Optimizing Life's Blueprint: Guiding DNA Replication through Modeling

Yug Shah

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1 Abstract

This report explores a simplified DNA replication model, focusing on the dynamics of DNA replication fork rates over time. The primary objective is to examine the effects of mutating environmental parameters, such as temperature and pH, on both DNA replication fork rates and the total number of replicated DNA pairs. Our observations align with theoretical predictions, revealing significant influences of temperature and pH mutations on DNA replication dynamics. This study provides valuable insights into the sensitivity of DNA replication to microenvironmental variations, offering implications for broader biological contexts.

2 Introduction

DNA replication is more than just a biological process; it's the very essence of life's continuity. Imagine each cell as a meticulous librarian, tasked with copying an entire library of genetic information. This process starts with helicase, an enzyme that unwinds the DNA, much like opening a book to its central spine. As the two strands of DNA are exposed, single-strand binding proteins come in, ensuring these strands don't snap back together. Next, primase lays down RNA primers, akin to setting bookmarks for where DNA polymerases begin their work. These enzymes then add nucleotides, crafting a new DNA strand. In our complex human cells, this occurs at numerous starting points, ensuring the vast genetic material is copied efficiently. The process isn't uniform, though. While one strand (the leading strand) is replicated smoothly, the other (the lagging strand) is constructed in bits and pieces, later joined together seamlessly by DNA ligase [5].

The accuracy of this replication process is nothing short of remarkable, given the vastness of the genetic material involved. Each cell division requires an exact genetic copy, making this precision crucial. But, as with any complex process, there's room for error. These mistakes, or mutations, can have far-reaching consequences, from harmless quirks to serious genetic disorders. Understanding DNA replication isn't just about appreciating a biological wonder; it's also about unraveling the mysteries behind various genetic diseases and the aging process. This insight into DNA replication gives us a glimpse into the intricate dance of life at its most fundamental level, highlighting its significance as a cornerstone of biological inheritance and cellular function [4].

The imperative to monitor the evolution of DNA replication is rooted in its fundamental role in shaping the genetic landscape of organisms over time, offering a window into the dynamics of evolutionary change and resilience. This evolutionary perspective is crucial in deciphering how organisms adapt at a molecular level, with mutations acting as both the progenitors of genetic variation and key indicators of environmental influence. Such insights are invaluable across various fields, from medicine, where they inform the development of therapies for genetic disorders and cancer, to agriculture, where they underpin

efforts in crop improvement and biodiversity conservation.

The impacts of environmental changes on DNA replication, whether through radiation, chemical exposure, or other factors, underscore the importance of this monitoring for assessing ecological and human health risks. In the realm of evolutionary biology, tracing these genetic shifts aids in understanding the phylogenetic relationships among species and the evolutionary history of life. By delving into these genetic modifications, scientists can better comprehend biodiversity and its conservation, ultimately leveraging this knowledge to navigate the complexities of a changing world and harness the power of genetics for societal benefit.

In this report, we delve into a simplified modeling of the DNA replication process, with a keen focus on how alterations in environmental conditions, specifically temperature and pH levels, affect the dynamics of DNA replication. This model aims to simulate changes in the DNA replication fork rate and the quantity of DNA pairs replicated under varying environmental conditions. The significance of mutating environmental factors in our model extends beyond mere academic curiosity; it serves as a critical tool for examining the evolutionary implications of DNA replication. Environmental factors like temperature and pH can induce stress on the genetic replication machinery, leading to mutations that might confer evolutionary advantages or disadvantages. By simulating these changes, we gain a deeper understanding of how such mutations emerge and influence evolutionary trajectories. This exploration is not only central to evolutionary biology but also crucial in comprehending how organisms adapt and survive in fluctuating environments, offering valuable insights into the resilience and adaptability of life at a molecular level.

3 Designing the Model

In our quest to quantitatively understand the DNA replication process, we turn to the realm of differential equations. These mathematical tools are indispensable for modeling complex biological systems, offering a framework to describe the rate of change in biological processes. In the context of DNA replication, differential equations allow us to encapsulate the dynamic nature of the replication fork rate and the number of DNA pairs replicated over time [1].

3.1 Differential Equations for DNA Replication

3.1.1 Replication Fork Rate (RF)

The replication fork rate is modeled by the equation:

$$\frac{d(RF)}{dt} = \frac{RF_{max} \times EA \times RP \times TS}{1 + \exp\left(-\frac{(T_{opt} - \text{time})}{T_{width}}\right)} - RF_{decay} \times RF \tag{1}$$

This equation represents the rate of movement of the DNA replication fork, influenced by enzyme activity (EA), replication proteins (RP), and template

stability (TS), modulated by temperature.

3.1.2 Enzyme Activity (EA)

The enzyme activity is given by:

$$\frac{d(EA)}{dt} = \frac{EA_{\max} \times (T_{\text{opt}} - \text{time})}{T_{\text{width}}} - EA_{\text{decay}} \times EA + EA_{\text{stress}} \times SC \tag{2}$$

This equation models the enzyme activity essential in the DNA replication process. It considers the optimal temperature for enzyme function (T_{opt}), the natural decay of enzyme activity over time (EA_{decay}), and the influence of cellular stress (SC) on enzyme effectiveness. The equation reflects the dynamic balance between these factors in maintaining efficient DNA replication [2].

3.1.3 Template Stability (TS)

Template stability is modeled by:

$$\frac{d(TS)}{dt} = TS_{max} \times (pH_{opt} - TS) - TS_{decay} \times TS - TS_{topo} \times TA \tag{3}$$

This represents the stability of the DNA template, influenced by optimal pH conditions, decay rate, and the activity of topoisomerase (TA).

3.1.4 Replication Proteins (RP)

The dynamics of replication proteins are described by:

$$\frac{d(RP)}{dt} = \frac{RP_{synthesis} \times (ROE \times CCP)}{1 + \exp\left(-\frac{(SC - SC_{threshold})}{SC_{slope}}\right)} - RP_{decay} \times RP \tag{4}$$

This equation accounts for the synthesis and decay of replication proteins, crucial for DNA replication, modulated by replication origin efficiency (ROE) and cellular checkpoints (CCP).

3.1.5 Mismatch Repair Efficiency (MRE)

Mismatch repair efficiency is given by:

$$\frac{d(MRE)}{dt} = MRE_{methylation} \times (1 - DMS) - MRE_{decay} \times MRE - MRE_{stress} \times SC \tag{5}$$

This equation models the efficiency of DNA mismatch repair, considering the effects of DNA methylation, decay of repair efficiency, and the influence of cellular stress.

3.1.6 Cellular Stress (SC)

The level of cellular stress is modeled as:

$$\frac{d(SC)}{dt} = k_{SC_{growth}} \times SC \times \left(1 - \frac{SC}{SC_{max}}\right) - k_{SC_{decay}} \times SC \tag{6}$$

This represents the growth and decay of cellular stress, a critical factor affecting various aspects of DNA replication and repair mechanisms.

Solving these differential equations provides insights into the behavior of the replication process under different environmental conditions. We employ numerical methods to solve these equations, as analytical solutions are often unattainable due to the complexity of the system. Techniques such as Euler's method, Runge-Kutta methods, or more sophisticated algorithmic approaches are used to approximate the solutions of these differential equations.

3.2 Method

In this code, the differential equations are solved using a numerical method known as the Euler method, also sometimes referred to as the forward Euler method. The Euler method is a straightforward and intuitive way to approximate the solution of ordinary differential equations (ODEs) by discretizing time and updating the state variables at each time step.

3.2.1 Initialization

The code first initializes the time vector, state variables (RF, EA, TS, RP, MRE, SC, TA, ROE, CCP, DMS), and various parameters and constants needed for the simulation.

3.2.2 Simulation Loop

The primary simulation loop iterates over time steps (i) from 2 to $nSteps$, where $nSteps$ represents the total number of time steps. At each time step, the code updates the state variables based on their respective differential equations.

3.2.3 Updating State Variables

For each state variable (e.g., RF, EA, TS, RP, MRE, SC), the code uses the Euler method to update the variable's value at the current time step (i) based on its differential equation. The general form of updating a state variable X is as follows:

$$X(j, i) = X(j, i - 1) + dt \cdot \frac{dX}{dt}$$

Here, $X(j, i)$ represents the value of the state variable X for the j-th process at time step i. dt is the time step size, and $\frac{dX}{dt}$ represents the rate of change of X with respect to time.

For example, in the code, you can see lines like:

$$\begin{aligned} RF(j,i) = {} & RF(j,i-1) \\ & + dt \cdot \left(RF_{\max} \cdot \frac{EA(j,i-1) \cdot RP(j,i-1) \cdot TS(j,i-1)}{1 + \exp\left(-\frac{T_{\text{opt}} - \text{time}(i-1)}{T_{\text{width}}}\right)} \right. \\ & \left. - RF_{\text{decay}} \cdot RF(j,i-1) \right) \end{aligned} \tag{7}$$

This line updates the RF (Replication Fork) variable using the Euler method based on its differential equation.

3.2.4 Normalization

After the simulation loop is complete, the code normalizes the RF variable by dividing it by the maximum value of RF for the j-th process. This step ensures that the RF values are scaled between 0 and 1.

In summary, the Euler method is used to numerically approximate the solutions of the differential equations for various biochemical processes by updating the state variables at discrete time steps. While the Euler method is a simple and intuitive numerical technique, it may not always provide the highest accuracy, especially for stiff ODEs or when very small time steps are required. In some cases, more advanced numerical methods like the Runge-Kutta methods or adaptive step-size methods may be preferred for higher accuracy.

4 Monitoring Evolution by Introducing Mutations

In our study of DNA replication dynamics, we aim to investigate how intentional alterations in environmental conditions, specifically temperature and pH levels, can introduce mutations into the genetic replication process. By subjecting the DNA replication model to varying temperatures and pH values, we emulate the microenvironmental changes that organisms may encounter in their natural habitats. These mutations may arise due to the stress induced by temperature fluctuations and deviations from optimal pH conditions. As a result, we expect to observe changes in the DNA replication fork rate and the total number of replicated DNA pairs. Monitoring these alterations provides valuable insights into the sensitivity of DNA replication to environmental perturbations, shedding light on how mutations emerge and influence evolutionary trajectories. This exploration not only enhances our understanding of fundamental genetic processes but also has implications for understanding the adaptability and resilience of organisms in response to changing ecological conditions.

4.1 Mutation in Temperature

In this code, mutations in temperature are introduced to simulate variations in environmental conditions. The extent of these mutations is controlled by the `mutation_rate` parameter, which specifies the percentage of alteration in the mean temperature. For each simulation, a mutated temperature value is generated by applying a random variation to the mean temperature. This mutation is based on a normal distribution with a mean of 1 and a standard deviation determined by the mutation rate. The mutated temperature, known as the optimal temperature (`T_opt`), is calculated to reflect the effect of environmental changes.

The code records these mutated mean temperature values for each simulation in the `mean_temps` array. After conducting multiple simulations, the code plots the relationship between mean temperature and two critical variables: mean replication fork rate and total replicated DNA pairs. These plots help visualize how variations in temperature, introduced through mutations, influence DNA replication processes and provide insights into the system's response to changing environmental conditions without specifying specific temperature values. This approach allows for a dynamic exploration of the system's behavior under different temperature scenarios, enhancing our understanding of its robustness and adaptability.

4.2 Mutation in pH value

In this code, mutations in pH (acidity/alkalinity) are introduced to simulate variations in environmental conditions and their impact on biological processes. The degree of these mutations is governed by the `pH_mutation_rate` parameter, which determines the percentage of alteration in the mean pH value. During each simulation, a mutated pH value is calculated by applying a random perturbation to the baseline pH value, represented by `pH_opt`. This perturbation follows a normal distribution with a mean of 1 and a standard deviation influenced by the pH mutation rate.

To track the effects of these mutations, the code records the mutated mean pH values for each simulation in the `mean_pH_values` array. After executing multiple simulations, the code proceeds to create visual representations of the relationship between mean pH and two crucial variables: mean replication fork rate and total replicated DNA pairs. These plots provide a visual understanding of how variations in pH, introduced through mutations, influence DNA replication processes. Additionally, they help researchers gain insights into the system's response to changing environmental conditions, particularly regarding pH levels. This dynamic approach enhances our comprehension of how pH fluctuations impact biological systems and their adaptability in diverse pH environments.

5 Results

The chosen initial conditions in the code are based on the assumption that the cell cycle is in the S-phase, a crucial phase for DNA replication. These initial conditions are varied to explore the system's behavior under different starting states. By intentionally introducing variability in parameters like replication fork rate, enzyme activity, and DNA template stability, researchers can assess the system's adaptability to changing conditions. The variation in initial conditions enables a comparative analysis, highlighting how differences impact replication dynamics. This approach aids in identifying critical factors affecting DNA replication. Additionally, it aligns with the code's goal of understanding the system's response to diverse scenarios, contributing to a comprehensive exploration of DNA replication behavior.

5.1 DNA Replication Modeling

In Process 1, the replication fork rate exhibits dynamic behavior over time. Initially, it rapidly increases from 0 to 1 within the first 100 units of time, signifying an accelerated DNA replication process, possibly influenced by favorable conditions or resource availability. However, as time progresses from 100 to 500 units, the replication fork rate gradually decreases. This decline suggests a slowing down of DNA replication, potentially due to resource depletion, the impact of decay rates of biological components like replication proteins, or cellular stress.

This temporal pattern underscores the adaptability of DNA replication processes in response to changing environmental conditions. Comparing this behavior to the original process, with its unique parameter values and trends, offers valuable insights into how alterations in environmental factors influence DNA replication dynamics. The plot highlights the intricate interplay between biological parameters and environmental variables, shedding light on the system's ability to modulate replication rates to adapt to its surroundings [3].

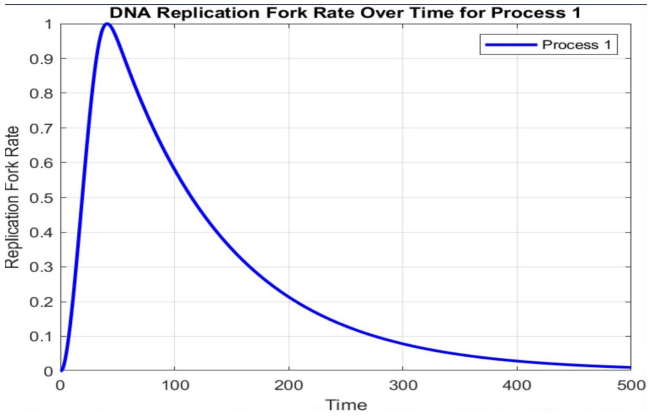

Figure 1: Modeling DNA Replication

5.2 Mutating Temperature

DNA replication dynamics were studied by subjecting the model to mutations in temperature. The plots reveal a consistent increase in DNA replication fork rate and the total number of replicated pairs with an increase in temperature up to 40°C. This behavior closely aligns with the original process and suggests that the DNA replication machinery operates optimally within this temperature range. The mean replication fork rate and the total number of replicated DNA pairs exhibit a positive linear relationship with mean temperature, indicating that higher temperatures enhance the efficiency of DNA replication as shown in figure.

If the temperature goes beyond the optimal temperature of 42°C, it is expected that DNA replication efficiency would begin to decline. This decrease is attributed to the detrimental effect of excessive heat on the biological components involved in replication. At elevated temperatures, enzymes and replication proteins may denature or become less active, leading to a reduction in the replication fork rate. Additionally, the stability of the DNA template may be compromised, further hindering the replication process. Therefore, maintaining temperature within the optimal range is crucial for ensuring efficient and accurate DNA replication.

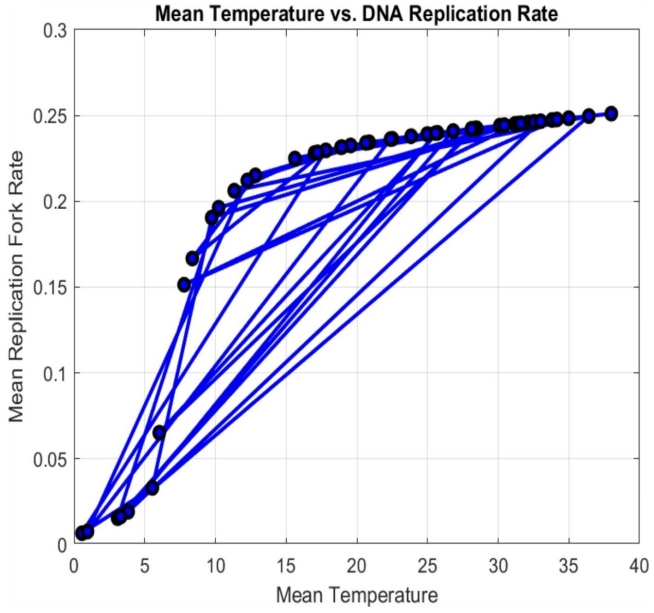

Figure 2: Effect of Mutations in Temperature on replication rate

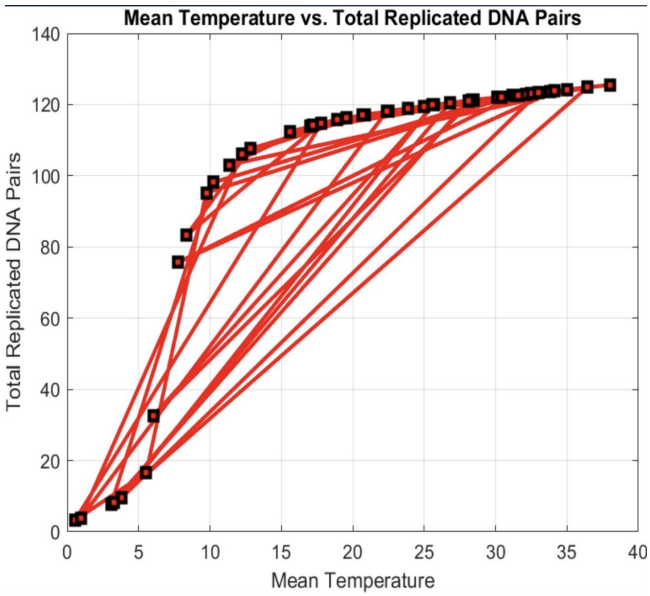

Figure 3: Effect of Mutations in Temperature on total number of replicated pairs

5.3 Mutating pH value

The provided code conducts a simulation to examine the influence of pH levels on DNA replication dynamics. It begins by initializing various parameters relevant to DNA replication and cellular processes, such as decay rates for replication fork rate and enzyme activity. Of particular interest is the pH level (pH_{opt}), representing the ideal pH for efficient DNA replication. The simulation is executed multiple times ($num_{\text{simulations}}$), with each iteration involving perturbations to the pH_{opt} value within a specified range, guided by a mutation rate ($pH_{\text{mutation\_rate}}$). The DNA replication process unfolds accordingly for each pH value, as cellular parameters like replication fork rate (RF) evolve over time based on a set of differential equations. Two plots are generated to visualize the outcomes: one illustrating the relationship between mean pH and mean replication fork rate and another demonstrating the connection between mean pH and the total number of replicated DNA pairs. These plots offer insights into how pH fluctuations influence DNA replication efficiency.

If the pH deviates from the optimal value of 8 in this simulation, one can anticipate a decrease in DNA replication efficiency. This reduction arises because non-optimal pH conditions negatively affect enzyme activity and DNA template stability. Enzymes crucial for replication may become less active or undergo denaturation, resulting in a diminished replication fork rate. Furthermore, the stability of the DNA template may become compromised, impeding the replication process. Therefore, maintaining pH levels within the optimal range is

vital to ensure that DNA replication transpires efficiently and accurately. It's essential to note that this explanation assumes the usage of pH as a parameter; adjustments would be needed if the intention was to simulate temperature instead.

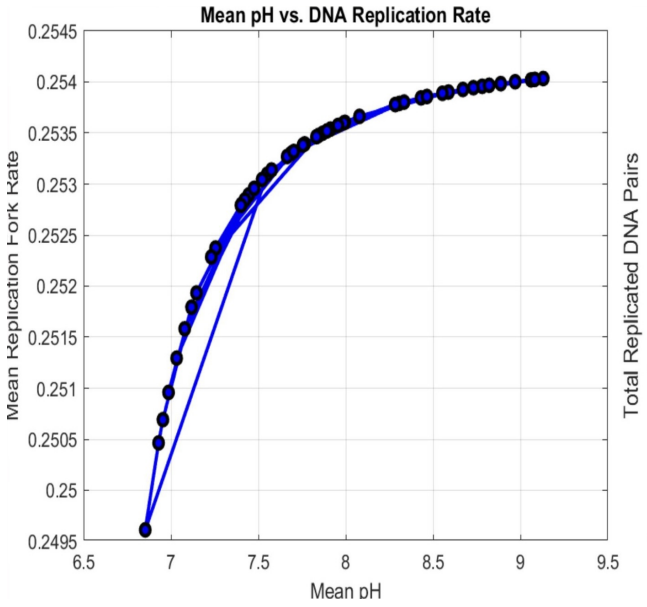

Figure 4: Effect of Mutations in pH value on replication rate

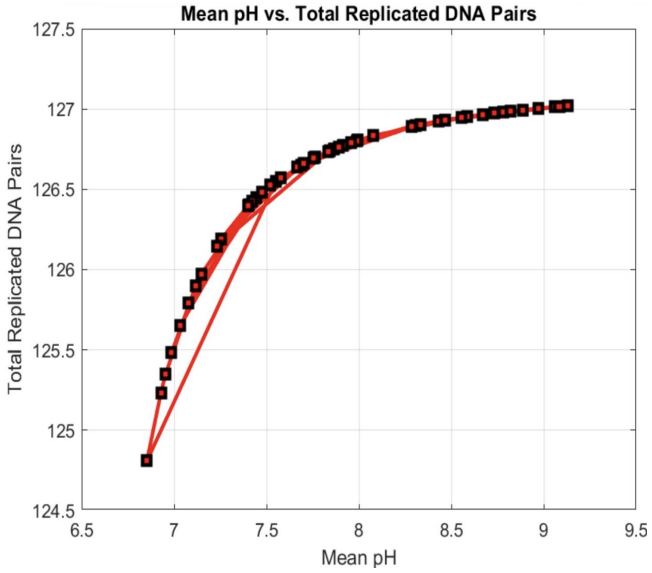

Figure 5: Effect of Mutations in pH value on total number of replicated pairs

6 Conclusions

Temperature ($T_{\mathbf{opt}}$) Mutation: When investigating the impact of temperature mutations in the simulation, we observed a consistent increase in DNA replication fork rate and the total number of replicated DNA pairs as the temperature increased up to approximately 42°C. This trend closely follows the original process's behavior, indicating that DNA replication is more efficient at higher temperatures within this range. Beyond 42°C, the model does not provide insights, but in practice, DNA replication efficiency typically decreases at extremely high temperatures due to enzyme denaturation and other factors.

pH ($pH_{\mathbf{opt}}$) Value Mutation: The simulation results for pH (pH_{opt}) value mutations revealed that deviations from the optimal pH of 8 led to a decrease in DNA replication efficiency. This decline occurs due to the sensitivity of enzyme activity and DNA template stability to pH variations. Suboptimal pH conditions negatively affect these crucial processes, resulting in a lower replication fork rate and fewer replicated DNA pairs. This finding emphasizes the importance of maintaining an appropriate pH environment for efficient and accurate DNA replication.

Insights from the Model:

1. **Environmental Sensitivity:** The model underscores the sensitivity of DNA replication dynamics to environmental factors, such as temperature and pH. These parameters can significantly influence cellular processes,

and maintaining them within optimal ranges is essential for efficient DNA replication.

2. **Experimental Guidance:** The simulation provides a valuable tool for researchers to predict how variations in temperature and pH can affect DNA replication. It offers guidance for experimental design, helping scientists make informed decisions about environmental conditions in the lab.

3. **Limitations:** While the model offers valuable insights, it is a simplified representation of complex biological processes. Real-world scenarios may involve additional factors and nuances. Therefore, experimental validation is crucial for confirming the model's predictions.

In summary, this model highlights the sensitivity of DNA replication to environmental conditions and demonstrates the importance of maintaining optimal temperature and pH levels. Researchers can use this simulation to inform experimental conditions and gain a deeper understanding of the factors that influence DNA replication efficiency.

7 Future Scope

Looking ahead, there is significant potential to enhance this model by incorporating feedback mechanisms that mimic the biological systems' ability to respond and adapt to changing environmental conditions. Future iterations of the model could integrate regulatory feedback loops that adjust enzyme activity, DNA template stability, or other parameters in real-time, depending on the system's needs. Additionally, this model could be expanded to explore the interactions between multiple environmental factors, allowing researchers to simulate more complex scenarios. Furthermore, the integration of experimental data could validate and refine the model's predictions, making it a powerful tool for optimizing DNA replication processes in various contexts, such as biotechnology and medicine. By continuously improving and expanding the model, scientists can gain deeper insights into the dynamic nature of DNA replication and develop strategies to enhance its efficiency and accuracy in response to diverse environmental challenges.

References

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[2] Mathematical modelling in dna replication. *PLoS Computational Biology*, 2023.

[3] Modeling and analysis of dna replication. https://www.sciencedirect.com/, 2023.

[4] National Human Genome Research Institute. Dna replication: Insights into the fundamental process. *NHGRI Educational Resources*, 2023.

[5] Khan Academy Editorial Team. Understanding dna replication. *Khan Academy Biology Resources*, 2023.

1. Modelling DNA Replication

```
% Define common parameters
T_width = 5; % Temperature width
RF_decay = 0.01; % Decay rate of replication fork rate
EA_decay = 0.02; % Decay rate of enzyme activity
EA_stress = 0.1; % Effect of cellular stress on enzyme activity
TS_max = 1; % Maximum DNA template stability
TS_decay = 0.005; % Decay rate of template stability
TS_topo = 0.1; % Effect of topoisomerase activity on stability
RP_synthesis = 0.05; % Replication protein synthesis rate
RP_decay = 0.01; % Decay rate of replication proteins
RP_slope = 0.5; % Slope for replication proteins synthesis
SC_threshold = 0.5; % Cellular stress threshold
SC_slope = 0.2; % Slope for cellular stress effect
MRE_methylation = 0.02; % Effect of DNA methylation on MRE
MRE_decay = 0.01; % Decay rate of mismatch repair efficiency
MRE_stress = 0.1; % Effect of cellular stress on MRE
pH_opt = 7.4; % Optimal pH
k_SC_growth = 0.1; % Growth rate of cellular stress
k_SC_decay = 0.05; % Decay rate of cellular stress
SC_max = 1; % Maximum cellular stress
% Simulation parameters
dt = 0.01; % Reduced time step
T_sim = 500; % Extended simulation time
% Number of DNA replication processes
num_processes = 1; % Set to 1 for a single process
% Initialize variables for each process
time = 0:dt:T_sim;
nSteps = numel(time);
RF = zeros(num_processes, nSteps);
EA = zeros(num_processes, nSteps);
TS = zeros(num_processes, nSteps);
RP = zeros(num_processes, nSteps);
MRE = zeros(num_processes, nSteps);
SC = zeros(num_processes, nSteps);
TA = zeros(num_processes, nSteps);
ROE = zeros(num_processes, nSteps);
CCP = zeros(num_processes, nSteps);
DMS = zeros(num_processes, nSteps);
% Simulation loop for each process (in this case, just one process)
j = 1; % Single process
% Define parameters for the process
T_opt = 35 + j * 2;
RF_max = 1.2 - 0.2 * j;
EA_max = 1 + 0.2 * j;
% Initial conditions for the process
RF(j, 1) = 0.1 + 0.1 * j;
EA(j, 1) = 0.8 - 0.1 * j;
TS(j, 1) = 0.9 - 0.1 * j;
RP(j, 1) = 0.5 + 0.1 * j;
MRE(j, 1) = 0.9 - 0.1 * j;
```

```
SC(j, 1) = 0.2 + 0.1 * j;
TA(j, 1) = 0.5 - 0.1 * j;
ROE(j, 1) = 0.7 + 0.1 * j;
CCP(j, 1) = 0.6 - 0.1 * j;
DMS(j, 1) = 0.1 + 0.1 * j;
% Define colors and linestyles for plotting
colors = {'b', 'g', 'r', 'c', 'm', 'y', 'k'};
linestyles = {'-', '--', ':', '-.'};
% Simulation loop for the process
for i = 2:nSteps
% Update variables using the differential equations
 RF(j, i) = RF(j, i-1) + dt * (RF_max * (EA(j, i-1) * RP(j, i-1) * TS(j,
i-1)) / (1 + exp(-(T_opt - time(i-1))/T_width)) - RF_decay * RF(j, i-1));
     EA(j, i) = EA(j, i-1) + dt * (EA_max * (T_opt - time(i-1))/T_width -
EA_decay * EA(j, i-1) + EA_stress * SC(j, i-1) + pH_opt* (pH_opt -7 ));
   TS(j, i) = TS(j, i-1) + dt * (TS_max * (pH_opt - TS(j, i-1)) + TS_decay *
TS(j, i-1) - TS_topo * TA(j, i-1));
    RP(j, i) = RP(j, i-1) + dt * (RP_synthesis * (ROE(j, i-1) * CCP(j,
i-1)) / (1 + exp(-(SC(j, i-1) - SC_threshold)/SC_slope)) - RP_decay * RP(j,
i-1));
    MRE(j, i) = MRE(j, i-1) + dt * (MRE_methylation * (1 - DMS(j, i-1)) -
MRE_decay * MRE(j, i-1) - MRE_stress * SC(j, i-1));
    SC(j, i) = SC(j, i-1) + dt * (k_SC_growth * SC(j, i-1) * (1 - SC(j,
i-1)/SC_max) - k_SC_decay * SC(j, i-1));
end
% Normalize RF for the process by dividing by the maximum value
RF = RF ./ max(RF, [], 2);
% Plotting the replication fork rate for the process
figure;
plot(time, RF(j, :), 'LineWidth', 2, 'Color', colors{j}, 'LineStyle',
linestyles{j}, 'DisplayName', ['Process ' num2str(j)]);
xlabel('Time');
ylabel('Replication Fork Rate');
title('DNA Replication Fork Rate Over Time for Process 1');
legend('show');
grid on;
% Calculate the total number of DNA replicated pairs for the process
total_replicated_DNA = trapz(time, RF(j, :));
fprintf('Total Replicated DNA Pairs for Process %d: %.2f\n', j,
total_replicated_DNA)
```

2. Mutating Temperature

```
% Define common parameters
T_width = 5; % Temperature width
RF_decay = 0.01; % Decay rate of replication fork rate
EA_decay = 0.02; % Decay rate of enzyme activity
EA_stress = 0.1; % Effect of cellular stress on enzyme activity
TS_max = 1; % Maximum DNA template stability
TS_decay = 0.005; % Decay rate of template stability
TS_topo = 0.1; % Effect of topoisomerase activity on stability
RP_synthesis = 0.05; % Replication protein synthesis rate
RP_decay = 0.01; % Decay rate of replication proteins
RP_slope = 0.5; % Slope for replication proteins synthesis
SC_threshold = 0.5; % Cellular stress threshold
SC_slope = 0.2; % Slope for cellular stress effect
MRE_methylation = 0.02; % Effect of DNA methylation on MRE
MRE_decay = 0.01; % Decay rate of mismatch repair efficiency
MRE_stress = 0.1; % Effect of cellular stress on MRE
pH_opt = 7.4; % Optimal pH
k_SC_growth = 0.1; % Growth rate of cellular stress
k_SC_decay = 0.05; % Decay rate of cellular stress
SC_max = 1; % Maximum cellular stress
RF_max=1;
EA_max=1;

% Simulation parameters
dt = 0.01; % Reduced time step
T_sim = 500; % Extended simulation time
num_simulations = 50; % Number of simulations

% Number of DNA replication processes
num_processes = 1;  % Set to 1 for a single process

% Initialize variables for each process
time = 0:dt:T_sim;
nSteps = numel(time);

% Initialize arrays to store mean values
mean_temps = zeros(1, num_simulations);
mean_replication_rate = zeros(1, num_simulations);
total_replicated_DNA_values = zeros(1, num_simulations);

% Loop for multiple simulations
for sim = 1:num_simulations
    % Initialize variables for each process
    RF = zeros(num_processes, nSteps);
    EA = zeros(num_processes, nSteps);
    TS = zeros(num_processes, nSteps);
    RP = zeros(num_processes, nSteps);
    MRE = zeros(num_processes, nSteps);
    SC = zeros(num_processes, nSteps);
    TA = zeros(num_processes, nSteps);
```

```
    ROE = zeros(num_processes, nSteps);
    CCP = zeros(num_processes, nSteps);
    DMS = zeros(num_processes, nSteps);

    % Define the mutation rate (% of parameters altered)
    mutation_rate = 0.05; % Adjust as needed

    % Initialize mean temperature in the range [0, 38]
    mean_temps(sim) = rand() * 38;

    % Mutation for T_opt with a limit of 38
    T_opt_mutation = mean_temps(sim) * (1 + mutation_rate * randn());
    T_opt = min(T_opt_mutation, 38);  % Limit T_opt to 38
    % Loop through all parameters and perturb them based on mutation rate
    for param = {'T_opt'}
        eval([param{1} ' = ' num2str(T_opt) ';']);
    end

    % Simulation loop for each process (in this case, just one process)
    j = 1;  % Single process

    % Initial conditions for the process
    RF(j, 1) = 0.1 + 0.1 * j;
    EA(j, 1) = 0.8 - 0.1 * j;
    TS(j, 1) = 0.9 - 0.1 * j;
    RP(j, 1) = 0.5 + 0.1 * j;
    MRE(j, 1) = 0.9 - 0.1 * j;
    SC(j, 1) = 0.2 + 0.1 * j;
    TA(j, 1) = 0.5 - 0.1 * j;
    ROE(j, 1) = 0.7 + 0.1 * j;
    CCP(j, 1) = 0.6 - 0.1 * j;
    DMS(j, 1) = 0.1 + 0.1 * j;

    % Simulation loop for the process
    for i = 2:nSteps
        % Update variables using the differential equations
        RF(j, i) = RF(j, i-1) + dt * (RF_max * (EA(j, i-1) * RP(j, i-1)
* TS(j, i-1)) / (1 + exp(-(T_opt - time(i-1))/T_width)) - RF_decay * RF(j,
i-1));
        EA(j, i) = EA(j, i-1) + dt * (EA_max * (T_opt - time(i-1))/T_width -
EA_decay * EA(j, i-1) + EA_stress * SC(j, i-1));
        TS(j, i) = TS(j, i-1) + dt * (TS_max * (pH_opt - TS(j, i-1)) -
TS_decay * TS(j, i-1) - TS_topo * TA(j, i-1));
        RP(j, i) = RP(j, i-1) + dt * (RP_synthesis * (ROE(j, i-1) * CCP(j,
i-1)) / (1 + exp(-(SC(j, i-1) - SC_threshold)/SC_slope)) - RP_decay * RP(j,
i-1));
        MRE(j, i) = MRE(j, i-1) + dt * (MRE_methylation * (1 - DMS(j, i-1))
- MRE_decay * MRE(j, i-1) - MRE_stress * SC(j, i-1));
        SC(j, i) = SC(j, i-1) + dt * (k_SC_growth * SC(j, i-1) * (1 - SC(j,
i-1)/SC_max) - k_SC_decay * SC(j, i-1));
```

```
    % Ensure RF values are non-negative
    RF(j, i) = max(0, RF(j, i));
    end

    % Normalize RF for the process by dividing by the maximum value
    RF = RF ./ max(RF, [], 2);

    % Calculate the total number of DNA replicated pairs for the process
    total_replicated_DNA_values(sim) = trapz(time, RF(j, :));

    % Calculate mean temperature and mean replication fork rate
    mean_temps(sim) = T_opt;
    mean_replication_rate(sim) = mean(RF(j, :));
end

% Plot mean temperature vs. DNA replication rate with lines and markers
figure;
plot(mean_temps, mean_replication_rate, 'b-', 'LineWidth', 2, 'Marker', 'o',
'MarkerFaceColor', 'b', 'MarkerEdgeColor', 'k');
xlabel('Mean Temperature');
ylabel('Mean Replication Fork Rate');
title('Mean Temperature vs. DNA Replication Rate');
grid on;

% Plot mean temperature vs. total number of DNA replication pairs with lines
and markers
figure;
plot(mean_temps, total_replicated_DNA_values, 'r-', 'LineWidth', 2,
'Marker', 's', 'MarkerFaceColor', 'r', 'MarkerEdgeColor', 'k');
xlabel('Mean Temperature');
ylabel('Total Replicated DNA Pairs');
title('Mean Temperature vs. Total Replicated DNA Pairs');
grid on;
```

3. Mutating pH Value

```
% Define common parameters
T_width = 5; % Temperature width
RF_decay = 0.01; % Decay rate of replication fork rate
EA_decay = 0.02; % Decay rate of enzyme activity
EA_stress = 0.1; % Effect of cellular stress on enzyme activity
TS_max = 1; % Maximum DNA template stability
TS_decay = 0.005; % Decay rate of template stability
TS_topo = 0.1; % Effect of topoisomerase activity on stability
RP_synthesis = 0.05; % Replication protein synthesis rate
RP_decay = 0.01; % Decay rate of replication proteins
RP_slope = 0.5; % Slope for replication proteins synthesis
SC_threshold = 0.5; % Cellular stress threshold
SC_slope = 0.2; % Slope for cellular stress effect
MRE_methylation = 0.02; % Effect of DNA methylation on MRE
MRE_decay = 0.01; % Decay rate of mismatch repair efficiency
MRE_stress = 0.1; % Effect of cellular stress on MRE
T_opt = 38; % Optimal temperature
k_SC_growth = 0.1; % Growth rate of cellular stress
k_SC_decay = 0.05; % Decay rate of cellular stress
SC_max = 1; % Maximum cellular stress
RF_max=1;
EA_max=1;

% Simulation parameters
dt = 0.01; % Reduced time step
T_sim = 500; % Extended simulation time
num_simulations = 50; % Number of simulations

% Number of DNA replication processes
num_processes = 1;  % Set to 1 for a single process

% Initialize variables for each process
time = 0:dt:T_sim;
nSteps = numel(time);

% Initialize arrays to store mean values
mean_pH_values = zeros(1, num_simulations);
mean_replication_rate = zeros(1, num_simulations);
total_replicated_DNA_values = zeros(1, num_simulations);

% Loop for multiple simulations
for sim = 1:num_simulations
    % Initialize variables for each process
    RF = zeros(num_processes, nSteps);
    EA = zeros(num_processes, nSteps);
    TS = zeros(num_processes, nSteps);
    RP = zeros(num_processes, nSteps);
    MRE = zeros(num_processes, nSteps);
    SC = zeros(num_processes, nSteps);
    TA = zeros(num_processes, nSteps);
```

```
    ROE = zeros(num_processes, nSteps);
    CCP = zeros(num_processes, nSteps);
    DMS = zeros(num_processes, nSteps);

    % Define the mutation rate (% of parameters altered)
    mutation_rate = 0.05; % Adjust as needed

   % Define the mutation rate for pH
pH_mutation_rate = 0.05; % Adjust as needed

% Loop through pH parameter and perturb it based on mutation rate
for param = {'pH_opt'}
    eval([param{1} ' = ' param{1} ' * (1 + pH_mutation_rate * randn());']);
end
    % Simulation loop for each process (in this case, just one process)
    j = 1;  % Single process

    % Initial conditions for the process
    RF(j, 1) = 0.1 + 0.1 * j;
    EA(j, 1) = 0.8 - 0.1 * j;
    TS(j, 1) = 0.9 - 0.1 * j;
    RP(j, 1) = 0.5 + 0.1 * j;
    MRE(j, 1) = 0.9 - 0.1 * j;
    SC(j, 1) = 0.2 + 0.1 * j;
    TA(j, 1) = 0.5 - 0.1 * j;
    ROE(j, 1) = 0.7 + 0.1 * j;
    CCP(j, 1) = 0.6 - 0.1 * j;
    DMS(j, 1) = 0.1 + 0.1 * j;

    % Simulation loop for the process
   % Simulation loop for the process
for i = 2:nSteps
    % Update variables using the differential equations
    RF(j, i) = RF(j, i-1) + dt * (RF_max * (EA(j, i-1) * RP(j, i-1) * TS(j,
i-1)) / (1 + exp(-(T_opt - time(i-1))/T_width)) - RF_decay * RF(j, i-1));
     EA(j, i) = EA(j, i-1) + dt * (EA_max * (T_opt - time(i-1))/T_width -
EA_decay * EA(j, i-1) + EA_stress * SC(j, i-1) + pH_opt* (pH_opt -7 ));
   TS(j, i) = TS(j, i-1) + dt * (TS_max * (pH_opt - TS(j, i-1)) + TS_decay *
TS(j, i-1) - TS_topo * TA(j, i-1));
    RP(j, i) = RP(j, i-1) + dt * (RP_synthesis * (ROE(j, i-1) * CCP(j,
i-1)) / (1 + exp(-(SC(j, i-1) - SC_threshold)/SC_slope)) - RP_decay * RP(j,
i-1));
    MRE(j, i) = MRE(j, i-1) + dt * (MRE_methylation * (1 - DMS(j, i-1)) -
MRE_decay * MRE(j, i-1) - MRE_stress * SC(j, i-1));
    SC(j, i) = SC(j, i-1) + dt * (k_SC_growth * SC(j, i-1) * (1 - SC(j,
i-1)/SC_max) - k_SC_decay * SC(j, i-1));
end

    % Normalize RF for the process by dividing by the maximum value
    RF = RF ./ max(RF, [], 2);
```

```
    % Calculate the total number of DNA replicated pairs for the process
    total_replicated_DNA_values(sim) = trapz(time, RF(j, :));

    % Calculate mean pH and mean replication fork rate
    mean_pH_values(sim) = pH_opt;
    mean_replication_rate(sim) = mean(RF(j, :));
end

% Plot mean pH vs. DNA replication rate with lines and markers
figure;
plot(mean_pH_values, mean_replication_rate, 'b-', 'LineWidth', 2, 'Marker',
'o', 'MarkerFaceColor', 'b', 'MarkerEdgeColor', 'k');
xlabel('Mean pH');
ylabel('Mean Replication Fork Rate');
title('Mean pH vs. DNA Replication Rate');
grid on;

% Plot mean pH vs. total number of DNA replication pairs with lines and
markers
figure;
plot(mean_pH_values, total_replicated_DNA_values, 'r-', 'LineWidth', 2,
'Marker', 's', 'MarkerFaceColor', 'r', 'MarkerEdgeColor', 'k');
xlabel('Mean pH');
ylabel('Total Replicated DNA Pairs');
title('Mean pH vs. Total Replicated DNA Pairs');
grid on;
```