3-D Molecular Designs
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MSOE UNIVERSITY Center for BioMolecular Modeling

CHROMOSOME WEBINAR

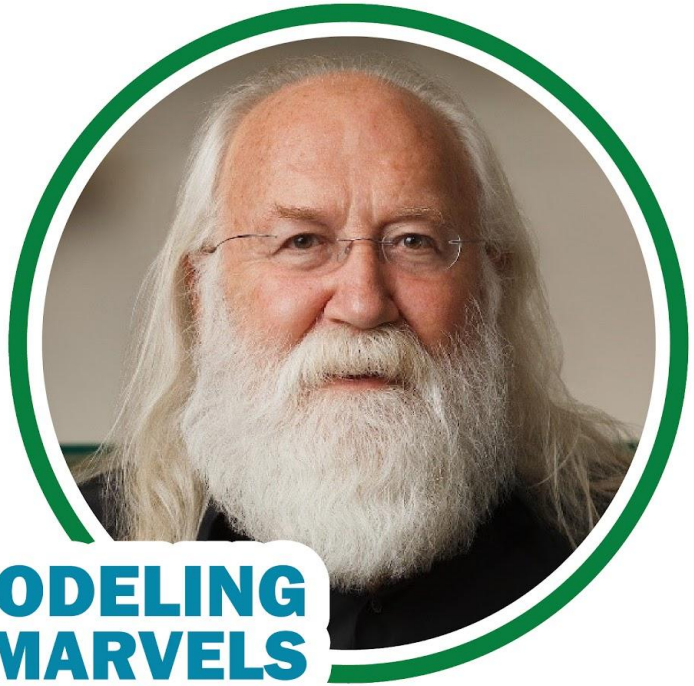
TUESDAY | MARCH 22 6:30 - 8 PM CST

PRESENTER:

TIM HERMAN, PhD

MSOE Center for BioMolecular Modeling &
3D Molecular Designs

Modeling Methylation in Epigenetics



MODELING MARVELS
2022 EDUCATORS WEBINARS

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Modeling Methylation in Epigenetics.

Reviewing the past two weeks….

Methylation of CpG… in epigenetics

Deamination of C's to U's... and why RNA

And now, Epigenetics Part II

Methylation of *histones*…in *nucleosomes*… found in *chromatin*… that makes up *chromosomes*

Epigenetics, *the reversible chemical modifications of both DNA and histones, that can influence how genes are expressed.*

In epigenetics, the Cytosine of the dinucleotide sequence CpG ….is methylated at the #5 carbon.

And now… the rest of the story

Remember, that methylated #5 carbon of C is found in the major groove of DNA.

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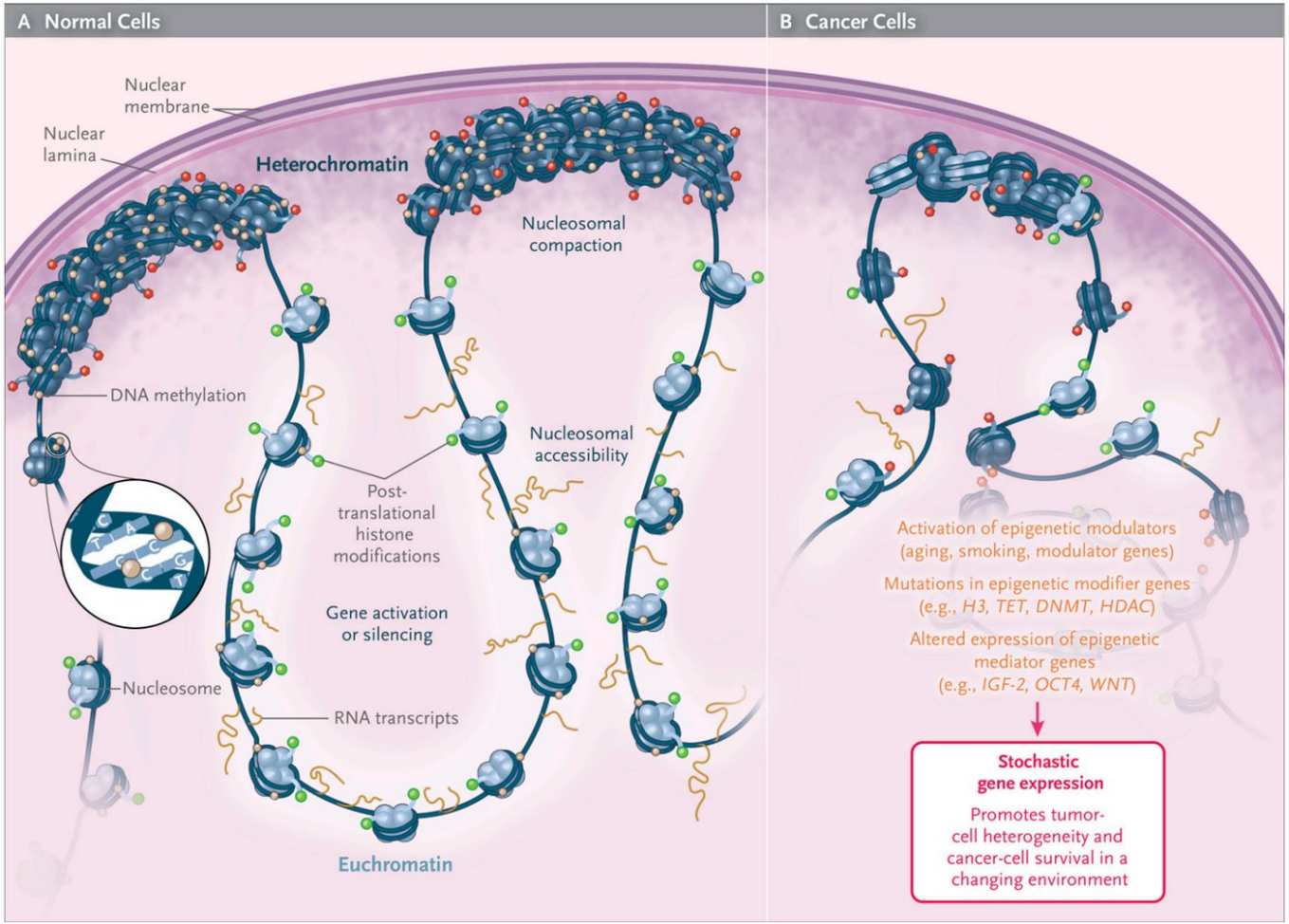
The chemical modification of histones…

Histones… to Nucleosomes…

to Chromatin… to Chromosomes



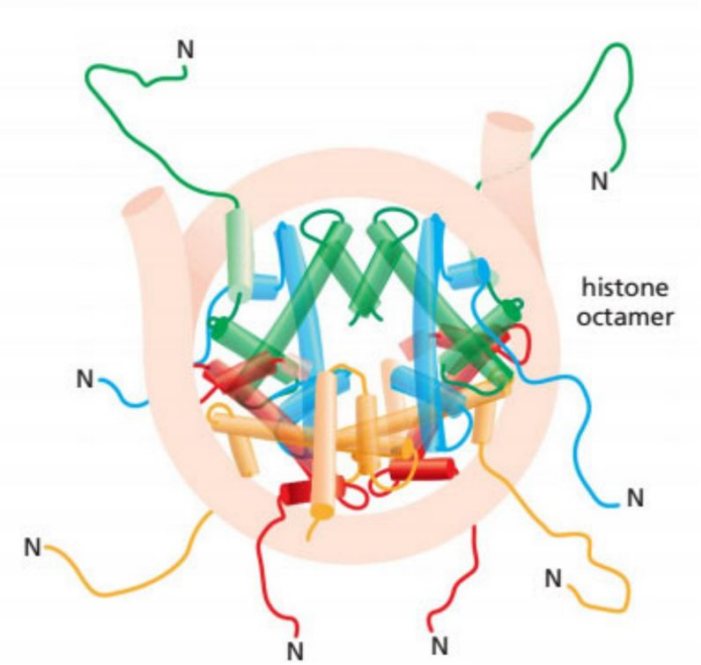
The Cellular Nature of Epigenetic Information.

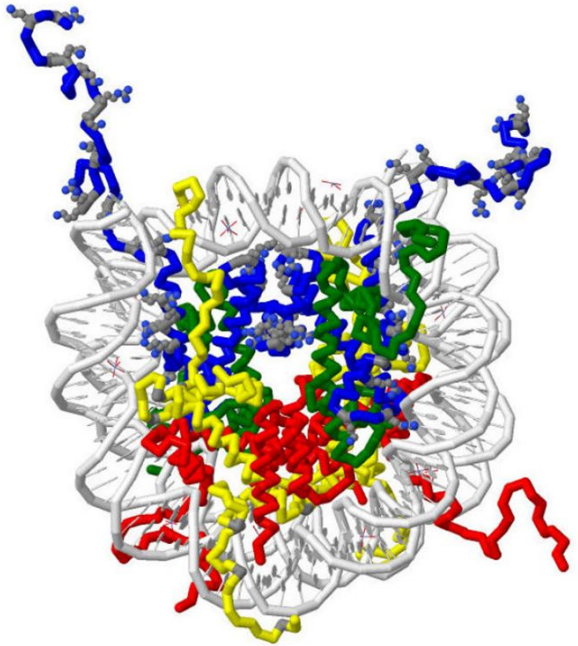
The DNA double helix is modified at the nucleotide cytosine by DNA methylation (brown dots). The nucleosomes around which the DNA is coiled undergo post-translational modifications of their component histones (green dots, depicting activation marks; red dots depict silencing marks), leading to gene activation (light-blue nucleosomes, with RNA transcripts originating nearby) or silencing (dark-blue nucleosomes). Higher-order chromatin structure involves nucleosomal compaction often near the nuclear membrane (heterochromatin) or nucleosomal accessibility (euchromatin). The nuclear periphery is primarily repressive but probably also contains transcriptionally permissive subcompartments. Higher-order large blocks of heterochromatin often involve large epigenomic domains termed lamina-associated domains (LADs) and large, organized chromatin lysine (K) modifications (LOCKs). In cancer, both large and smaller heterochromatic domains become euchromatic. In addition, epigenetic modulators such as environmental exposure and aging, as well as cancer mutations in epigenetic modifier genes, affect the expression of epigenetic mediators controlling pluripotency and cellular self-renewal. All these factors lead to increased stochastic gene expression in cancer, promoting tumor-cell heterogeneity and cancer-cell survival in a changing environment (e.g., as a result of metastasis or chemotherapy).

From NEJM 378:1323-34; 2018

Nucleosomes,… the repeating structural unit of chromatin

- 8 histones,…2 each of H2a, H2b, H3 and H4
- 145 base pairs of DNA / 1 ¾ turns

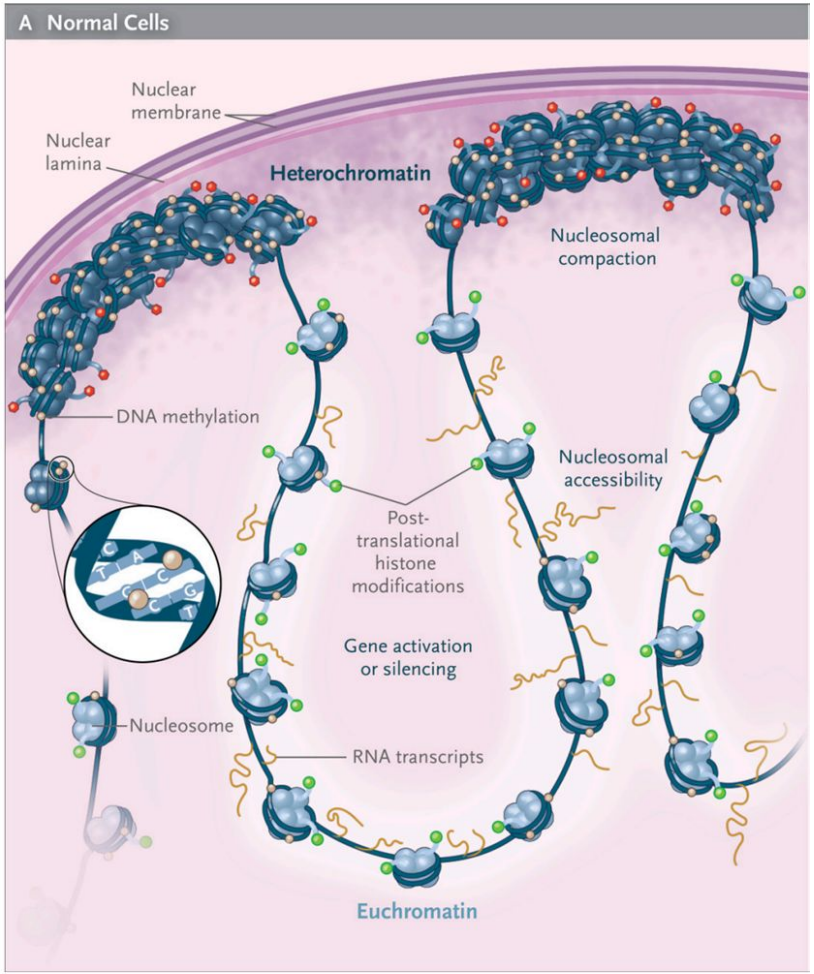




WHY…Nucleosomes?

- Compacting, without entangling
- Regulation of gene expression

…an octamer of 8 small histones???



Epigenetics…

Modification of DNA….

- Methylated CpGs

Modification of Histones….

- Silencing Marks (methylation)
- Activation Marks (acetylation)

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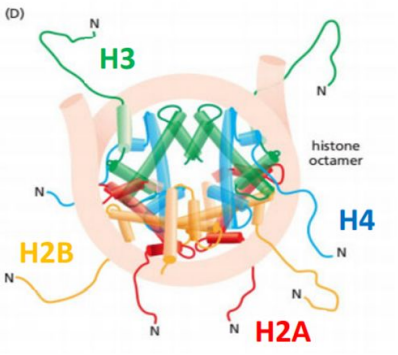
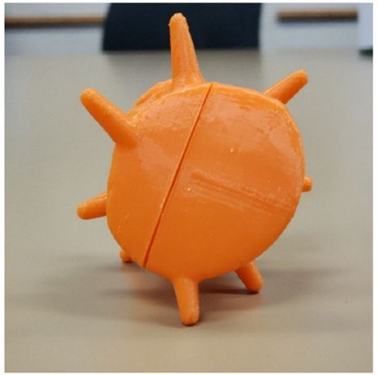
Let's explore chromatin structure and nucleosomes!

What is chromatin? Chromatin is the term used for the material that forms chromosomes in eukaryotes *and* archaea (but not prokaryotes). It is made up of DNA, histone proteins, and non-histone proteins, in approximately equal mass. DNA is wound around the histone proteins to form a unit called a nucleosome (see illustration below, left). Non-histone proteins are diverse and have a number of different functions that we will revisit later in regard to epigenetics.





Histone core particle

Basic unit of chromatin = the nucleosome (histone core particle + approximately 146 bp DNA)

Histone core particle is an octamer made up of 8 proteins: [H2A + H2B + H3 + H4] x 2

Each histone protein is small (~100 aa), consisting of 3 α-helices and 2 loops which make up the globular part and an N (amino)-terminal flexible tail that protrudes from the nucleosome.

SnapShot: Histone Modifications

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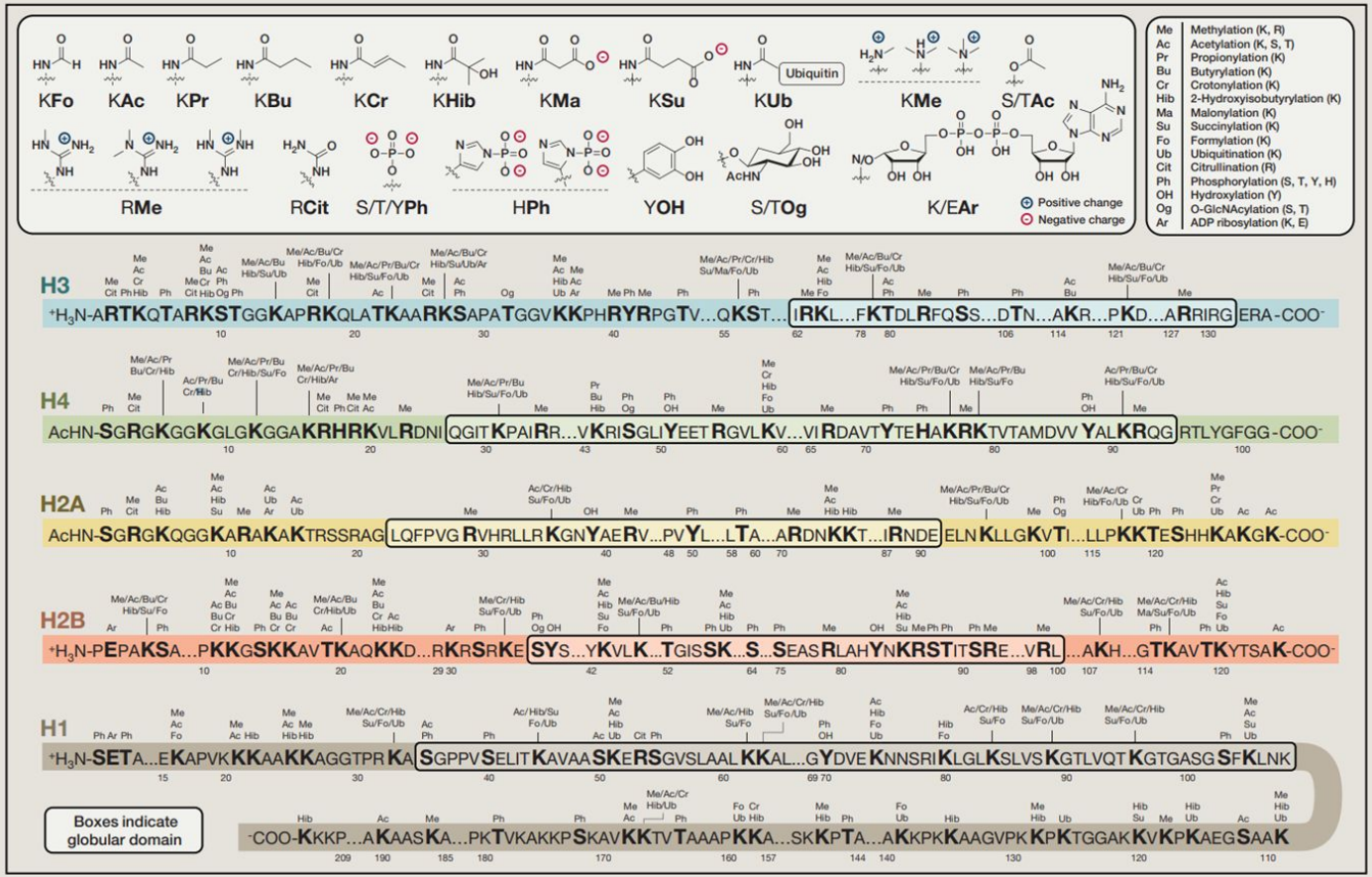
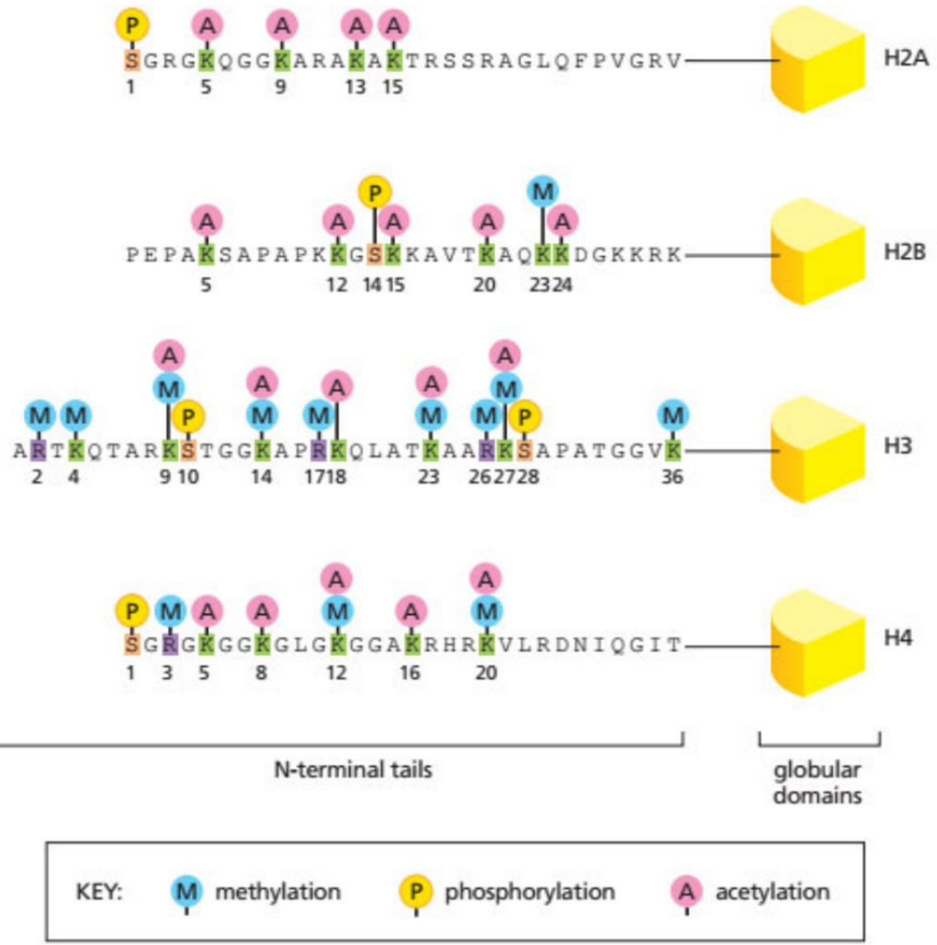
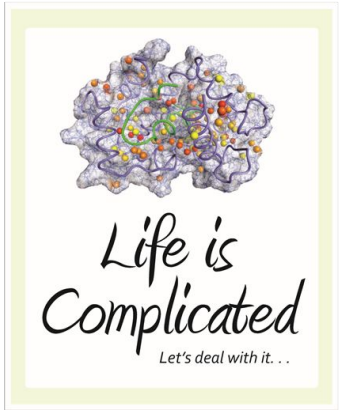
Cell



These chemical markers are added by a family of proteins (enzymes) known as epigenetic writers



Remember….



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Let's explore Chromatin Function and Epigenetics!

Now you should have a good idea of how DNA is wrapped around histone proteins to form nucleosomes and understand that nucleosomes can be tightly packed (heterochromatin) or loosely packed (euchromatin). We will now explore how this basic structure allows for all the necessary functions of DNA and chromatin.

DNA and chromosomes are involved in many important functions of the cell, such as:

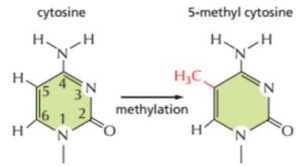
- Transcription of DNA into RNA for gene expression
- Replication of DNA leading to cell division
- DNA repair when a mismatch or DNA break is detected

All these functions and many others require specialized proteins to gain access to the DNA and to be directed to the correct locations to carry out their functions. The way that this is achieved is through markings added to DNA and the histone protein. Collectively these markings are called "epigenetics", meaning "above genetics" because they do not change the nucleotide sequence or base-pairing properties of DNA.

Both DNA and histone proteins can accumulate these markings that direct various structural and functional outcomes. These modifications are reversible allowing the functional changes to be dynamic, depending on input from the environment of the cell. To clarify this complex area, we will model DNA and histone epigenetic modifications separately, but it is important to remember that the modifications work together to carry out a specific function.

DNA Modification: Cytosine methylation

The primary epigenetic modification of DNA is methylation of the 5 carbon of cytosine. Use a cytosine from the Dynamic DNA Kit and identify the 1 through 6 positions of cytosine.



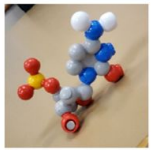
Which positions are involved in base-pairing of cytosine to guanine?

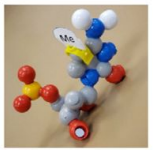
Positions 2, 3, and 4

Which position is bound to the sugar-phosphate backbone?

Position 1

Place a methyl group clip on the 5 position. Notice where it is in relation to other functional groups so that you can easily methylate cytosines within DNA.





Where have all the CpG's gone?

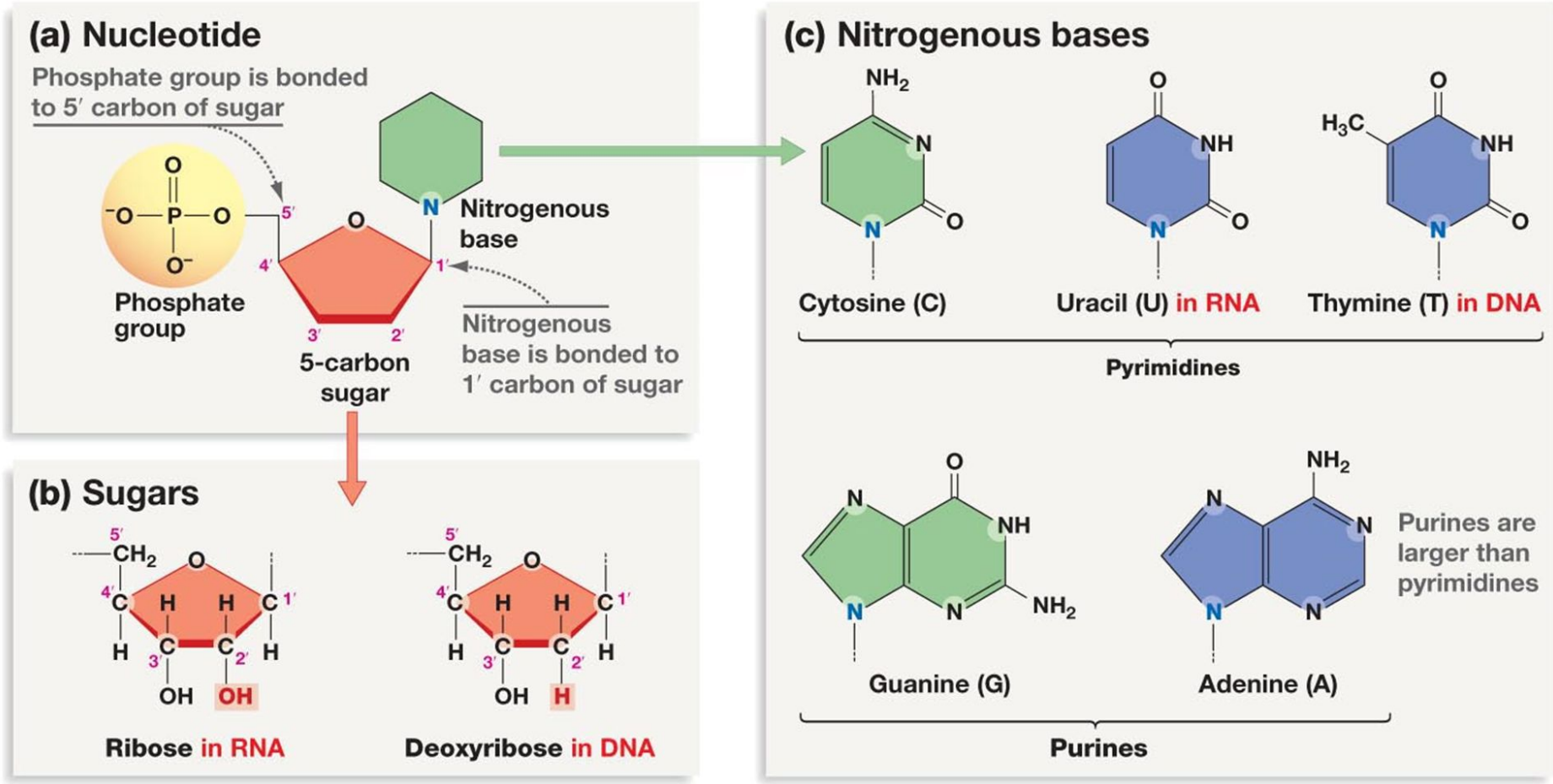
long time passing….

You would expect to find a CpG dinucleotide once every 16 nucleotides in a random DNA sequence.

But… when you analyze the human genome, you only find a CpG every 100 nucleotides.

So… *where have all the CpG's gone?*

One more note: dense clusters of CpG's – called CpG islands – are often found immediately upstream from protein encoding genes.



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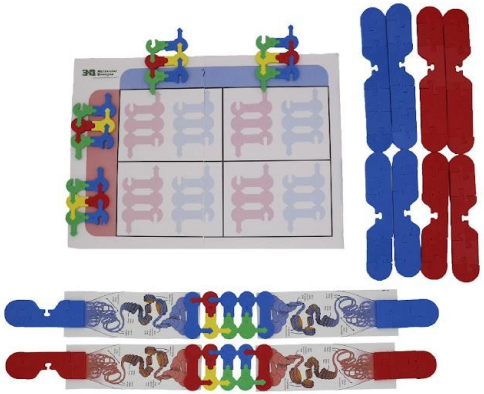
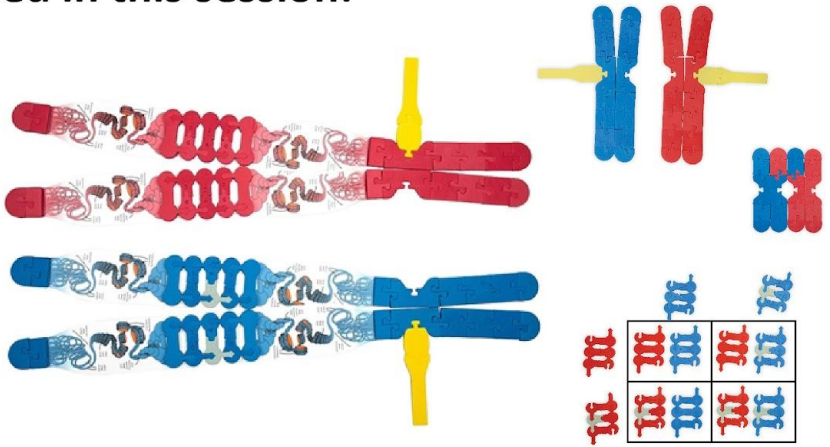
THANK YOU FOR ATTENDING!

Kits and models used in this session:





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