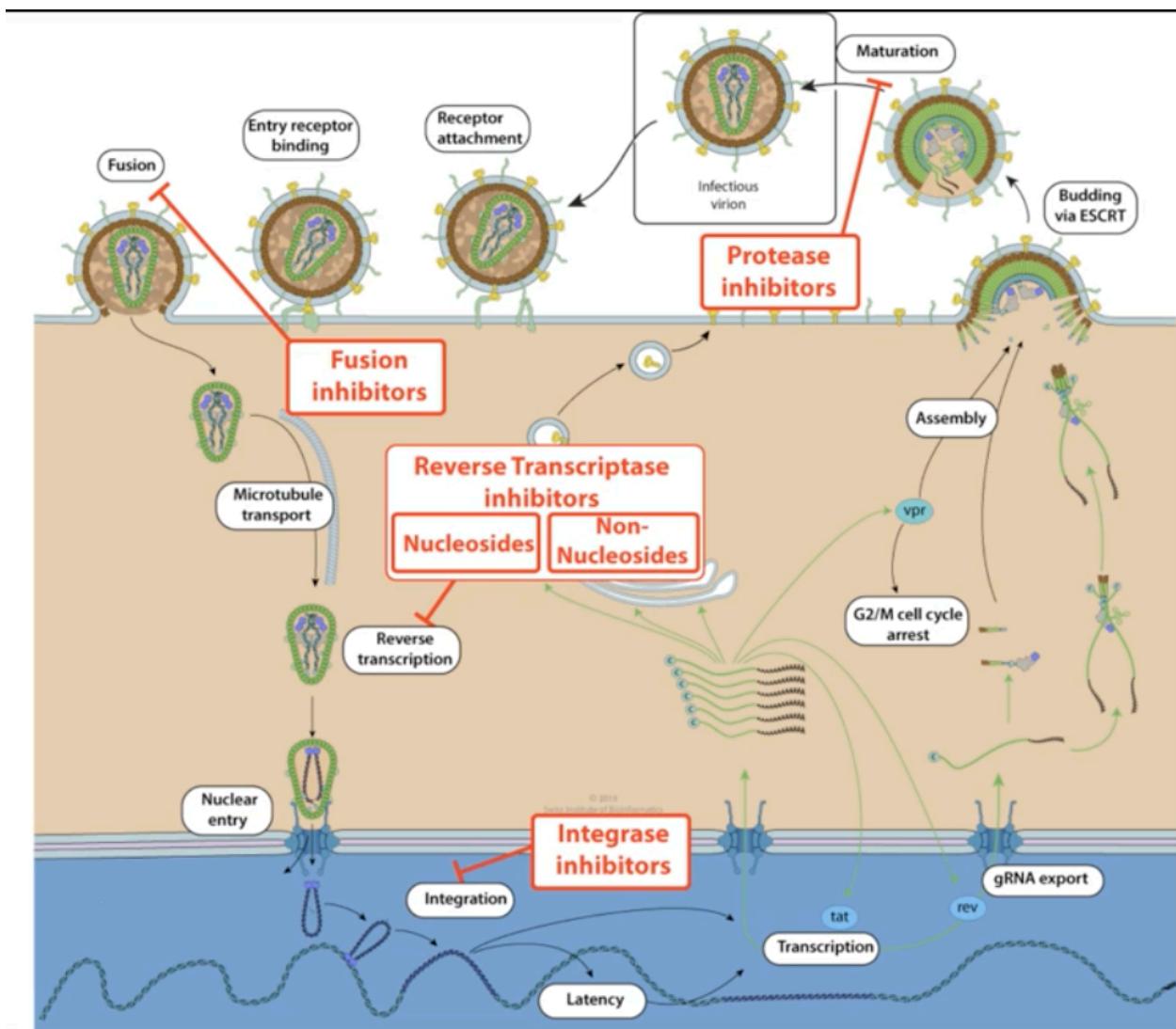


Figure 5: Screen Shot 2020-10-12 at 11.22.35 PM.png

### Preventing Retroviruses

- Prevent Fusion gp120, gp41, CCR5
- Prevent reverse transcription RT
- Prevent intergration via intergrase IN
- Prevent viron maturation PR

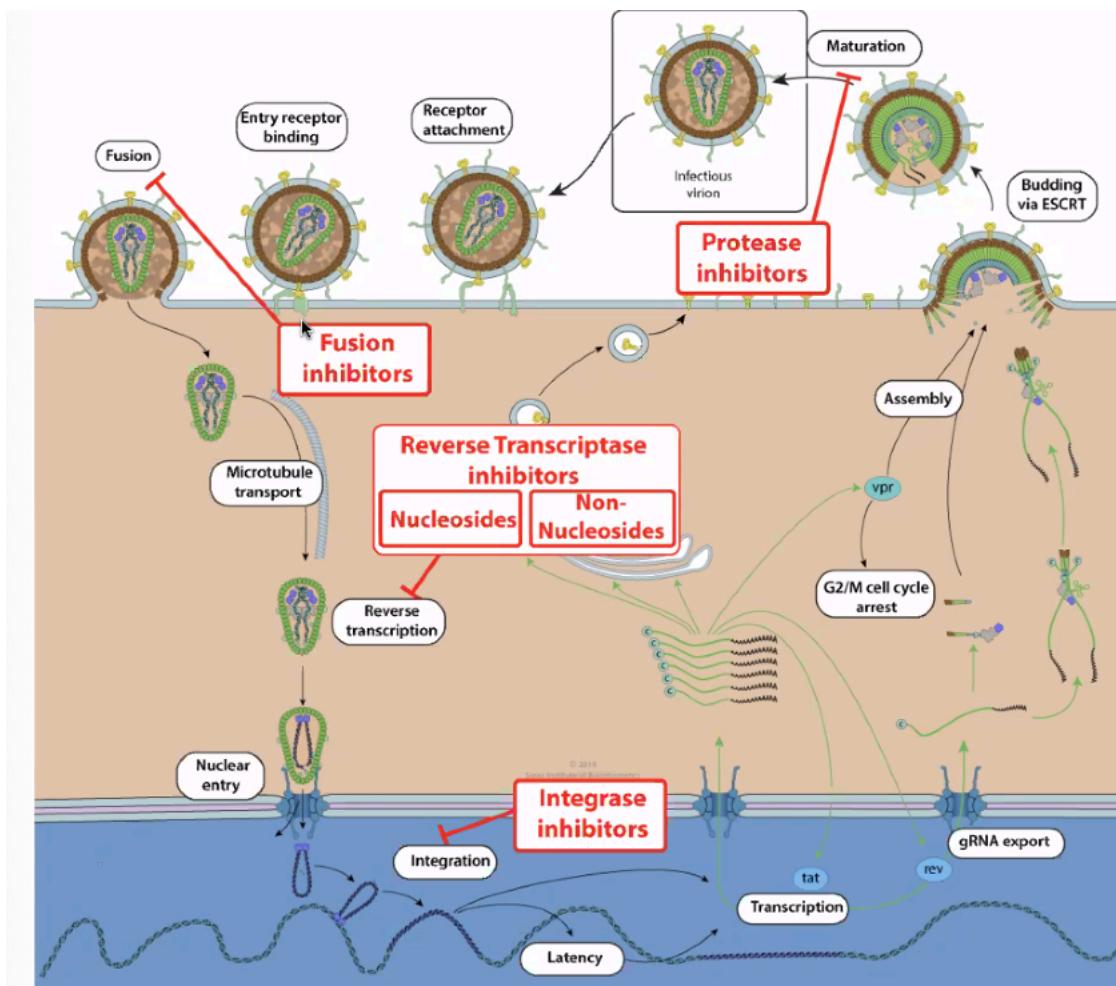


Figure 6: stophiv.png

- Most advanced: HAART (Highly-Active Anti-Retroviral Therapy)
  - Cocktail drug works together for inhibition
  - Two drugs to stop intergration, one to stop protease (viron maturation)
  - Could develop resistance

### 1.6.6 | Viral Genome vs Mutation Rate

## Viral genome size vs. mutation rate

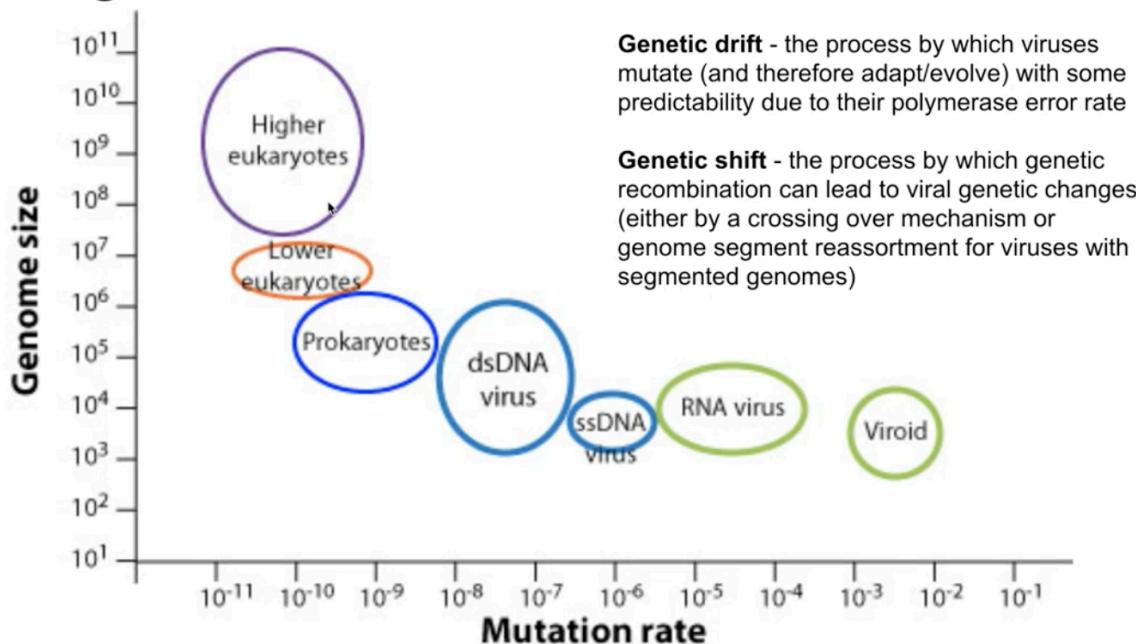


Figure 7: Screen Shot 2020-10-12 at 11.24.39 PM.png

- RNA viruses could mutate more because it does not have checks
- More complex+largest viruses harder to mutate

**Genetic drift** — viruses mutate due to polymerase error

**Genetic shift** — viruses recombine without mutating by crossing-over mechanism or genome segment reassortment. Think! the flu

### 1.7 | Why are viruses bad

Damage host cells/tissues by...

- Reducing gene expression capacity
- Depleting cellular resources
- Causing cell lysis (to explode)
- Promoting tumorigenesis — cancer
- Creating damaging immunological response

### 1.8 | Preventing Viruses

Let's talk about **Remdesivir**! A drug developed by Pfizer that's used to combat Ebola + influenza viral replication.

Modified nucleotide triphosphate which adds onto the RNA strand copied by the RNA-Dependent RNA Polymerase carried by viruses

- Pretends + gets inserted as a nucleotide
- Once added onto the RNA chain, jams further actual nucleotides from being inserted

*Could* but usually does not jam up normal RNA polymerase which does normal transcription

- Inhibiting transcription in the short term won't kill you immediately
- So, we hurt normal cell transcription a little in order to rid of the virus
- Need hospital treatment for regular and safe dosing for this exact reason
- Viral proteins are usually easy to assemble

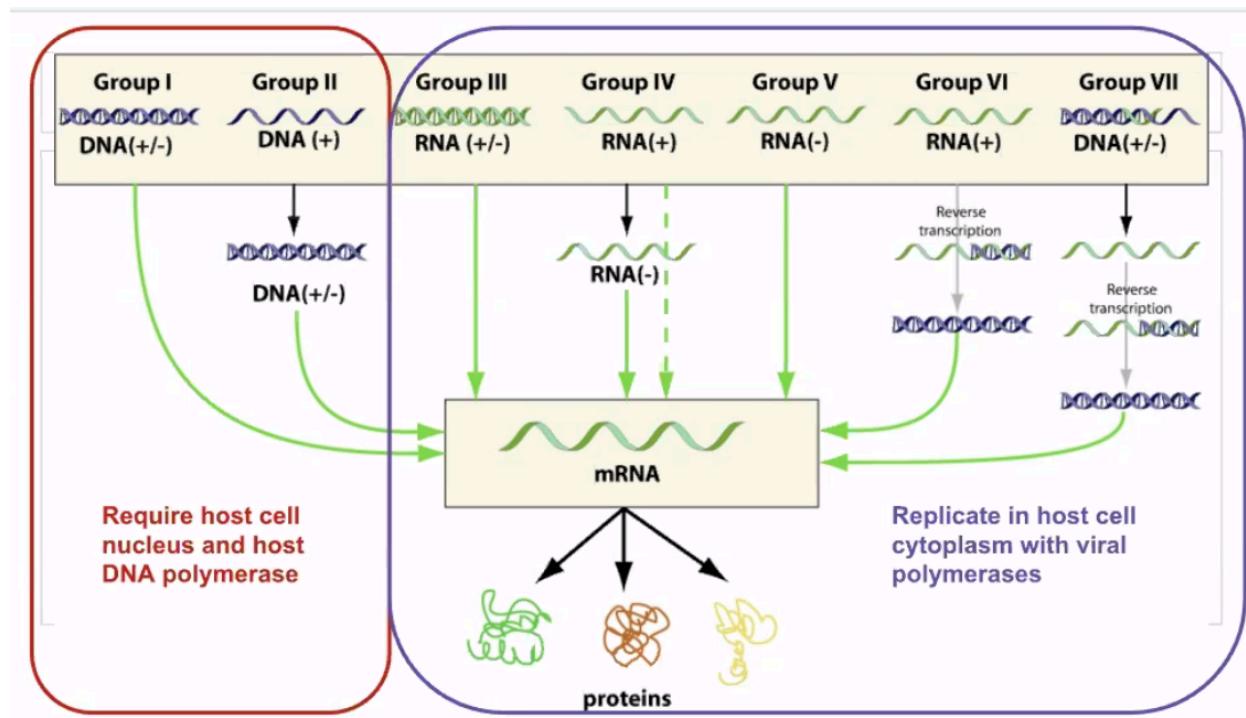


Figure 8: Screen Shot 2020-11-02 at 2.48.22 PM.png

#### Question: how are proteins made in the viral genome

- No viruses produce ribosomes
- Ribosomes become centrally important for the virus
- What serves as the template to make new virus copies

Viruses attempt to overwhelm the enzyme to entry.

- **DNA Polymerase** takes DNA and makes more DNA
  - Duplicates cell DNA
  - Could be hijacked during cell cycle to duplicate DNA viruses
  - DNA viruses may also carry their DNA Polymerease to not wait for the cell cycle
- **RNA Polymerease** takes DNA and makes mRNA

- Have lower fidelity with an error about 1/100,000
- Hence why safety mechanism needed

**Capping and Tailing** \* 3' end => AAAAAA tail (using poly-adenine tailing enzyme) \* 5' end => GGGGGG cap (using guanine-capping enzyme)

**DNA** viruses are “less complex”, in that as long as they are able to get into the nucleaus, the rest would just be the body’s work automatically.

### 1.8.1 |List of Kool Proteins

Name	Function
RNA Polymerase	<i>transcripts</i> : takes DNA and turns into mRNA
DNA Polymerase	<i>replicates</i> : takes DNA and makes more copy of it
RNA-Dependent RNA Polymerase	<i>replicates</i> : takes RNA and makes more copy of it. Basically only viruses use it.
Promoter	<i>signals</i> : DNA signal of the start of the DNA.
Terminator	<i>signals</i> : DNA signal of the end of the DNA.

## 1.9 |DNA Replication and the Cell Cycle

### 1.9.1 |So, why do cell divide

The ability to produce organisms more of their kind is one characteristic that best distinguishes living things from nonliving matter

Viruses + Organelles challenge this definition => they are symbiotic and cannot reproduce on their own.  
We tend to think that cells

- Everyday, 50-70 Billion die => **programmed cell death**
- To compensate this, Mitosis (cell division) happen
  - Cell divide in opposite directions
  - Two strands ANTI<sub>P</sub>ARALLEL to each other

### 1.9.2 |Levels of DNA structure

- DNA Double Helix => Unwrapped, raw DNA
- Histones => coiler proteins at which DNA coils around
  - Four histones
  - H3, H4, H2a, H2b wraps, H1 seals the four together
  - Each protein has 1.65 wraps
- Nucleosomes => stack of 2 histone groups to create a spool of 8 histone proteins wrapping DNA
- Nucleosomes wraps around into a large fiber called “chromatin”
- A pair of chromatin entangle to form a chromosome

### 1.9.3 | Cell division process

- Chromosomes line up in equator
- Each chromosome has two chromatid exactly the same
- Microtubials to pull chromosomes apart connected to kinecore, a joint in the chromatid
- Kinetore senses tension, and when it is correct, molecules are sent down the microtubials to send a split signal

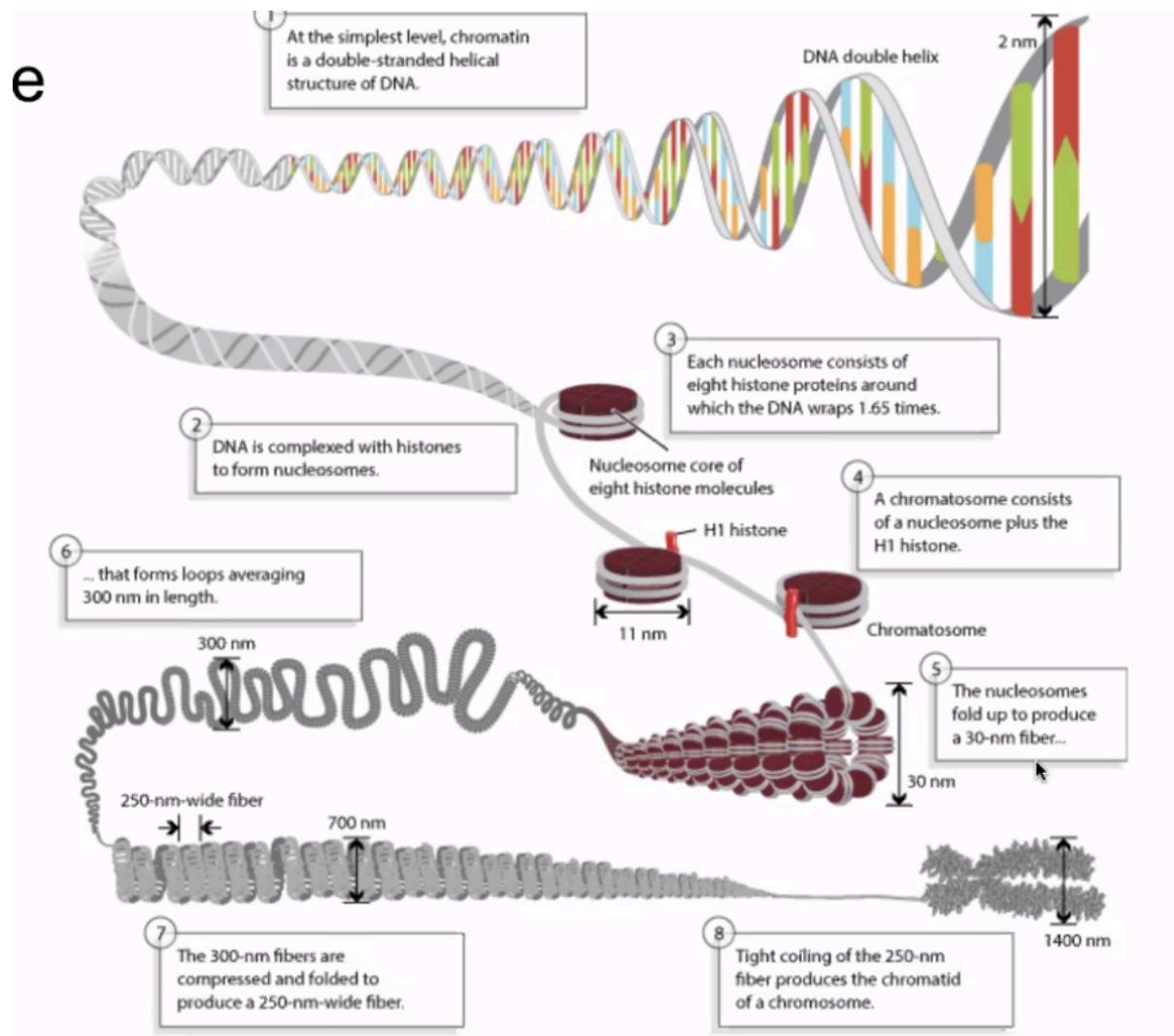


Figure 9: levelsofdna.png

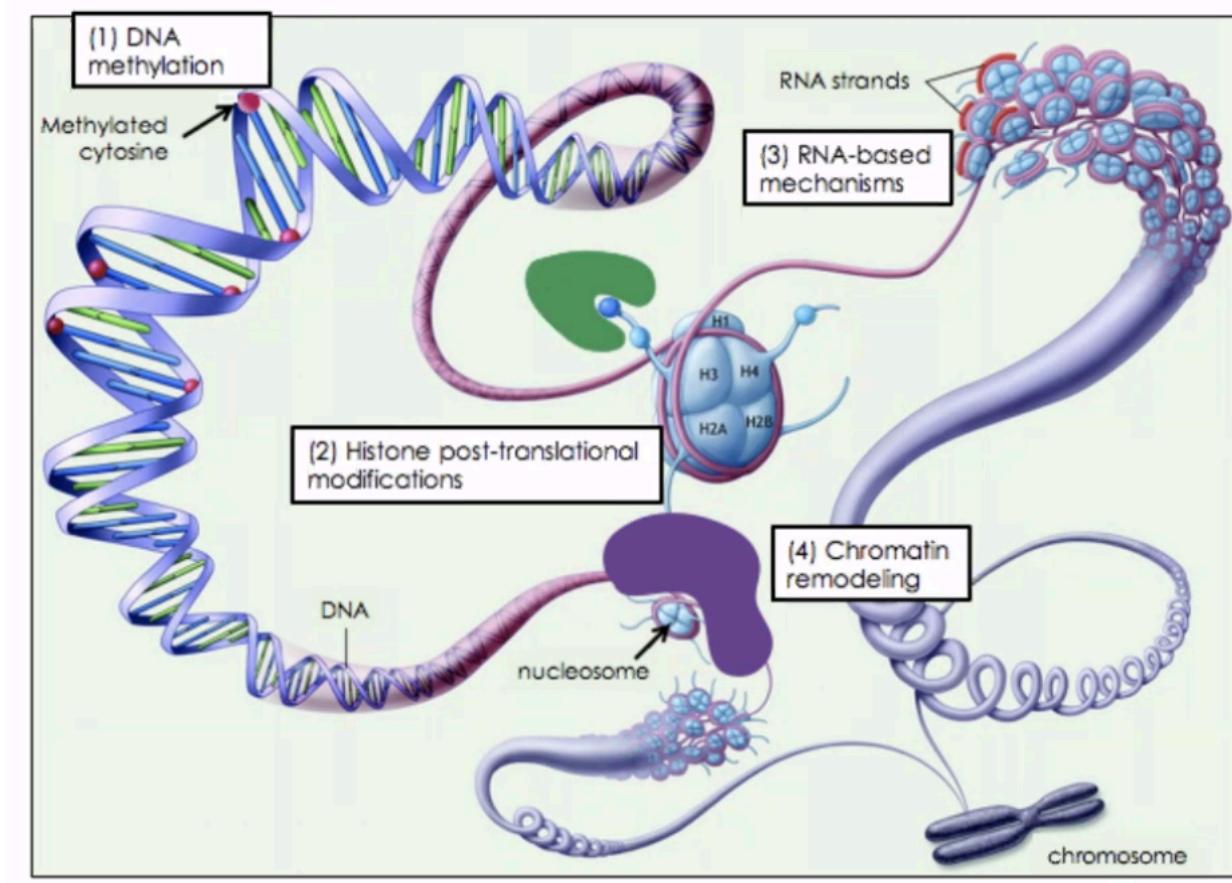


Figure 10: histones.png

### Most cell division results in genetically identical daughter cell

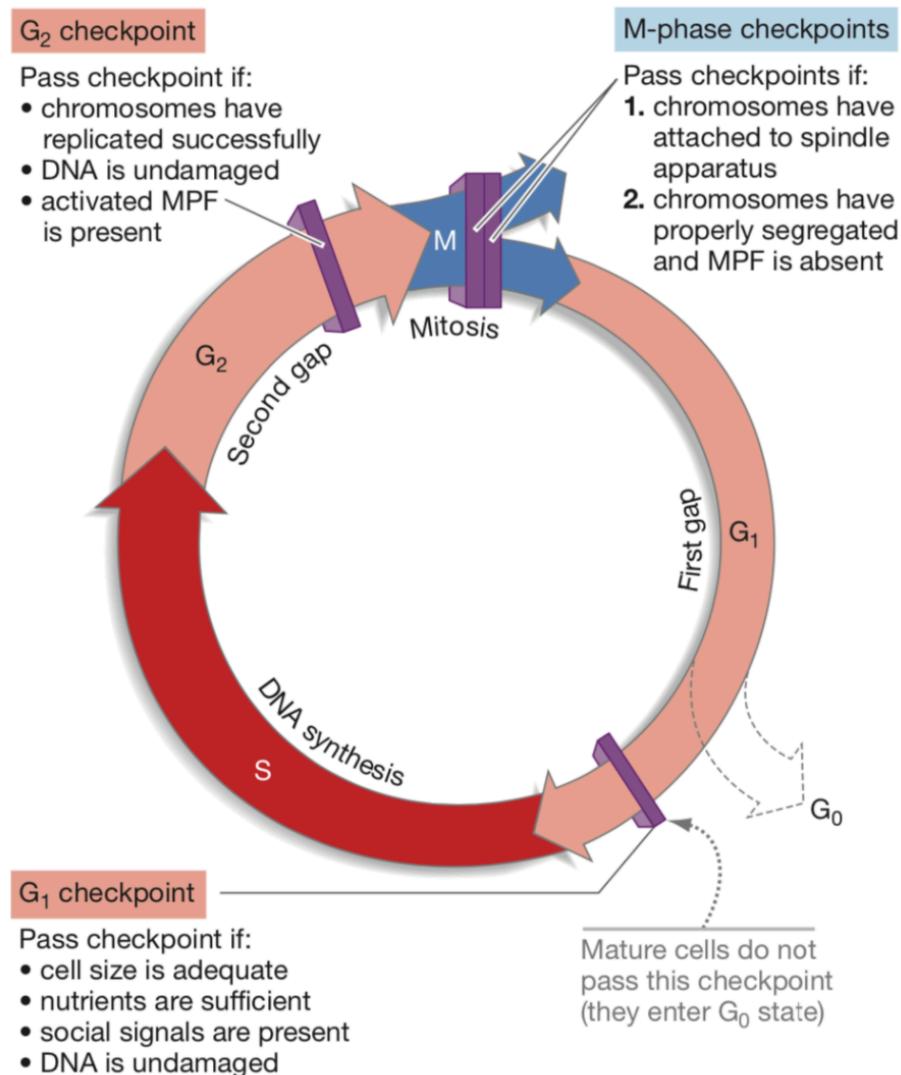
Each cell, once specialised, chooses what parts of their chromosome to unwrap + permanently wrap.

Difference in transcription results in different phenotypes.

Sperm + Egg (imcomplete cells) combine together to form a “zygote” => a single cell. Each person is from a zygote.

For Eukarotes, cells divide using Mytosis.

Paul's Cell Cycle Primer



**Figure 12.12 The Four Cell-Cycle Checkpoints.**

Figure 11: Screen Shot 2020-11-09 at 3.16.12 PM.png

#### 1.9.4 | Major Cell Cycle Parts

- G<sub>1</sub> => Rest Phase, Gap 1
  - May hit s.a. to volume checkpoint => if ratio too big, the cell is too big
  - May hit diffusion checkpoint => larger cells would need to work harder to transport things to the centre
- S => S Phase, duplicate DNA. 150 mins
- G<sub>2</sub> => Rest Phrase, Gap 2. The pairs of DNA begins bundling and condensing; the DNA is also checked upon and verified for consistency
- M => Mitosis!
  - Prophase: condensation of chromosome
  - Chromatin aligns in the center => (metaphase)

- A divit (DEFINITION?) forms
- Two chromatin becomes pulled apart => forming two cells via cytokinesis (anaphase)

Cell regulators are proteins that manage and shepherd the process of cell division. They respond to molecular signals throughout the cell and check for internal signals like DNA damage to control the rate and progress of cell division.

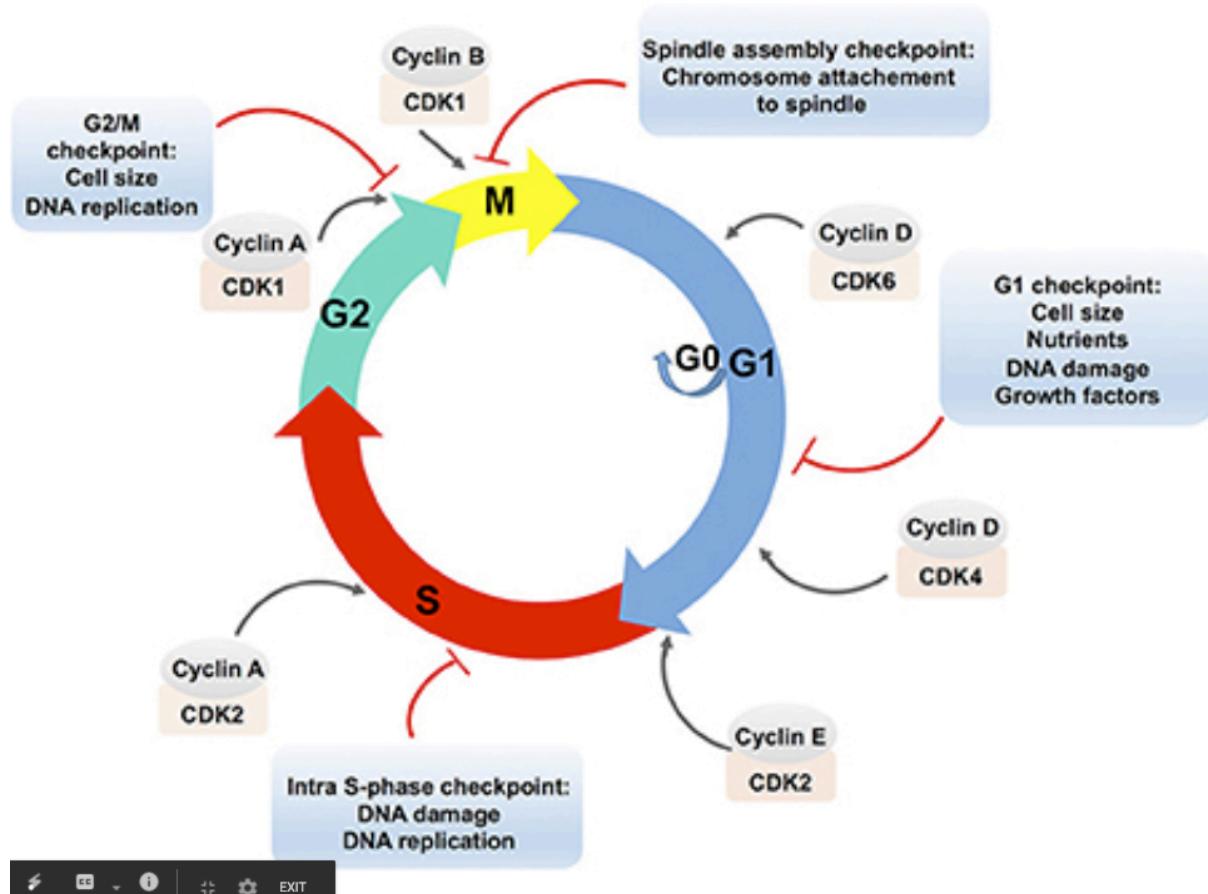


Figure 12: lecellcycle.png

### 1.9.5 | DNA Replication Process

DNA replication is known to be “semi-conservative” — meaning that it is a process that pairs a synthesized half of the DNA with an original half of the DNA (i.e. takes the ORIGINAL template strand + makes the NEW coding strand & takes the ORIGINAL coding strand + makes the NEW template strand.)

Because **polymerases copy uni-directionally** => DNA polymerase move along the 3' to 5' DNA to create a copy 5' to 3'. Meaning, the polymerase is able to add nucleotide onto the 3' end of the DNA.

- Open the DNA at an arbitrary point using the Helicase
  - Uses two helicase => one open rightward, and one leftward. The movement of the helicase opening the DNA is called the “fork movement”
  - DNA polymerase could only add nucleotides 5' to 3'
  - As helicase opens a little bit of the DNA, polymerases rushes to copy the area that opened

- In the **leading** strand (3' to 5'), polymerase will run alongside the helicase for they are opening and replicating on the same direction
- In the **lagging** strand (5' to 3'), polymerase will wait until the helicase opens a little segment, and rushes forward and move backwards
  - NOTE: the lagging strand... 1) takes longer to transcribe 2) is done in small chunks (each "rush forward"). Each chunk is called an ogazaki fragment

## DNA replication fork and strand synthesis

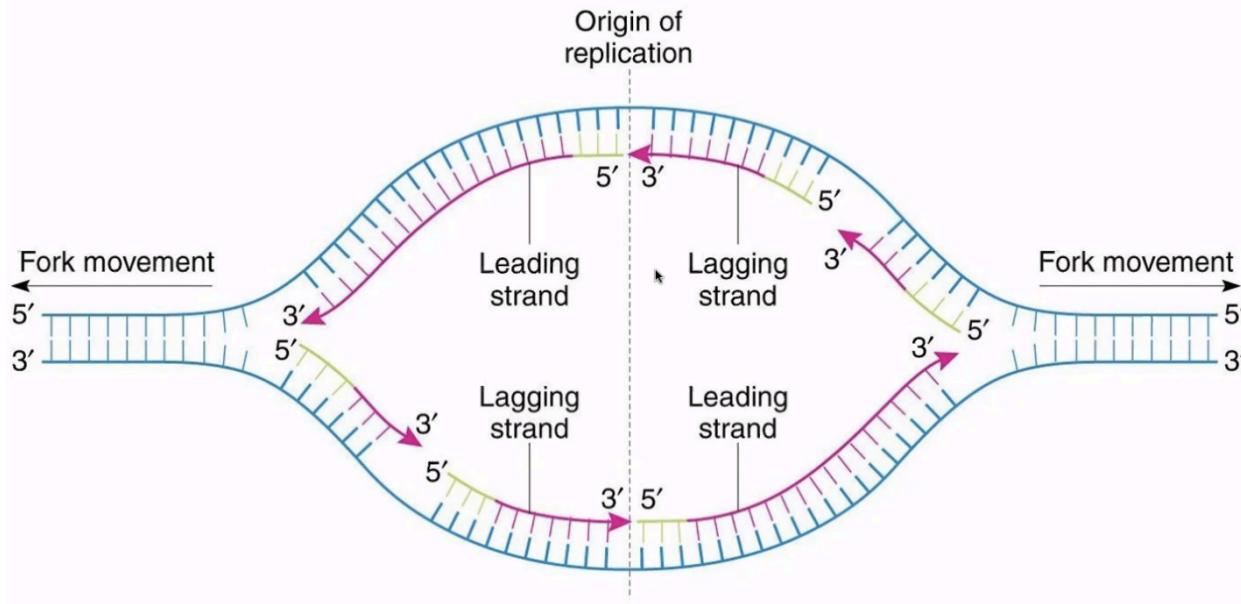


Figure 13: leadinglagging.png

- DNA polymerase will REQUIRE a double-stranded area to begin work from, so Primase synthesizes already double-stranded RNA primers that DNA polymerase could bootstrap to the single-stranded DNA to begin the replication process (think: create-react-app)
- DNA polymerase will detect unfitting bonds and remove leftover RNA primer bootstrap units to repair them in a process called "proofreading." DNA polymerase is assisted with "glue" ligase to help the DNA polymerase pick out and replace problematic/unneeded nucleotides and perhaps their neighbors. This is where the Ogazaki fragments get joined.

Steps of DNA replication, in Paul's words:

- Many proteins work together in DNA replication and repair.
- The process of DNA replication is semiconservative, such that takes place through complementary base pairing.
- The process of replication begins at the origin of replication, forming a replication fork. The enzymes involved include helicase, topoisomerase, and primase.
- Topoisomerase breaks, swivels, and rejoins the parent DNA to relieve strain caused by unwinding.
- DNA polymerase is the enzyme that catalyzes the process of complementary base pairing of nucleotides.
- New nucleotide strands always form in the 5' to 3' direction, therefore the leading strand forms continuously.
- The lagging strand is synthesized in Okazaki fragments.

- DNA polymerase is able to proofread pairing, and along with mismatch repair enzymes, DNA is carefully copied.
- The ends of a DNA molecule are called telomeres (not in circular genome e.g. bacteria), and shorten during cell division.