Viral Genomes: a Simulation of Viral Protein and Nucleic Acid Syntheses

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Authors

Marcia Cordts
University of Iowa
Iowa City, Iowa 52242
USA
Email: marcia-cordts@uiowa.edu

Eileen Gregory
Rollins College
Winter Park, Florida
USA
Email: EGREGORY@ROLLINS.EDU

Abstract

Students working in pairs or small groups receive a simulated virus: two paper cups taped together, enclosing a strip of paper listing an RNA or DNA sequence (an abbreviated viral genome). The students break open the cups (simulating viral uncoating in the host cell) and decide how host and/or viral enzymes will convert the genome into viral proteins and new genomes. The sequences provided describe a double-stranded DNA virus, single-stranded RNA viruses (+ or - strand), a retrovirus, and a double-stranded RNA virus. Templates for photocopying the genomes, sample worksheets, and an instructor's answer key are included.

Activity

Invitation for User Feedback. If you have used the activity and would like to provide feedback, please send an e-mail to MicrobeLibrary@asmusa.org. Feedback can include ideas which complement the activity and new approaches for implementing the activity. Your comments will be added to the activity under a separate section labeled "Feedback." Comments may be edited.

Editor’s Note (2008): This Curriculum Resource was published prior to establishment of current criteria of submission, and as such, does not contain all criteria required of current publications. However, the Editorial Committee felt that the activity itself remained worthwhile and relevant, and encourages potential users to contact the authors for clarification as needed. If you do update this activity for use with your students, and are interested in updating the resource for distribution in the library, please contact ASM at MicrobeLibrary@asmusa.org.

INTRODUCTION

Time Required.
One regular class period or about 50 minutes of lab time. This activity works well on "light" lab days when students may have a few other tasks to complete.

Pedagogical Function.
This activity was designed to help students to understand better how viruses (strict parasites which use various nucleic acids as their genetic material) differ from cells (living entities which always use double-stranded DNA as their genetic material). In working through this activity, students benefit from the opportunity to clarify differences between the processes of genome replication and protein synthesis.

Background.
This activity is a good follow-up to a lecture on viruses that introduces capsid structure and the diversity of viral genome types. The activity serves as an excellent review for the basic processes of transcription, translation, and DNA replication which students probably learned about prior to the virus lecture(s).

PROCEDURE

Materials. Appendix I contains template genome sequences for 5 different viruses, which may be printed out and photocopied, if desired. The three single-stranded viruses each have 7 copies of the "genome" per page, while the double-stranded DNA and double-stranded RNA viruses each have 5 copies of the "genomes" per page, making a total of 31 genomes per set. For each 10 to 15 groups of students, plan on one set.

Other materials needed include 62 paper cups per each set of 31 genomes, Time tape or other tape (using 5 different colors of tape allows for easy color coding), and a marker to number the viral capsids 1 to 5.

This exercise has worked well when the instructor assembles and numbers the viral capsids before class and tosses them all into a box. During the activity, students choose a virus from the box, work on it at their seats, then reseal the genome into the capsid and return it to the box, choosing another if desired.
**Student Version.** A four-page write-up for students—including introduction, instructions, a sample problem, and worksheets—is included.

**Student Handout**

**Safety Issues.** Not applicable.

**ASSESSMENT and OUTCOMES**

**Suggestions for Assessment.**
No specific assessment of this activity is required. Generally, walking around the room as student groups are working through the viral genome simulation provides excellent evidence of students who understand vs. students who are having difficulty with the concepts. The single most common remark overheard during this exercise is “oh, negative-strand and positive-strand viruses never get converted into DNA—only retroviruses have a DNA stage.” Often, this exercise has proven useful in identifying students who have fundamental confusion about specific aspects of the central dogma. In general, students have recognized the value of this activity and express satisfaction with the time spent working through the simulation.

**Problems and Caveats.**
The tasks to do in preparation for this activity require about 25 minutes per each set of 31 “nucleocapsids.” Specifically, the instructor must (1) print out and/or make photocopies of the 5 pages of genome sequences, (2) cut the photocopies into strips (one sequence per strip), (3) place a genome strip into a paper cup and tape a second cup to the first with two pieces of tape, (4) label the outside of the capsid with #1, #2, #3, #4, or #5 to match the genome inside, and (5) put a mixture of virions into boxes for students to grab.

In general, it has been useful to work through the sample problem with students before turning them loose to choose their own viruses. When demonstrating how to solve the example problem, it’s important to actually write out the complete base sequences on the chalkboard or overhead. Otherwise, some students will assume that all that is required to answer the questions are the words “DNA” or “RNA,” and they’ll miss much of the value of the exercise.

Answers to the sample problem in the students’ write-up and answers for each of the 5 viruses are included in Appendices II and III, respectively. Copies of these can be provided to any TAs in the course.

Finally, note that there is some symbolism to each of the viral genome sequences. All genomes are of course much abbreviated, compared to reality. In each case, a box delineates part of the genome and this is meant to represent a portion of the genome that is transcribed/translated into protein. This boxed region is shorter than the genome by a few bases, to symbolize the fact that each genome contains multiple genes plus noncoding sequences. Within each boxed “gene” is an open reading frame of about 5 amino acids, plus a few extra bases to symbolize the nucleotides needed for ribosome binding, transcription termination sequences, etc.

**SUPPLEMENTARY MATERIALS**

**Possible Modifications.** An additional question — appropriate in some courses — could ask the students to read their text to identify the name of a virus that uses a given genome type. For medically oriented courses, this simulation could be modified further to focus on why some types of viral genomes provide more antiviral drug targets than others.

**References.** No specific references are applicable.

**Appendices.**
- **Appendix I** - Contains templates (suitable for photocopying) of #1 (a positive-strand RNA virus), #2 (a negative-strand RNA virus), #3 (a retrovirus), #4 (a double-stranded RNA virus), and #5 (a double-stranded DNA virus).
- **Appendix II** - Contains the answers to the sample problem given in the students’ write-up.
- **Appendix III** - Contains the answers for viruses 1 to 5.

**User Feedback**

From: Debra L. Carlson, Associate Professor of Biology, Augustana College, Sioux Falls, SD

Sent: Thursday, January 09, 2003 3:47 PM

I used a modified version of your exercise "Viral Genomes: a simulation of viral protein and nucleic acid synthesis" in my virology class today (Soph, Jr, and Sr Biology majors).

I used plastic two-part Easter eggs for the capsids (not quite the proper symmetry, no paper cups at hand), strips of paper for the genomes and two paper clips of two different colors to represent viral enzymes (RT and RNA-dep RNAP) packaged in the capsids. I used the five given genomes plus two of my own to represent all 7 classes in the Baltimore scheme. The genome strips only had the virals sequences (no other info about virus) on them.

Students (1) identified the virus class (based on sequence data and color of paper clip, if present -- they were not given the color code for the viral proteins), (2) wrote a diagram indicating viral and cellular enzymes required to synthesize mRNA, and (3) translated the viral proteins (using overhead of genetic code).

The students feedback was very positive. It was a good review for some, and a real learning experience for others. It took them about one hour working in teams of two.

Thanks for the great exercise!

Deb
Student Handout -
Viral genomes: a simulation of viral protein and nucleic acid syntheses

Different viruses have different types of genomes; yet all viruses must somehow replicate their genome and synthesize proteins in order to complete their life cycle. It is important to appreciate the contrast between viruses (which may have unusual types of genomes) and cells (which all have double-stranded DNA genomes and strictly adhere to the "central dogma"—making their proteins from a DNA code via RNA intermediates). The purpose of this simulation is to better understand the problems that some viruses must overcome when they parasitize a host cell. The exercise will also serve as a review of the processes of transcription and translation, and how these contrast with replication.

For this simulation, you and your partner(s) will carry out the following steps:

1. Obtain a viral "capsid" (taped paper cups) containing a small portion of a viral genome. This genome may be composed of double-stranded DNA, double-stranded RNA, negative strand RNA, positive strand RNA, or single-stranded retroviral RNA. Each of these viruses goes about the making of new virions (genetic material PLUS protein) in different ways.

2. "Uncoat" the viral genome (the type of genome will then be indicated).

3. Record the virus number and viral type in the space provided in this hand-out.

4. Note the boxed portion of the genome; located within this highlighted portion is a sequence symbolizing a viral protein (although this will be much shorter than any real viral gene).

5. Determine any nucleic acid intermediate(s) required for this boxed portion to be translated into protein. Recall that ribosomes read an mRNA molecule from 5'—>3', based upon the frame set by a 5'AUG 3' codon.

6. Record the sequence of any intermediates, including their 5', 3' directionality.

7. Write the protein sequence ultimately produced (refer to the mRNA codon chart below, in which each codon is listed with its 5' base on the left).

8. Determine the nucleic acid intermediate(s) required for the entire genome to be replicated.

9. Record the sequence of any intermediate(s), including their 5’, 3’ directionality.

10. Note with an asterisk any nucleic acids that are not typical of processes of the central dogma.

11. Check with an instructor to verify that all intermediates are correct.

12. Reseal the viral capsid with the original viral genome inside, and exchange it for another one.

13. Repeat steps 1 to 12 until you feel confident that you understand how different viruses
express and replicate their genes.

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Complete this sample problem prior to class. Please note that the composition of the viral genome, like capsid symmetry, is useful for categorizing viruses.

**Sample problem:**
You uncoat a viral genome from its capsid (following attachment to and penetration of the host cell, of course) to reveal the following information:

"This virus is a double-stranded DNA virus in which a portion of its genome reads:

\[
\text{UAAGGCAUGGGUUCUUCGCCUGAGG} \ 3' 
\]

This virus makes a protein after RNA polymerase uses the **top strand** as a template."

**Production of viral proteins:**

1. Write down any nucleic acid intermediate(s) that must be produced prior to translation of the boxed region; if no nucleic acid intermediates are produced, write "none".

2. Write down the sequence of the polypeptide chain encoded.

**Replication of viral genome:**

3. Write down any intermediate(s) produced in the replication of this viral genome; if no nucleic acid intermediates are produced, write "none".

4. Write down the final sequence of the viral genome.
5. Indicate with an **asterisk** any nucleic acids above that would not be produced by cellular enzymes or normal (uninfected) cell processes.

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**Worksheet**

Virus # _______; type of virus genome:

**Production of viral proteins:**

1. Write down any nucleic acid intermediate(s) that must be produced prior to translation of the boxed region; if no nucleic acid intermediates are produced, write "none":

2. Write down the sequence of the polypeptide chain encoded:

**Replication of viral genome:**

3. Write down any intermediate(s) produced in the replication of this viral genome; if no nucleic acid intermediates are produced, write "none":

4. Write down the final sequence of the viral genome:

5. Indicate with an asterisk any nucleic acids above that would not be produced by cellular enzymes or normal (uninfected) cell processes.

---

Virus # _______; type of virus genome:

**Production of viral proteins:**

1. Write down any nucleic acid intermediate(s) that must be produced prior to translation of the boxed region; if no nucleic acid intermediates are produced, write "none":

2. Write down the sequence of the polypeptide chain encoded:

**Replication of viral genome:**

3. Write down any intermediate(s) produced in the replication of this viral genome; if no nucleic acid intermediates are produced, write "none":

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4. Write down the final sequence of the viral genome:

5. Indicate with an asterisk any nucleic acids above that would not be produced by cellular enzymes or normal (uninfected) cell processes.

Virus # _______; type of virus genome:

**Production of viral proteins:**

1. Write down any nucleic acid intermediate(s) that must be produced prior to translation of the boxed region; if no nucleic acid intermediates are produced, write "none":

2. Write down the sequence of the polypeptide chain encoded:

**Replication of viral genome:**

3. Write down any intermediate(s) produced in the replication of this viral genome; if no nucleic acid intermediates are produced, write "none":

4. Write down the final sequence of the viral genome:

5. Indicate with an asterisk any nucleic acids above that would not be produced by cellular enzymes or normal (uninfected) cell processes.

Virus # _______; type of virus genome:

**Production of viral proteins:**

1. Write down any nucleic acid intermediate(s) that must be produced prior to translation of the boxed region; if no nucleic acid intermediates are produced, write "none":

2. Write down the sequence of the polypeptide chain encoded:

**Replication of viral genome:**

3. Write down any intermediate(s) produced in the replication of this viral genome; if no
nucleic acid intermediates are produced, write "none":

4. Write down the final sequence of the viral genome:

5. Indicate with an asterisk any nucleic acids above that would not be produced by cellular enzymes or normal (uninfected) cell processes.
Appendix I. Templates

The virus (#1) that has just been uncoated is a (+) strand RNA virus:

\[ 5'\text{UAAGGCAUGGGUUCUUUCGCCUGAGG} 3' \]

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\[ 5'\text{UAAGGCAUGGGUUCUUUCGCCUGAGG} 3' \]

The virus (#1) that has just been uncoated is a (+) strand RNA virus:

\[ 5'\text{UAAGGCAUGGGUUCUUUCGCCUGAGG} 3' \]

The virus (#2) that has just been uncoated is a (-) strand RNA virus:

\[ 3'\text{UGCCUACGCUGUCCUCAAGUACUA} 5' \]

The virus (#2) that has just been uncoated is a (-) strand RNA virus:

\[ 3'\text{UGCCUACGCUGUCCUCAAGUACUA} 5' \]
The virus (#2) that has just been uncoated is a (-) strand RNA virus:

3’ CUGCCUACGCUGUUUCCUCAAGUAACUA 5’

The virus (#2) that has just been uncoated is a (-) strand RNA virus:

3’ CUGCCUACGCUGUUUCCUCAAGUAACUA 5’

The virus (#2) that has just been uncoated is a (-) strand RNA virus:

3’ CUGCCUACGCUGUUUCCUCAAGUAACUA 5’

The virus (#2) that has just been uncoated is a (-) strand RNA virus:

3’ CUGCCUACGCUGUUUCCUCAAGUAACUA 5’

The virus (#3) that has just been uncoated is a retrovirus:

5’ GCJUCUCAUGGCJGGGUJUAUUGJUAUGGAA 3’

The virus (#3) that has just been uncoated is a retrovirus:

5’ GCJUCUCAUGGCJGGGUJUAUUGJUAUGGAA 3’

The virus (#3) that has just been uncoated is a retrovirus:

5’ GCJUCUCAUGGCJGGGUJUAUUGJUAUGGAA 3’

The virus (#3) that has just been uncoated is a retrovirus:

5’ GCJUCUCAUGGCJGGGUJUAUUGJUAUGGAA 3’

The virus (#3) that has just been uncoated is a retrovirus:

5’ GCJUCUCAUGGCJGGGUJUAUUGJUAUGGAA 3’

The virus (#3) that has just been uncoated is a retrovirus:
The virus (#3) that has just been uncoated is a retrovirus:

\[
5' \text{GCUCAUUGGCGGGAUUGAUAGA} 3' \\
\]

The virus (#4) that has just been uncoated is a double-stranded RNA virus. Here, the bottom strand acts as a template for a viral RNA-dependent RNA polymerase. The RNA strand that is transcribed from this bottom strand then acts as an mRNA:

\[
5' \text{CUAUUGAAACGUGGCAGCAUAAGCA} 3' \\
3' \text{GAUAUACUUUGCACCACGUAUUGC} 5' \\
\]

The virus (#4) that has just been uncoated is a double-stranded RNA virus. Here, the bottom strand acts as a template for a viral RNA-dependent RNA polymerase. The RNA strand that is transcribed from this bottom strand then acts as an mRNA:

\[
5' \text{CUAUUGAAACGUGGCAGCAUAAGCA} 3' \\
3' \text{GAUAUACUUUGCACCACGUAUUGC} 5' \\
\]

The virus (#4) that has just been uncoated is a double-stranded RNA virus. Here, the bottom strand acts as a template for a viral RNA-dependent RNA polymerase. The RNA strand that is transcribed from this bottom strand then acts as an mRNA:

\[
5' \text{CUAUUGAAACGUGGCAGCAUAAGCA} 3' \\
3' \text{GAUAUACUUUGCACCACGUAUUGC} 5' \\
\]

The virus (#4) that has just been uncoated is a double-stranded RNA virus. Here, the bottom strand acts as a template for a viral RNA-dependent RNA polymerase. The RNA strand that is transcribed from this bottom strand then acts as an mRNA:

\[
5' \text{CUAUUGAAACGUGGCAGCAUAAGCA} 3' \\
3' \text{GAUAUACUUUGCACCACGUAUUGC} 5' \\
\]

The virus (#5) that has just been uncoated is a double-stranded DNA virus. Here, the virus makes a protein after RNA polymerase uses the **bottom strand** as a template.
The virus (#5) that has just been uncoated is a double-stranded DNA virus. Here, the virus makes a protein after RNA polymerase uses the **bottom strand** as a template.

5' TCCGCTATGTTCCTCATTGTCTGATATG 3'
3' AGGCGATACAAGGAGTAACAGACTATAC 5'

The virus (#5) that has just been uncoated is a double-stranded DNA virus. Here, the virus makes a protein after RNA polymerase uses the **bottom strand** as a template.

5' TCCGCTATGTTCCTCATTGTCTGATATG 3'
3' AGGCGATACAAGGAGTAACAGACTATAC 5'

The virus (#5) that has just been uncoated is a double-stranded DNA virus. Here, the virus makes a protein after RNA polymerase uses the **bottom strand** as a template.

5' TCCGCTATGTTCCTCATTGTCTGATATG 3'
3' AGGCGATACAAGGAGTAACAGACTATAC 5'

The virus (#5) that has just been uncoated is a double-stranded DNA virus. Here, the virus makes a protein after RNA polymerase uses the **bottom strand** as a template.

5' TCCGCTATGTTCCTCATTGTCTGATATG 3'
3' AGGCGATACAAGGAGTAACAGACTATAC 5'
Appendix. II - Answers to sample problem in student write-up

1. The nucleic acid intermediate needed for translation of this virus’ genes is mRNA. The sequence that will be transcribed when RNA polymerase reads the top strand is:

   \[ 3' \text{UCGAUGCUAGAGGCAUCCAUUUAGUAG} \ 5' \].

   Note: Since this is complementary to the top strand of the virus, it’s identical to the bottom strand, except for the T to U switch. Remind TA’s that they should write this sequence out on the board, hopefully with input from the students. If TA’s don’t actually write a sequence, some students won’t get the idea that they’re supposed to write a sequence, and instead will merely write "RNA" or "DNA"—hence missing the whole point of the exercise. Also, make sure that the TA’s convey that this message is too short to really be a protein; a ribosome binding site, transcriptional stop sequences and several hundred other bases are missing compared to a real mRNA sequence.

2. The polypeptide chain generated from question 1 will be:

   met ile tyr pro leu gly ser STOP

   TA’s should point out that it will probably be easier to rewrite the sequence from question 1 above, backwards. Although the ribosome won’t care as long as it reads 5’ → 3’, humans make fewer mistakes reading left to right. TA’s should also emphasize the 5’ AUG 3’ that sets the ribosome frame.

   \[ 5' \text{G AUG AUU UAC CCA UUA GCA UCG UAG CU} \ 3' \]

3. "None". (No intermediates are needed for replication of a DS-DNA virus, since the top strand is itself a template for the bottom strand, while the bottom strand is the template for the top strand.)

4. The students should write down the entire viral sequence, identical to that received in the "capsid". This will aid them in reviewing the material later.

5. No asterisks are used for this virus, as a DS-DNA virus does not require any unique enzymes because it adheres to the central dogma. (Some students may point out that some larger DNA viruses do utilize virally encoded DNA polymerases and other enzymes.)
Appendix III. Answer Key

Virus # __1___; type of virus genome: (+) strand RNA virus

1. Write down any nucleic acid intermediate(s) that must be produced prior to translation of the boxed region; if no nucleic acid intermediates are produced, write "none":

—none—

2. Write down the sequence of the polypeptide chain encoded:

met-gly-ser-phe-ala-STOP

3. Write down any intermediate(s) produced in the replication of this viral genome; if no nucleic acid intermediates are produced, write "none":

* 3’AUUCCGUACCCAAGAAAGCGGACUCC 5’

4. Write down the final sequence of the viral genome:

*5’ UAAGGCAUGGGUUCUUUCGCCUCUGAGG 3’

   (start codon)                (stop codon )

5. Indicate with an asterisk any nucleic acids above that would not be produced by cellular enzymes or normal (uninfected) cell processes.

(The two nucleic acids above are starred because each one is an RNA molecule transcribed from an RNA sequence; cells don’t generally do this.)

Virus # __2___; type of virus genome: (-) strand RNA virus

1. Write down any nucleic acid intermediate(s) that must be produced prior to translation of the boxed region; if no nucleic acid intermediates are produced, write "none":

* 5’ ACGGCAUGGGUUCUUUCGCCUCUGAGG 3’

2. Write down the sequence of the polypeptide chain encoded:

met-arg-lys-gly-val-his-STOP

3. Write down any intermediate(s) produced in the replication of this viral genome; if no nucleic acid intermediates are produced, write "none":

*5’ GACGGAUGGCAAAAGGAGUUCAUGA 5’

4. Write down the final sequence of the viral genome:

*3’ CUGCCUACGCGUUCUCUCAAGUAACU 5’

   (complement to start codon)                (complement to stop codon)

5. Indicate with an asterisk any nucleic acids above that would not be produced by cellular enzymes or normal (uninfected) cell processes.

(The two nucleic acids above are starred because each one is an RNA molecule transcribed from an RNA sequence; cells don’t generally do this.)
Virus # ___3___; type of virus genome: retrovirus

1. Write down any nucleic acid intermediate(s) that must be produced prior to translation of the boxed region; if no nucleic acid intermediates are produced, write "none":

   (cellular RNA polymerase makes this mRNA at some point after reverse transcription and integration)

   5’ UUCAUGGCGGGUAUUGUAUGA 3’

2. Write down the sequence of the polypeptide chain encoded:

   met-ala-gly-ile-val-STOP

3. Write down any intermediate(s) produced in the replication of this viral genome; if no nucleic acid intermediates are produced, write "none":

   * 5’ CGAAGTACCACCAATAACATACTT 3’ DNA, complementary to retroviral genome

   * 3’ CGAAGTACCACCAATAACATACTT 5’

   5’ GCTTCATGGC GGTTATTGTATGAA 3’

   second DNA strand (complementary to first) is produced via normal cell DNA polymerases

4. Write down the final sequence of the viral genome:

   5’ GCUUCAUGGCGGGUAUUGUAUGA 3’

5. Indicate with an *asterisk* any nucleic acids above that would not be produced by cellular enzymes or normal (uninfected) cell processes.

   Only the DNA strand that is complementary to the retroviral genome should be asterisked. Normal cellular DNA and RNA polymerases can make the second DNA strand and mRNA, respectively. Most students recognize how reverse transcriptase transcribes the RNA into DNA.

Virus # __4__; type of virus genome: double-stranded RNA virus

1. Write down any nucleic acid intermediate(s) that must be produced prior to translation of the boxed region; if no nucleic acid intermediates are produced, write "none":

   * 5’ AUUGGAAACGUGGCUGCAUGGC 3’ This is the same sequence as the top strand, but RNA-dependent RNA polymerases make many copies of this to allow rapid protein production.

2. Write down the sequence of the polypeptide chain encoded:

   met-lys-arg-gly-ala-STOP

3. Write down any intermediate(s) produced in the replication of this viral genome; if no nucleic acid intermediates are produced, write "none":

   none

4. Write down the final sequence of the viral genome:

   Each strand is a template for the other’s replication:
5' CUAUAUGAAACGUGGCGCAUAAGCA 3'

*3' GAUAUACUUGCACCGCGUAAUCGU 5'*

This strand acts as template for mRNA synthesis.

5. Indicate with an asterisk any nucleic acids above that would not be produced by cellular enzymes or normal (uninfected) cell processes.

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Virus #_5_; type of virus genome: double-stranded DNA virus

1. Write down any nucleic acid intermediate(s) that must be produced prior to translation of the boxed region; if no nucleic acid intermediates are produced, write "none":

5' CGCUAUGUUCCUUAUGUCGAU 3' (mRNA)

2. Write down the sequence of the polypeptide chain encoded:

    met-phe-leu-ile-val-STOP

3. Write down any intermediate(s) produced in the replication of this viral genome; if no nucleic acid intermediates are produced, write "none":

   none

4. Write down the final sequence of the viral genome:

   5' TCCGCTATGTTCCATTGTCTGATATG 3'

   3' AGGCGATACCAAGGAGTAACAGACTATAC 5'*

   For this particular gene, RNA polymerase uses the bottom strand as a template.

5. Indicate with an asterisk any nucleic acids above that would not be produced by cellular enzymes or normal (uninfected) cell processes.