CS4624
Multimedia, Hypertext, and Information Access

Final Report
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CellCycleViz

Virginia Tech, Blacksburg VA 24061

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1.0 Abstract

Professor John Tyson has been studying biological systems from a rigorous mathematical perspective, and building realistic models that help us gain a deeper understanding of physiology. Most of the lab's work is on the mechanism of cell division cycle control as seen in budding yeast, fission yeast, Xenopus embryos and egg extracts, Drosophila embryos, and mammalian cells. The Cell Cycle Visualization team is working in conjunction with Professor Young Cao to redesign the website containing mathematical models for Professor Tyson's experiment data.

Our job has been to design new webpages that expand on the research done by Professor Tyson and make the website more accessible to younger students and the general public. This has meant creating a new Home Page; devising pages for various cell models including the frog egg, budding yeast and Caulobacter models; and regrouping the mathematical models that visualize data from Professor Tyson's lab. When we first began our project, the website included five pages with just the cell cycle visualizations and a 'contact us' page. In our first meeting with Professor Cao, he outlined a plan for the website where the new content would fit a wider audience, containing introductory information for elementary students, more in-depth cell cycle breakdowns for the general public, and experiment data for experienced users.

As a team of four, we split up the work and began designing the new webpages. The new layout of the website begins with the pages at the top of the navigation bar containing simple, introductory information and pages further down having more detailed examples and mathematical models. Most of the background information answering the questions "What is the Cell Cycle" and "Why is it Important to Study the Cell Cycle" is included on the new Home page, which gives new users an overview of the cell cycle and what information is discussed on the rest of the website. Pages dedicated to the budding yeast, frog egg, and fission yeast cell growth models are housed under the "Cell Growth Models" banner. These pages are aimed at users that are familiar with the characteristics of the generic cell cycle and want to know more about research being done on these unique cell cycles.

Following the "Cell Growth Models" sub-navigation menu is the "Caulobacter Model" menu, which includes the "Caulobacter Introduction", "Temporal Cell Modules", and "Spatial Cell Modules" pages. These pages include information collected from Professor Tyson's lab where Caulobacter cells, a type of bacteria found in freshwater lakes and streams, is studied. Below the "Caulobacter Model" menu is the "Interesting Cell Cycle Facts" page, which includes insightful facts about the cell cycle. The second to last page is the "Visualization" page, which lets users select one or more species of cells and generates an animated visualization to show how those cell species grow and divide. At the bottom of the navigation sidebar is the "Contact" page, which includes ways to contact Professor Tyson and Professor Cao.

2.0 Introduction

Professor John Tyson has been studying biological systems from a rigorous mathematical perspective, and building realistic models that help us gain a deeper understanding of physiology. Most of the lab's work is on the mechanism of cell division cycle control as seen in budding yeast, fission yeast, Xenopus embryos and egg extracts, Drosophila embryos, and mammalian cells. The Cell Cycle Visualization team is working in conjunction with Professor Young Cao to redesign the website containing mathematical models for Professor Tyson's experiment data to reach a wider audience of younger students and the general public.

2.1 Objective

Our primary objective was to add content to the cell cycle visualization website to reach a wider audience that may not be familiar with the cell cycle. We also wanted to include more background information so that anyone using the cell growth mathematical models would understand the parameters and variables used to modify the results shown. Lastly, we set out to create pages for unique cell cycle models, including the budding yeast, frog egg, fission yeast, and the Caulobacter cell cycle, containing clear and up to date information. The new layout of the website will have pages near the top of the navigation bar containing simple, clear introductory information and pages further down having more detailed examples and mathematical models.

2.2 Deliverables

The goal of our project is to create a website that is accessible and helpful for students and the general public no matter how much knowledge they have of the cell cycle. We built on the existing website provided by Professor Cao, to which we added introductory pages, detailed cell cycle pages, and incorporated new mathematical models. To accomplish our team goal, the following deliverables were produced:

1. An updated website that is suitably designed. The content includes all the existing mathematical models, detailed cell growth model pages and introductory information included on the home, interesting facts, and generic cell cycle pages.
2. Accurate, up to date information describing each of the cell cycle models included on the website. There are links to external websites and databases for further learning.
3. Detailed explanation for each of the mathematical models, where the parameters and variables used to create the visualization are thoroughly explained. The user should have a clear understanding of the purpose and unique features of each model.

2.3 Client

Our client is Professor Young Cao, an Associate Professor in the Department of Computer Science at Virginia Tech. Professor Cao specializes in high-performance computing, computational science, computational biology, and bioinformatics.

2.4 Team

Our team consists of Cesar Smokowski, Shuai Lin, Donghyeon Shin, and Julia Van Dyke. Cesar was the team leader, website manager, and front end designer. Shuai served as the writer, also supporting graphics and web development. Donghyeon was the tester, also supporting graphics and web development. Julia was the editor, also supporting graphics and web development.

3.0 Requirements

We needed to fulfill several requirements in order to satisfactorily complete the project. These requirements are detailed in the subsections below.

3.1 Spark Interest for Beginners

For the website to be able to spark interest in users with little background knowledge in the cell cycle and the broader field of biology, several important features have been implemented. One important feature is the Home Page on the website which displays general, easily-understood, and introductory information on the general biology of the cell cycle. This page will prepare the beginning user with some lead-in knowledge. Then the next page will give more detailed information on the general cell cycle. The Home Page will contain multiple visuals and information that gives some explanation of the general biological terminology such as mitosis and binary fission – important introductory knowledge about the cell cycle. The website will also include an "Interesting Cell Cycle Facts" page to give the user some fun facts on the cell cycle if the user doesn't want to dwell on the more professional and highly-technical information on the cell cycle; it supports users when they surf the internet for fun.

3.2 Detailed Information for the Intermediate

One important feature for users with some knowledge in biology is the "Generic Cell Cycle" page which will give intermediate information that connects the general starting information on biology to the specific cell cycle model. This page will give well defined definitions and visuals on the generic cell cycle which allows the user to obtain a basic knowledge on the terminology and general structure of the life cycle that the cell undergoes. Then the frog egg model page will help to lead the user into a more complex cell cycle model like the budding yeast cell cycle model, since the frog egg cycle model is much simpler; it undergoes fewer phases than in other models.

3.3 Accurate Research Data and Models for Experienced Users

Experienced users expect results from Professor Tyson's lab to be expressed in an understandable, intuitive manner. The website contains five mathematical modules, including the budding yeast cell, Bistable Histidine Kinase, PleC and DivL Localization, PopZ Localization, and Chromosome Segregation. The visualizations for these mathematical modules are created

using JavaScript files and the D3 library. In order to appeal to a wider audience, the “Temporal Cell Modules” and “Spatial Cell Modules” pages include an introductory section that explains how the data was collected and the purpose of each research study. Each of the mathematical models has been thoroughly tested and run by several people on the team to ensure the results are clear and understandable.

Content on the pages under the Cell Growth Models banner can also be useful to experienced users, since they represent accurate and up to date information for important areas of cell growth research. Each page on the site includes links to external sources for those interested in further learning, so the site also acts as a collection of helpful resources for experienced users.

4.0 Design

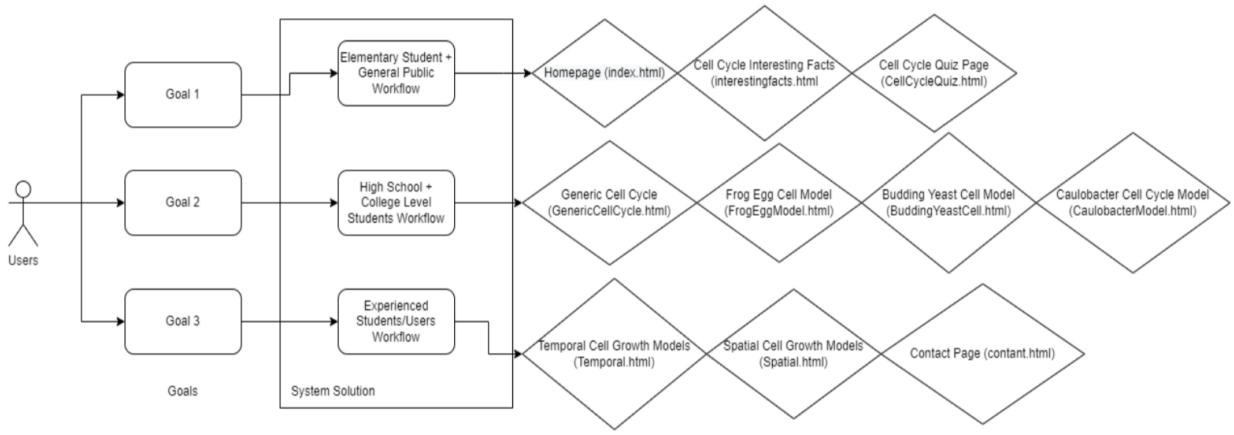

Figure 1: Basic design of our project

The design of the website was put together to present information at first in the simplest, most straightforward way, and then in more detailed and complex ways as the user investigates further. The navigation bar on the left side of the website groups related pages together and displays the content hierarchy where pages at the top contain introductory information and pages further down have interactive models using research data. Our goal was to create a balance of information conveyed through text, graphics, and mathematical models. The design elements of the site can be broken down into three areas: introductory pages, cell growth models, and research data visualizations.

4.1 Cell Cycle Models Design

The chosen design of this project is described in Figure 1. Our design of the website aims to give the user with different levels of biology knowledge the ability to learn and understand more about the cell cycle. In order to accomplish this task, the website's navigation sidebar is ordered from top to bottom with the top most tab being the "Home" page, which contains general biology information, and the second from the bottom is the "Visualization" page, which contains interactive mathematical models for a wide variety of cell species. For each Cell Cycle Model page, we organize the page's content to begin with an introduction section that explains what makes this cell cycle unique. Then the next section will provide more detailed information of the different phases the cell undergoes in its life cycle, and any major checkpoints or changes the cell goes through in its lifetime. The focus of the "Budding Yeast Cell Module", "Frog Egg Model", and "Fission Yeast Cell Model" page is to explain what makes each of these cell cycles unique and why researchers think these three cell models are important to study.

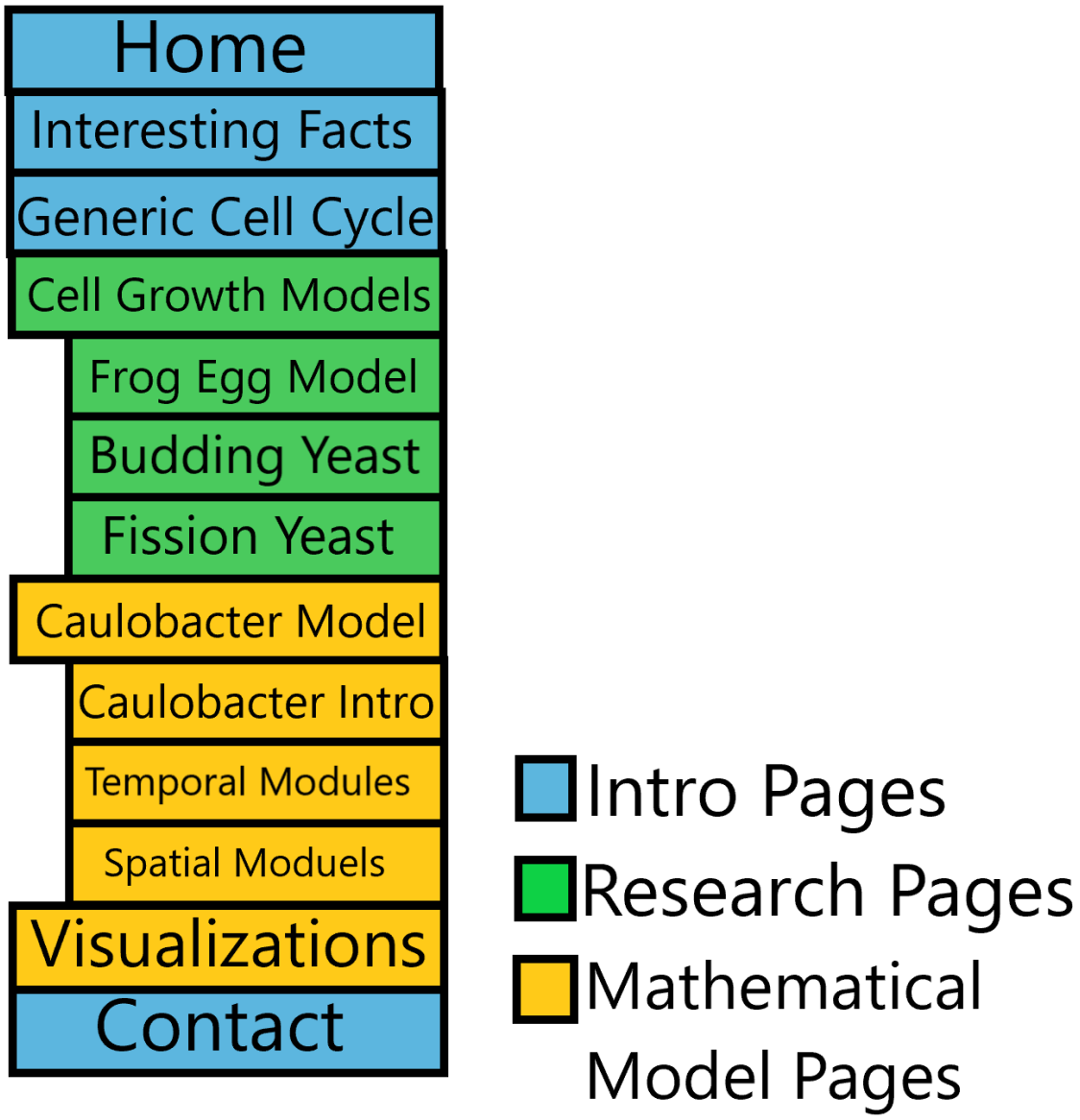

Figure 2: Navigation Bar Design.

4.2 Introductory Page Design

As shown in Figure 2, the “Home”, “Interesting Facts”, “Generic Cell Cycle”, and “Contact” pages implement the introductory page design schema. The goal of these pages is to convey information in a clear, organized fashion. The “Home” and “Interesting Facts” pages accomplish this goal by splitting the page up into sections separated by graphics or figures. Information is presented through short text sections, figures, GIFs, and links to resources for further learning. Similarly, the “Contact” page provides a brief description of our project clients, Professor Cao and Professor Tyson, and directs the users to websites where they can learn more about the work

that inspired the cell cycle website. Since the introductory pages do not include mathematical models, the content displayed on the page is generated from the host .html files and files for the photos and other resources embedded in the contents of the page.

4.3 Mathematical Models Design

The pages including mathematical models are the most complex in their design, since their goal is to convey the research done by Professor Tyson's lab in an organized, concise manner. Some pages in this section, the "Visualization" page for example, require separate JavaScript files that define the showPleC and showPopZ functions that are responsible for creating the animated cell growth visualizations. As referenced above, a cell cycle visualization is part of each mathematical model and its appearance can be modified based on the cell species parameter values chosen by the user. Table 1 indicates what information is included for each page.

Page Name	Content / Purpose	Required Resources	Links
Home	Provide users with introductory information and answer "What is the Cell Cycle" + "Why do we Study the Cell Cycle"	Index.html Stages-of-mitosis-gif binary_fission.gif stages_of_meiosis.png	https://microbiologysociety.org/why-microbiology-matters/what-is-microbiology.html https://www.ducksters.com/science/biology/cell_division.php
Interesting Facts	Give users additional information and a unique perspective on the growth of cells with engaging facts	interestingfacts.html human_cell.jpg tumor_cell.jpg blood_cell.jpg	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC281501/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2832345/
Frog Egg Model	Provide an overview of the cell division studies that have been done to understand frog egg reproduction	FrogEggModel.html Isolating_nucleus.jpg Poro_Nuclear_Ovoc-ell_Xenopus.jpg African_clawed_frog.png	https://commons.wikimedia.org/wiki/File:202101_African_clawed_frog.png\, https://commons.wikimedia.org/wiki/File:Isolating_the_nucleus_of_a_frog%27s_egg_(15682217330).jpg
Budding Yeast Model	Describe new research initiatives focused on studying species of yeast and the special circumstances that maximize their growth	BuddingYeast.html Buddingyeast.jpg Buddingyeast.css Text_only.css	https://www.phys.ksu.edu/gene/a1.html https://doi.org/10.1007/978-1-4419-9863-7_16
Fission Yeast Model	Give a detailed breakdown of the recent USC study of medial fission in fission yeast cells	FissionYeast.html Text_only.css	https://dornsife.usc.edu/pombenet/fission-yeast-cell-cycle/ https://doi.org/10.1371/journal.pone.0017175
Visualization	Provide users with a mathematical model of Caulobacter cell division	Visualization.html drawPleC.js drawPopZ.js	https://www.cell.com/current-biology/comments/S0960-9822(12)00589-1
Bistable Histidine Kinase	Explain Professor Tyson's research on the asymmetric cell division of several key proteins	PDM.html CCGraph/21.png CCGraph/22.png CCGraph/23A.png	https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.0040009 https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1000463
PleC and DivL Localization	Describe the crucial role two proteins play in the Caulobacter cell cycle	CCGraph/31.png CCGraph/32.png CCGraph/3e1.png	https://pubmed.ncbi.nlm.nih.gov/18455986/ https://journals.asm.org/doi/10.1128/JB.00992-09
PopZ Localization	Explain the research model used to study protein localization	TM.html CCGraph/4e2.png CCGraph/4e1.png CCGraph/52.png	https://journals.biologists.com/jcs/article/120/20/3501/29933/Cell-cycle-regulation-in-Caulobacter-location
Chromosome Segregation	Detail Professor Tyson's research of chromosome segregation in Caulobacter cells	CM.html CR.html CCGraph/61.png CCGraph/63.png	https://pubmed.ncbi.nlm.nih.gov/20802464/ https://elifesciences.org/articles/02758 https://pubmed.ncbi.nlm.nih.gov/24778223/
Contact	Give users background information and ways to reach Professor Tyson and Professor Cao	Contact.html CCGraph/mailto.gif	http://mpf.biol.vt.edu/lab_website/

Table 1: Table of Pages and Resources

5.0 Implementation

The implementation process for the cell cycle website was broken up into two phases: information collection and webpage design. Each page on the website consists of an HTML file and the resources incorporated into the contents of the page. Additionally, the "Visualization" page includes a mathematical model that is generated using the drawPleC.js and drawPopZ.js files. A graphical representation of how the mathematical model works is shown in Figure 3.

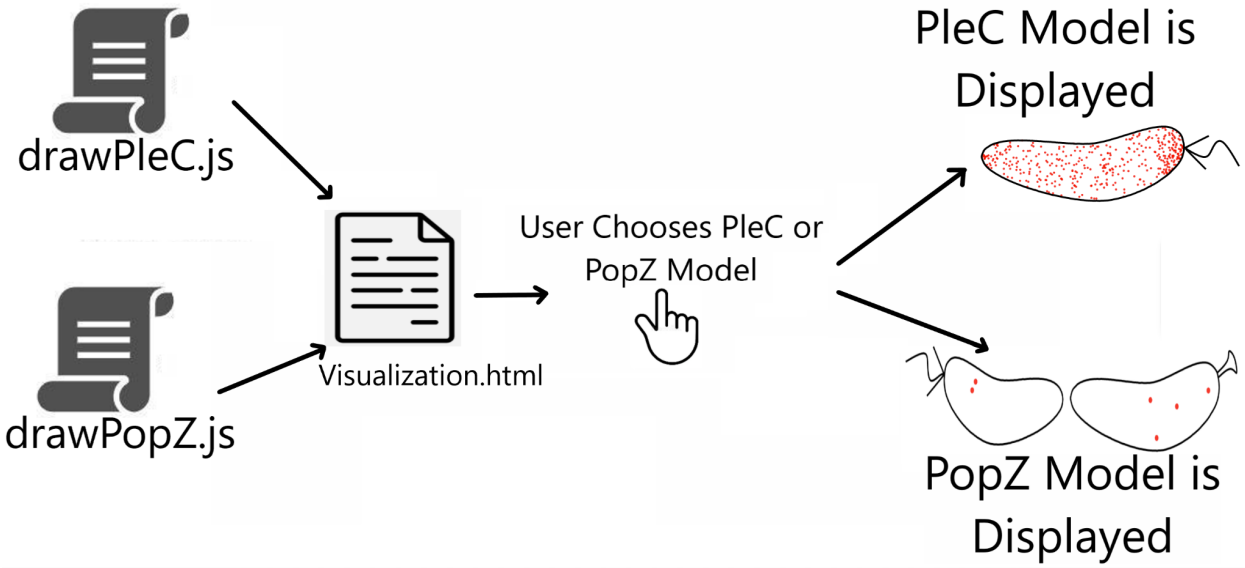

Figure 3: Visualization Page Flow Chart

5.1 Information Collection

Our team collected information through scholarly journals obtained from credible sources such as Google Scholar, Virginia Tech University Libraries, and the ACM Digital Library. Our team evaluated credible sources based on the objectivity, accuracy, and currency of the information. Our team focused on sources that contained unbiased information and were up to date with the latest research findings.

To obtain information for our website, a member typed a related keyword into the online scholarly databases. Then, the member chose a source that most accurately described the topic. For webpages intended for students, our team simplified the content to make it easier to understand. Multiple sources were used to check the accuracy of the information. Our team also referenced websites intended for students to present our topic in an easy-to-understand manner.

5.2 Webpage Design

Once we collected all the necessary information, we began the process of constructing the webpages using HTML files. Every page on the website was created using an HTML file, because the content and styling of a webpage is easily updated using an HTML and CSS file. The content of the introductory and research pages is split into sections, each beginning with a header, and all images include a concise caption. The “Visualization” page is the most complicated on the website, because depending on whether the user selects the PleC or PopZ cell model from the dropdown menu, either the showPleC function from drawPleC.js or the showPopZ function from drawPopZ.js is called. When either of these functions is called, the cell species that the user selected are passed through as the speFlag parameter values and the cell growth visualization is generated. Each webpage was designed to convey information in a clear, organized manner.

6.0 Testing

During the testing phase of the project, we wanted to make sure that the website functions correctly and the information displayed on every webpage is clear and concise with no grammar or spelling errors. In order to accomplish the first task of making sure that the website is functioning properly, each team member tested the navigation sidebar to confirm that every navigation tab linked to the correct webpage and the dropdown menus were responsive. We also went through each webpage to verify all links to external resources worked as intended. Testing also included making sure the “Home” page was the default starting page when a user visited the site.

The final step in the testing process was verifying that the mathematical model on the “Visualization” page worked properly for all possible inputs. Each group member individually tested the “Visualization” page’s mathematical model by making sure the animated visualization was generated correctly for every cell species combination.

7.0 User's Manual

In order to start navigating the website, please look to the left side of the webpage which contains the navigation sidebar. Each navigation tab in the navigation sidebar will lead to a new webpage of the website. Figure 4 shows the navigation sidebar, including the Cell Growth Models and Caulobacter Model dropdown menus expanded to show their subpages.

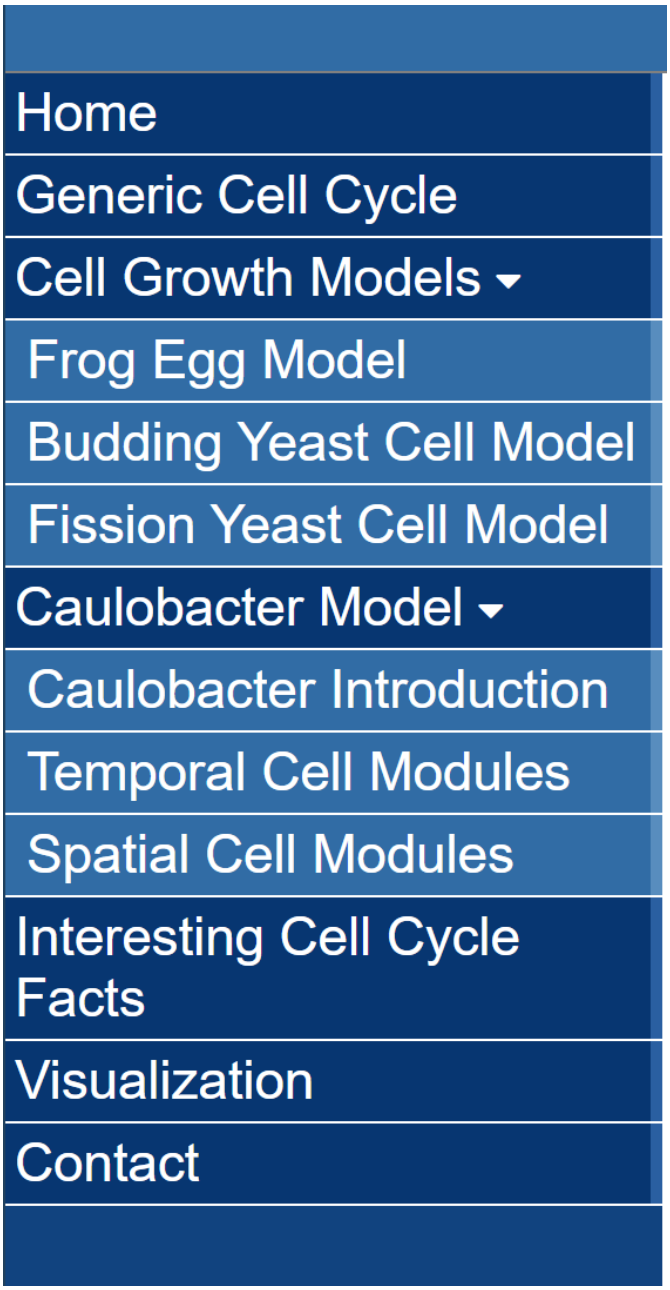

Figure 4: Navigation Sidebar

The first navigation tab called “Home” is the Home page, which is also the first webpage shown when the website is opened. The Home page contains the introductory information on some simple biological terms and concepts about cell cycle. It will be helpful for the user to read through it carefully if the user has not encountered related information in the past or has forgotten the detailed scope of the cell cycle. Figure 5 shows the top of the Home page, including the “What is the Cell Cycle?” and “3 Types of Cell Division” sections. Figure 6 shows the middle of the Home page and Figure 7 shows the bottom of the Home page, which includes the references section.

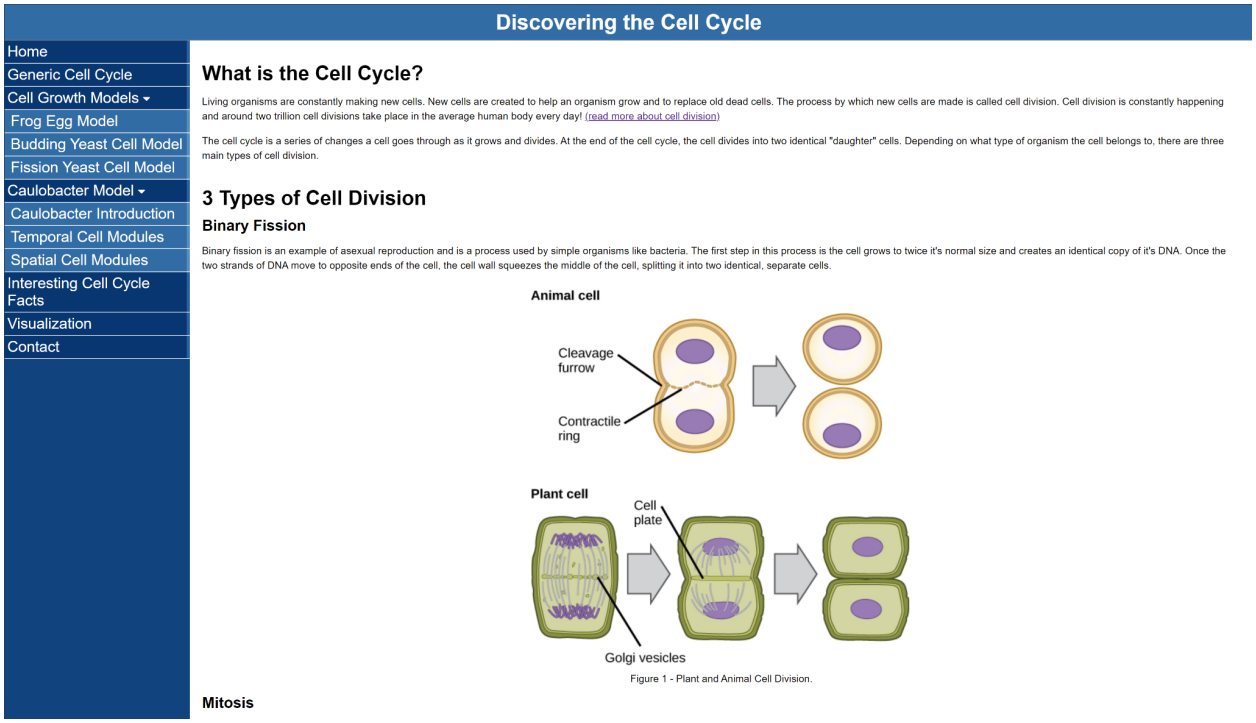

Figure 5: Home Page (1)

Mitosis

While simple organisms like bacteria use binary fission to duplicate, more complex organisms multiply using either mitosis or meiosis. Mitosis is an essential process for life. Cells that make up skin, blood and muscles in the human body use mitosis to create new cells that are exact replicates of the original cell. During mitosis, a cell duplicates all of its contents, including it's DNA strand, and splits into two identical daughter cells. Since Mitosis is such an important process for the body to grow and survive, the mitosis process is carefully controlled by certain genes in the cell. If the steps of mitosis are not regulated, then serious health problems such as cancer can occur.

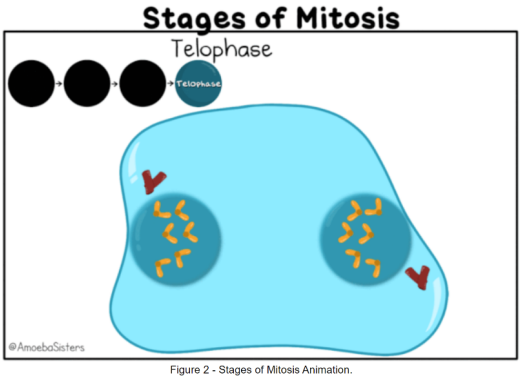

Figure 2 - Stages of Mitosis Animation.

Meiosis

The other type of cell divion used by more complex cells is meiosis, which creates new reproductive or sex cells. Sex cells include egg cells for women and sperm cells for men, which both contain half the genetic material (DNA) needed to create a fetus. Body cells are known as diploids, because they have two sets of chromosones, one from each parent. During meiosis one cell duplicates it's chromosones then divides twice to form four daughter cells. Each of the four daughter cells have half the number of chromosones of the parent cell, since the parent cell doubled it's number of chromosones and distributed them evenly amongst the daughter cells.

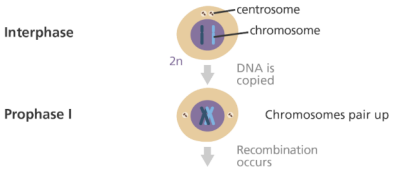

Figure 6: Home Page (2)

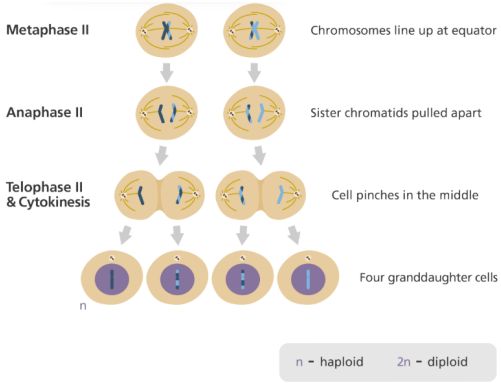

Figure 3 - Stages of Meiosis Chart.

Why is it Important to Study the Cell Cycle?

Studying the cell cycle and how new cells are created is incredibly relevant to the **health, well-being and bology of all organisms**. We have a much stronger understanding of diseases and injury recovery thanks to the work done by scientists who study the growth of cells. The cell cycle and cell division is the engine that powers the growth of all organisms. Microbiology, which is the study of all living organisms that are too small to be naked eye (Learn about Microbiology), will be a crucial role in the next wave of scientific breakthroughs related to animal and plant health.

Some of the areas where cell division research plays a significant role include:

1. Cancer Research:
2. Stem Cell Treatment:
3. Alzheimers Research:
4. Immunology and The Spread of Diseases:

Reference

1. "What Is Mitosis?" Facts, The Public Engagement Team at the Wellcome Genome Campus, 21 July 2021, https://www.yourgenome.org/facts/what-is-mitosis.
2. McIntosh, J. Richard, and Michael P. Koonce. "Mitosis." Science.org, 3 Nov. 1989, https://www.science.org/doi/abs/10.1126/science.2683078.
3. Nurse, Paul, et al. "Understanding the Cell Cycle." Nature Medicine, vol. 4, no. 10, 1998, pp. 1103–1106., https://doi.org/10.1038/2594.

Figure 7: Home Page (3)

“Generic Cell Cycle,” the second navigation tab counting from the top in the navigation sidebar, contains detailed information about each phase of the generic cell cycle. It is strongly advised for the user to look through it, as it contains in-depth terminology and information on the general cell cycle structure which will be helpful for the user to grasp the more complex version of the cell cycle. Figure 8 shows the first half of the “Generic Cell Cycle” page and Figure 9 includes the bottom half of the page.

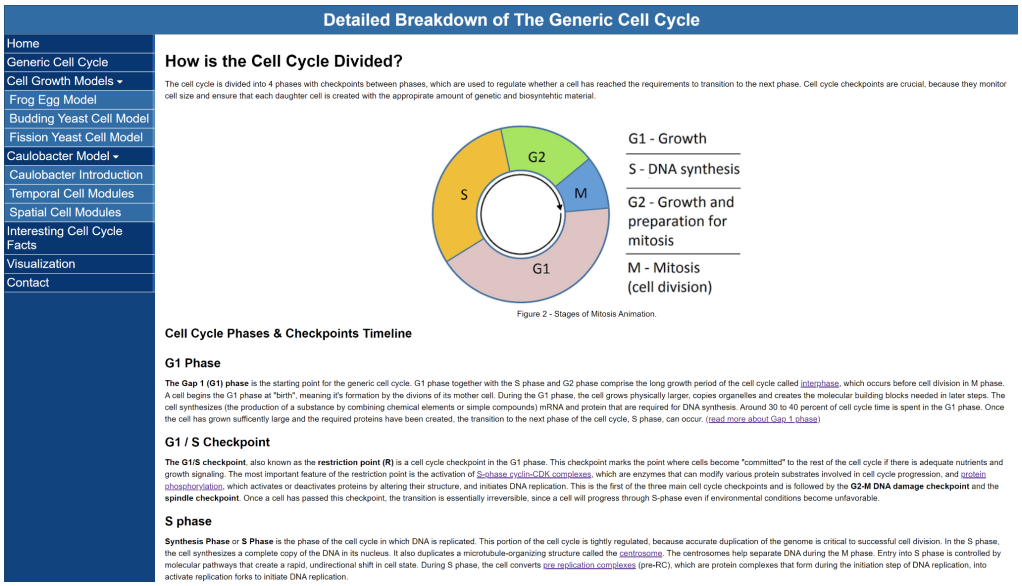

Figure 8: Generic Cell Cycle Page (1)

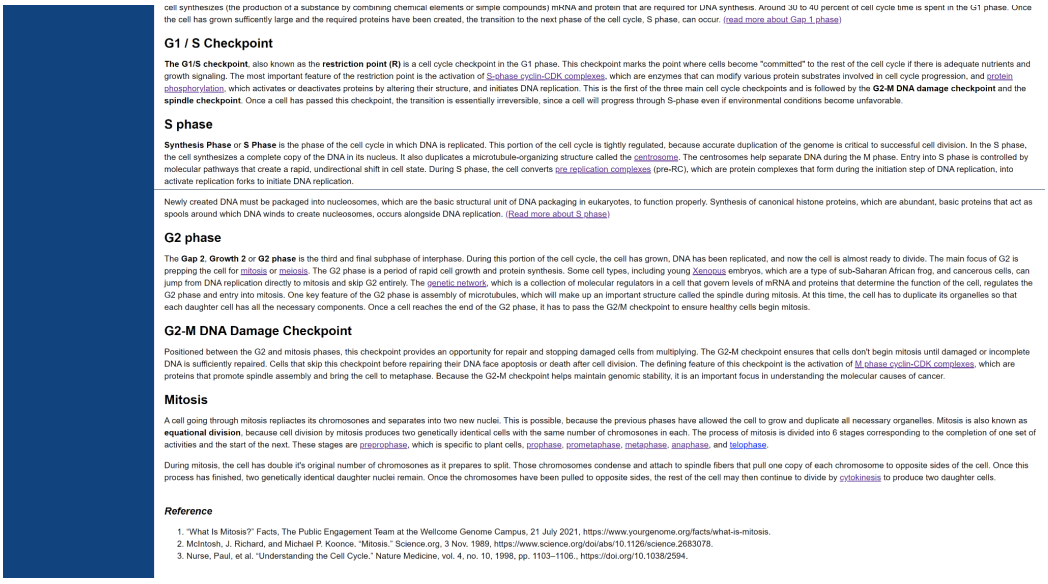

Figure 9: Generic Cell Cycle Page (2)

The third navigation tab counting from the top in the navigation sidebar is composed of three sub-navigation tabs. When the user clicks on the main navigation tab called “Cell Growth Models”, three sub-navigation tabs will appear under it. Figure 10 shows the “Cell Growth Models” sub-navigation menu expanded to show the “Frog Egg Model”, “Budding Yeast Cell Model” and “Fission Yeast Cell Model” subpages.

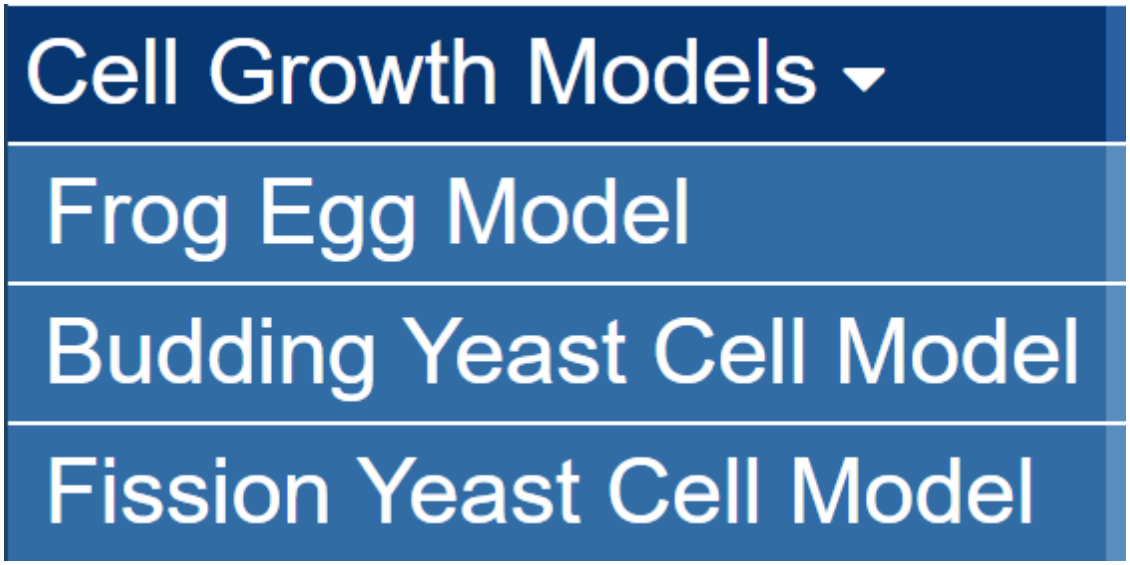

Figure 10: Cell Growth Models Dropdown Menu

The first sub-navigation tab called “Frog Egg Model” is the simplest of the three complex cell growth models. It contains a simple cell cycle structure due to the nature of the frog egg. The user is recommended to go through the first sub-navigation tab due to its simplicity relative to the three complex cell growth models. Figure 11 shows the first half of the “Frog Egg Model” page and Figure 12 shows the second half.

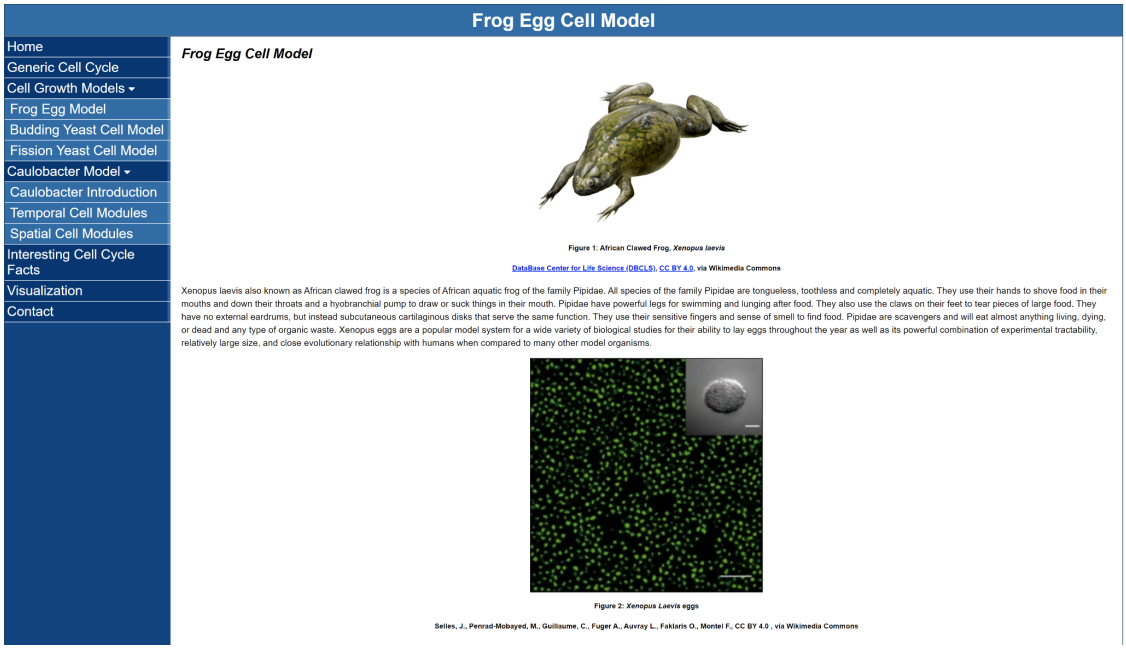

Figure 11: Frog Egg Model Page (1)

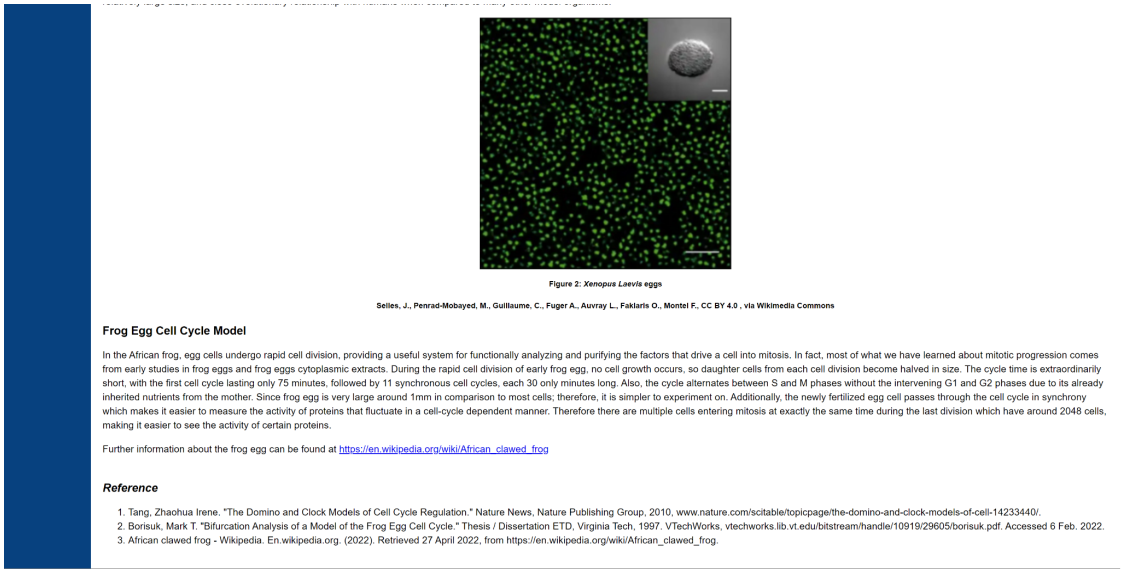

Figure 12: Frog Egg Model Page (2)

The “Budding Yeast Cell Model” page is the second sub-navigation tab underneath the “Cell Growth Models” section. This page includes recent research information about the unusual style of asymmetric division that budding yeast cells go through. Figure 13 shows the content of the “Budding Yeast Cell Model” page.

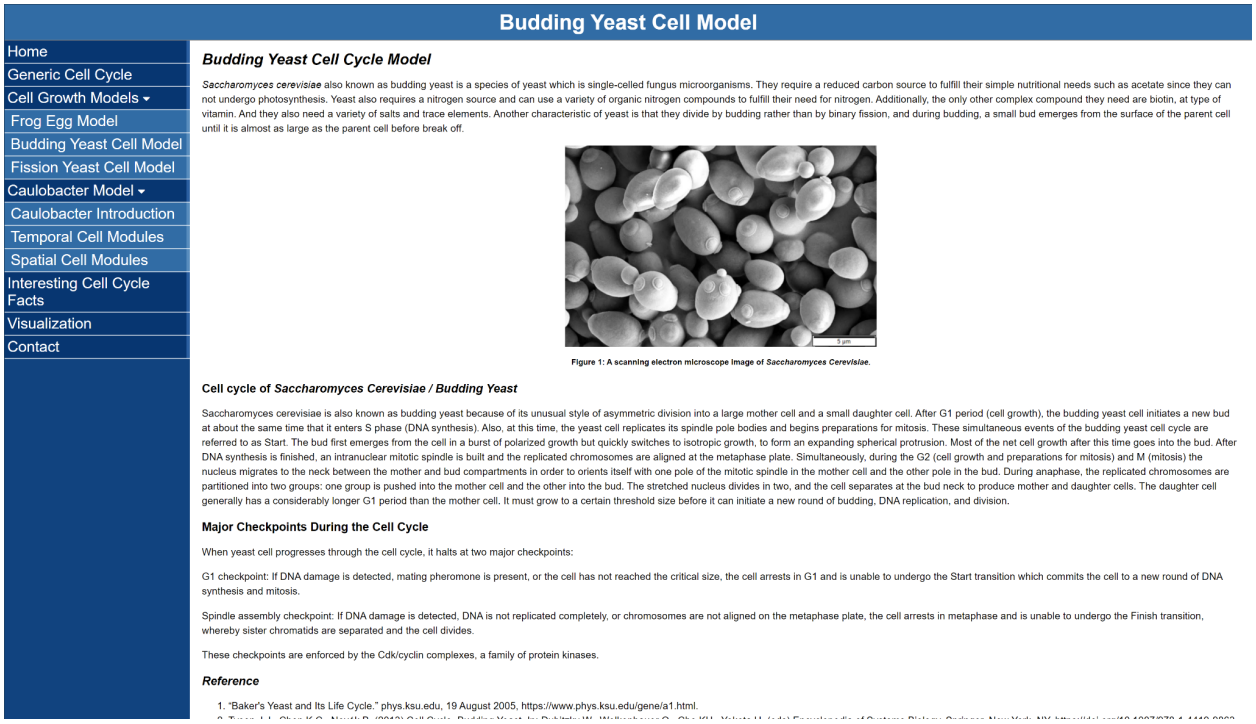

Figure 13: Budding Yeast Model Page

The final sub-navigation tab in this section is the “Fission Yeast Cell Model” page. This webpage includes information about a recent study done at USC, where researchers studied the rapid cell cycle and mutations of fission yeast cells. Figure 14 shows the top half of the “Fission Yeast Cell Cycle” page and Figure 15 shows the bottom half.

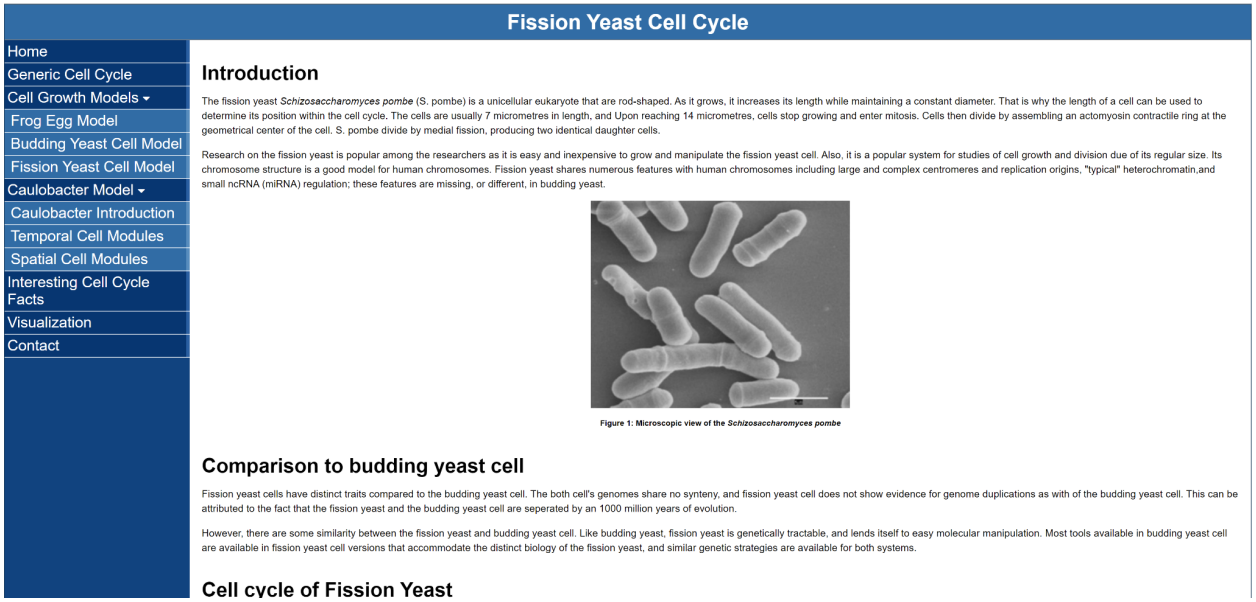

Figure 14: Fission Yeast Model Page Image (1)

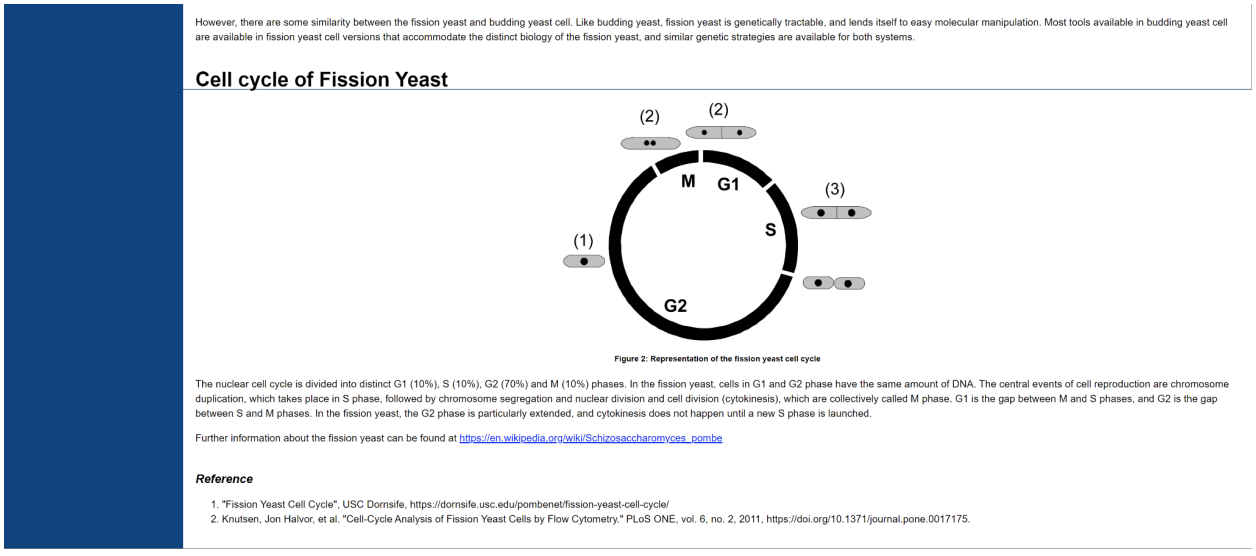

Figure 15: Fission Yeast Model Page (2)

Below the “Cell Growth Models” sub-navigation section is the “Caulobacter Model” dropdown menu. This menu contains pages that detail the information collected about Caulobacter cells, which are a type of bacteria widely distributed in freshwater lakes and streams, in Professor John Tyson’s research lab. Figure 16 shows the “Caulobacter Model” sub-navigation menu expanded, including the “Caulobacter Introduction”, “Temporal Cell Modules”, and “Spatial Cell Modules” subpages.

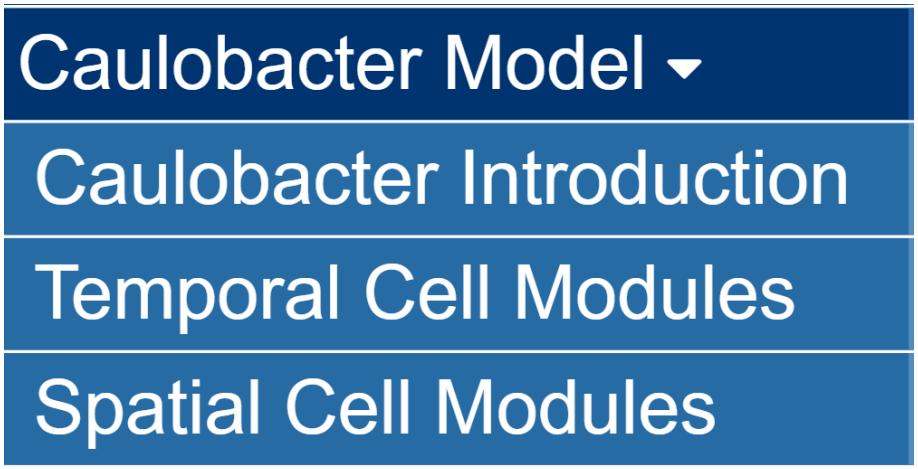

Figure 16: Caulobacter Model Sub-Navigation Menu

The first page in the “Caulobacter Model” dropdown menu is “Caulobacter Introduction”. This page explains what is unique about Caulobacter cells and the research methods used to study them. We recommend users start with this page before visiting the other tabs in the “Caulobacter Model” dropdown menu so they have some background knowledge about the subject of Professor Tyson’s research. Figure 17 shows the top half of the “Caulobacter Introduction” page and Figure 18 shows the bottom half.

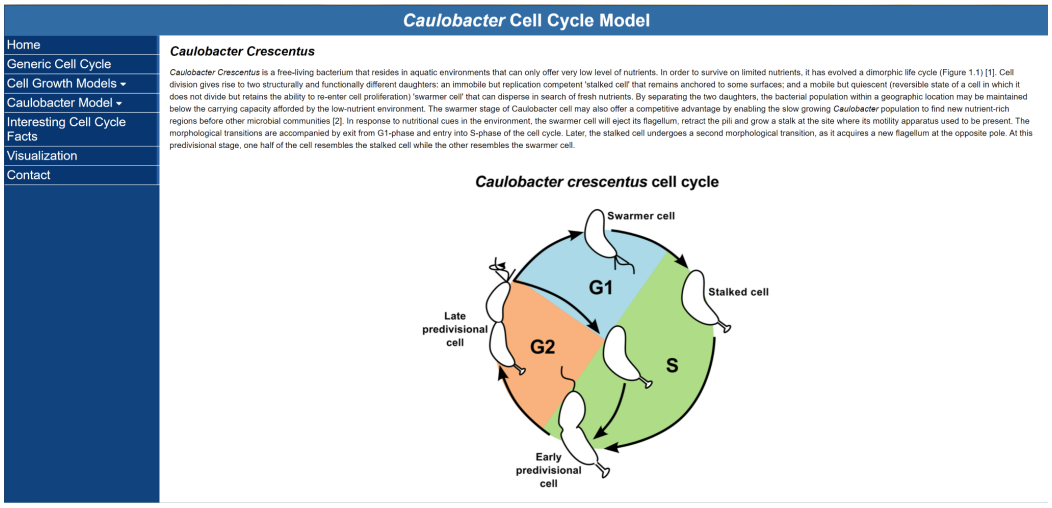

Figure 17: Caulobacter Introduction Page (1)

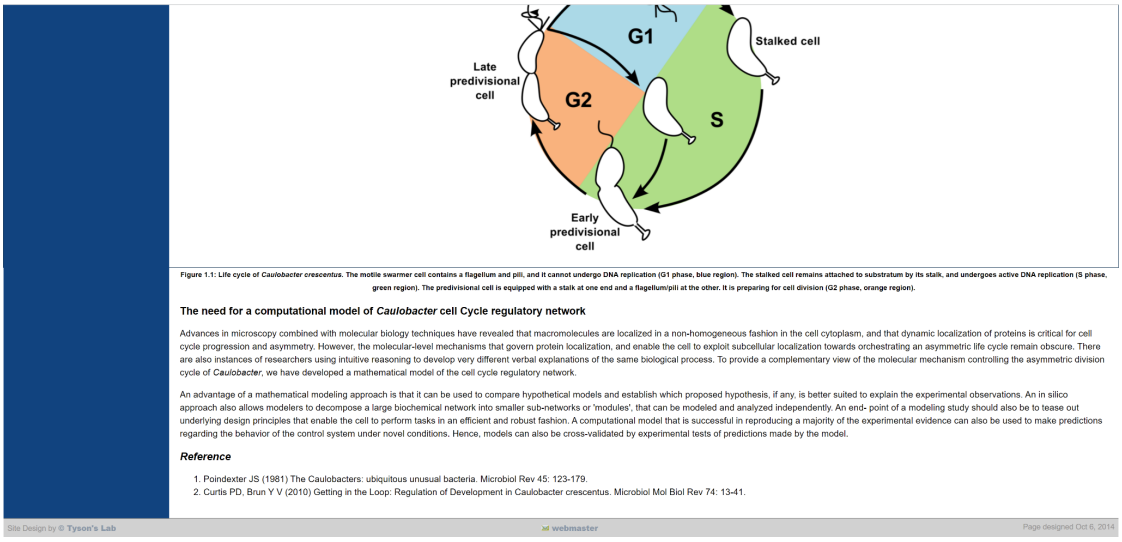

Figure 18: Caulobacter Introduction Page (2)

Following the "Caulobacter Introduction" page is the "Temporal Cell Modules" page. This page contains detailed information and graphics for the "Bistable Histidine Kinase" and "PleC and DivL Localization" research areas studied in Professor Tyson's lab. Both the "Temporal Cell Modules" and "Spatial Cell Modules" pages include highly technical information, so they are recommended for users with background knowledge or previous research experience. Figure 19 shows the first third of the "Temporal Cell Modules", Figure 20 shows the second third, and Figure 21 shows the final third.

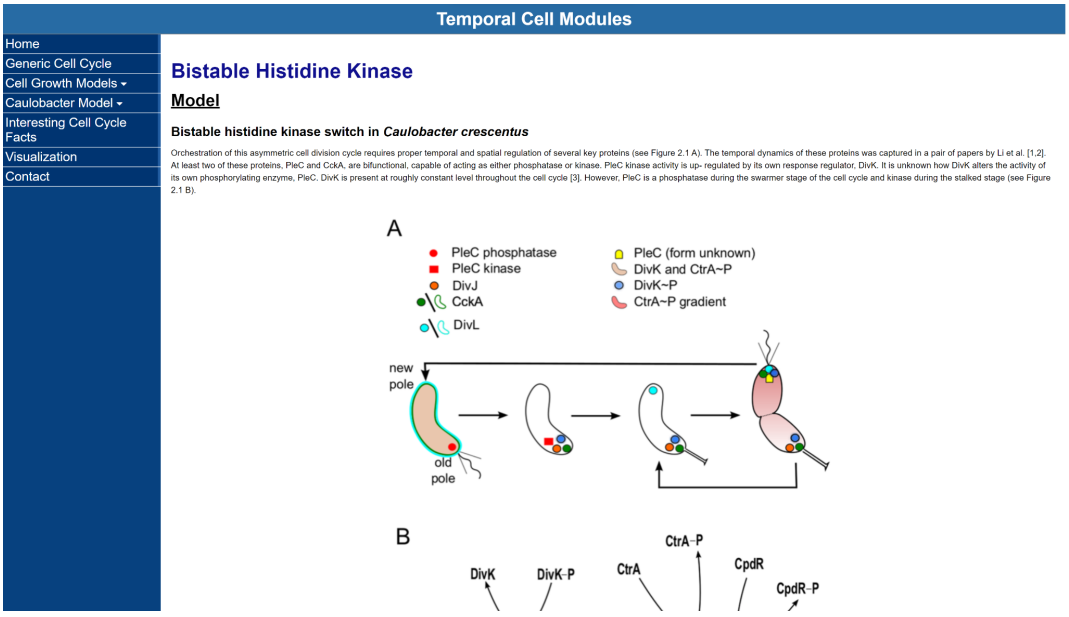

Figure 19: Temporal Cell Modules Page (1)

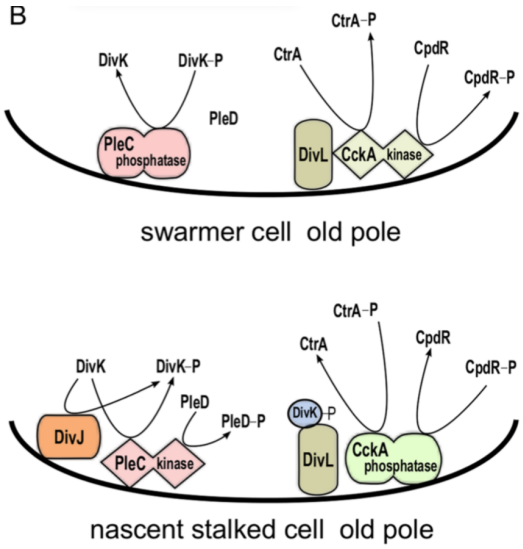

Figure 2.1: Morphological transitions in *Caulobacter crescentus* are governed by changes in localization and activity of proteins. (A) Schematic representation of the *Caulobacter crescentus* cell cycle. The cell undergoes a series of morphological changes from swarmer cell (left) →nascent stalked cell →stalked cell →pre-divisional cell (right). These events are driven by changes in the activity and localization of cell cycle proteins. In particular, notice that DivL (light blue) and CckA (green) are uniformly distributed on the membrane in the swarmer cell but localized at the poles in the stalked cell. (B) Model of the status of PleC and CckA activity at the old pole in the swarmer cell and in the nascent stalked cell. In the swarmer cell, DivJ is not localized or activated. As a result, PleC is a phosphatase and CckA is a kinase. In the stalked cell, DivJ is localized to the old pole, causing PleC to flip to the kinase form, which in turn induces CckA to switch to a phosphatase.

The phosphorylation states of DivK and CtrA are governed by the bifunctional histidine kinases PleC and CckA, respectively. Both PleC and CckA can switch between two conformations: a kinase conformation and a phosphatase conformation [4,5] (see Figure 2.1 B). Typically, in bacteria the change in activity of a bifunctional histidine kinase is brought about by an external signal molecule binding to the sensor region of the protein [6]. However, the change in PleC from a phosphatase to a kinase is brought about by its substrate, DivK [4]. In fact, the sensor domain of PleC is not essential for its function [7]. This interaction, where substrate binding to a bifunctional histidine kinase changes its function, has, to our knowledge, been observed only for PleC in *Caulobacter*. It has been suggested that DivK up-regulates PleC kinase activity preferentially in stalked cells because it is in stalked cells where DivK~P and PleC are co-localized at the poles [4].

Figure 20: Temporal Cell Modules Page (2)

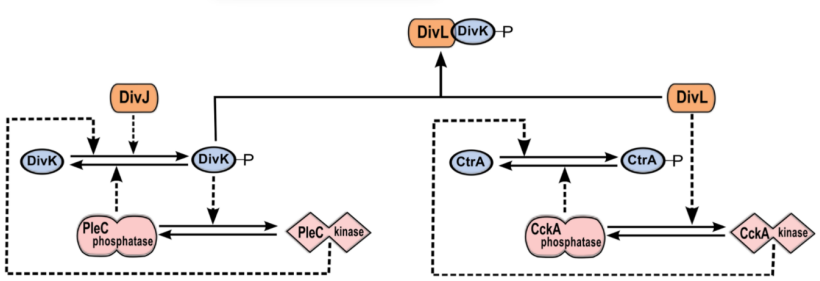

Figure 2.2: The DivJ-PleC-DivK and DivL-CckA-CtrA modules are coupled via DivK~P-DivL interaction. PleC kinase and DivK~P are involved in a positive feedback loop. By phosphorylating DivK, DivJ biases the positive feedback loop toward the PleC kinase state. DivL up-regulates the kinase form of CckA, which in turn phosphorylates CtrA. The phosphorylated form of DivK~P binds to and inactivates DivL, causing CckA to revert to the phosphatase form and dephosphorylate CtrA.

Taken together, these observations suggest that PleC-DivJ-DivK and DivL-CckA-CtrA are crucial drivers of the swarmer-to-stalked transition, as summarized in Figure 2.1 and Figure 2.2.

Method

Here, we propose a mechanism for ligand-dependent modifications of the bifunctional histidine kinase, PleC. The mechanism consists of elementary chemical reactions describing ligands (either DivK or DivK~P) binding to the histidine kinase dimer in either its phosphatase or kinase form. The binding states determine the rates of the autophosphorylation, phosphotransfer, and phosphatase reactions catalyzed by PleC. If DivK~P is more efficient than unphosphorylated DivK at promoting the transition of PleC from phosphatase to kinase, then PleC and DivK~P would be involved in a positive feedback loop. Such positive feedback loops are well known for their tendency to function as bistable toggle switches [8], and toggle switches are well known for their roles in cellular decision- making [9-11] including critical transitions in the eukaryotic cell cycle [12-14].

We have a detailed model of the interactions between DivK and PleC, under reasonable conditions on the rate constants (or propensities) of these reactions, exhibits robust bistability as a function of DivJ activity. The complete reaction network (Figure 2.3) was translated into a system of 52 non-linear ordinary differential equations using the mass-action law of chemical kinetics, with one exception. The mechanism by which DivL promotes the kinase form of CckA is unknown, so we modeled this step phenomenologically with a Hill function. Because there are many closed loops of elementary chemical reactions in Figure 2.3, we must choose rate constant values that respect the thermodynamic principle of detailed balance. As long as we satisfy these thermodynamic constraints, we find that the reaction network exhibits bistability over a robust range of parameter values.

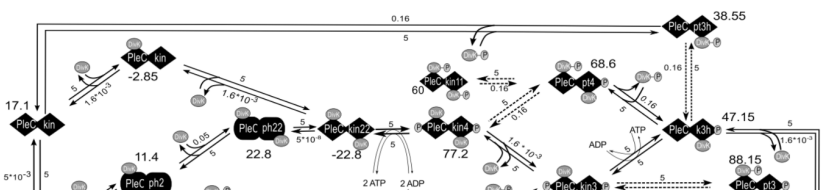

Figure 21: Temporal Cell Modules Page (3)

The final page in the "Caulobacter Model" sub-navigation menu is the "Spatial Cell Modules" page. This page contains detailed information about Professor Tyson's research in the areas of PopZ Localization and Chromosome Segregation. Similar to the "Temporal Cell Modules" page above it, the content on this page is dense and includes graphics to visualize the data collected in Professor Tyson's lab. Figure 22 shows the top of the "Spatial Cell Modules" page and Figure 23 shows the middle of the page.

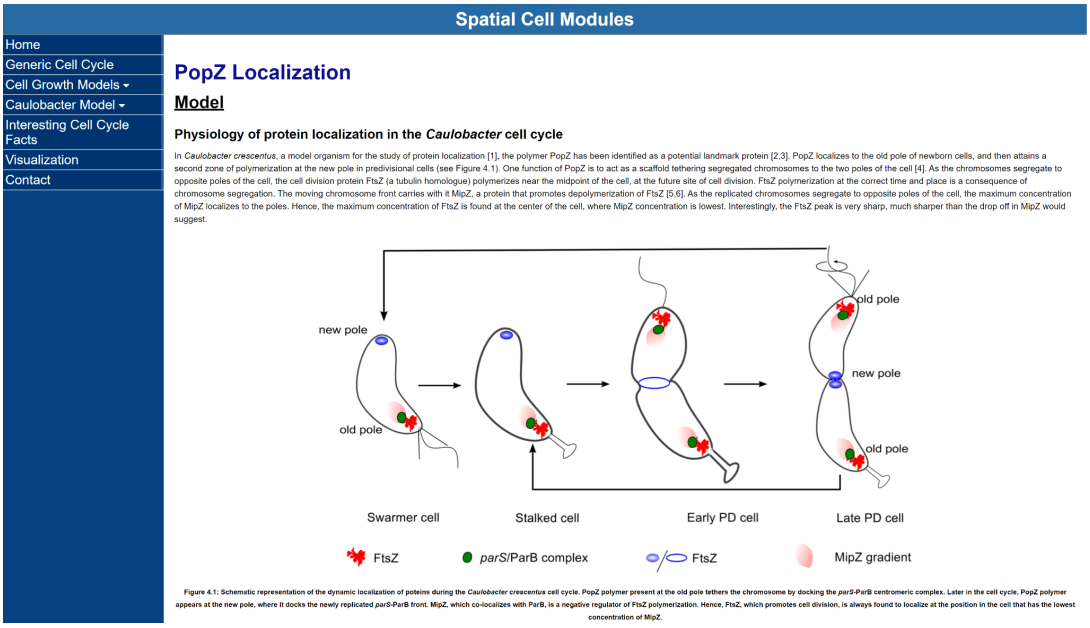

Figure 22: Spatial Cell Modules Page (1)

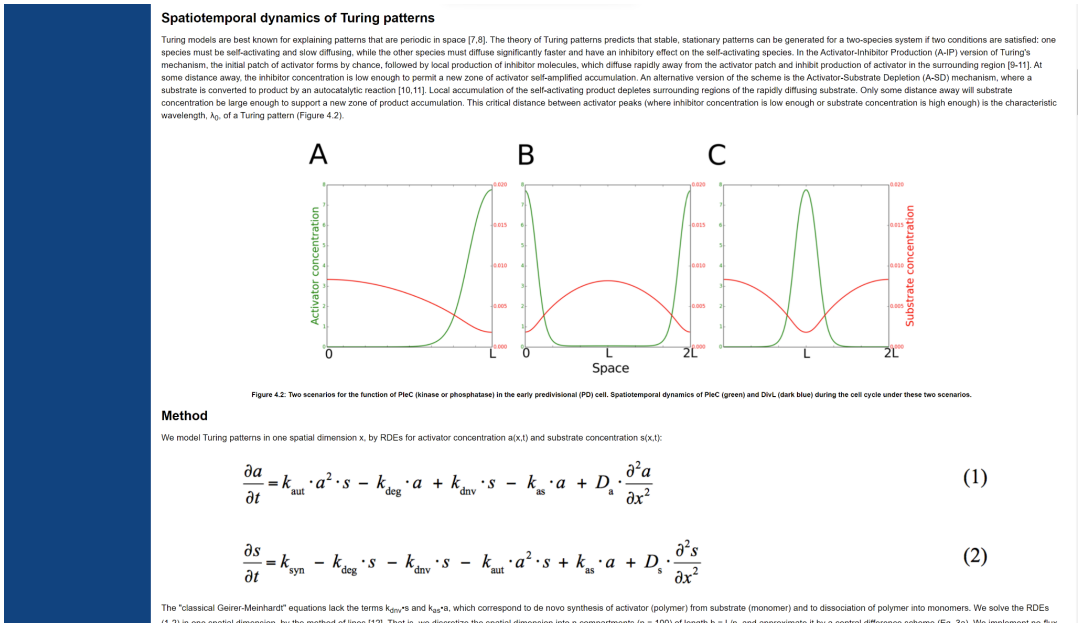

Figure 23: Spatial Cell Modules Page (2)

Right below the “Caulobacter Model” dropdown menu is the “Interesting Cell Cycle Facts” page. This page includes insightful information and memorable facts that will hopefully inspire users to investigate further and learn more about the cell cycle. Content on this page is suitable for any user, no matter their level of cell cycle knowledge. Figure 24 shows the top half of the “Interesting Cell Cycle Facts” page and Figure 25 shows the bottom half.

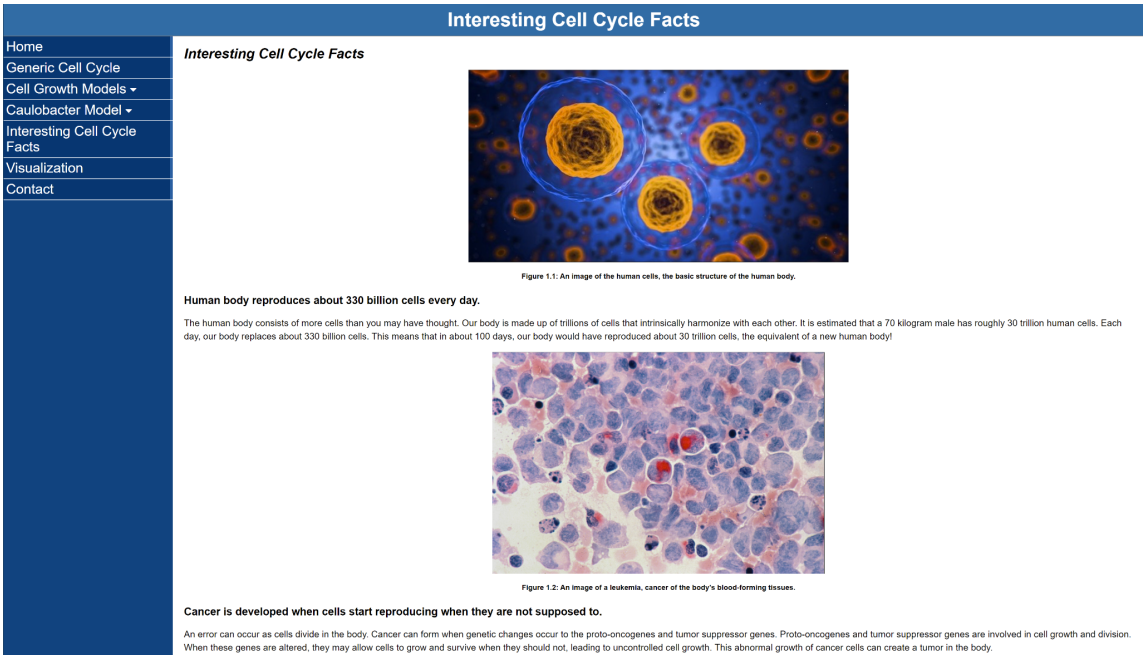

Figure 24: Interesting Cell Cycle Facts Page (1)

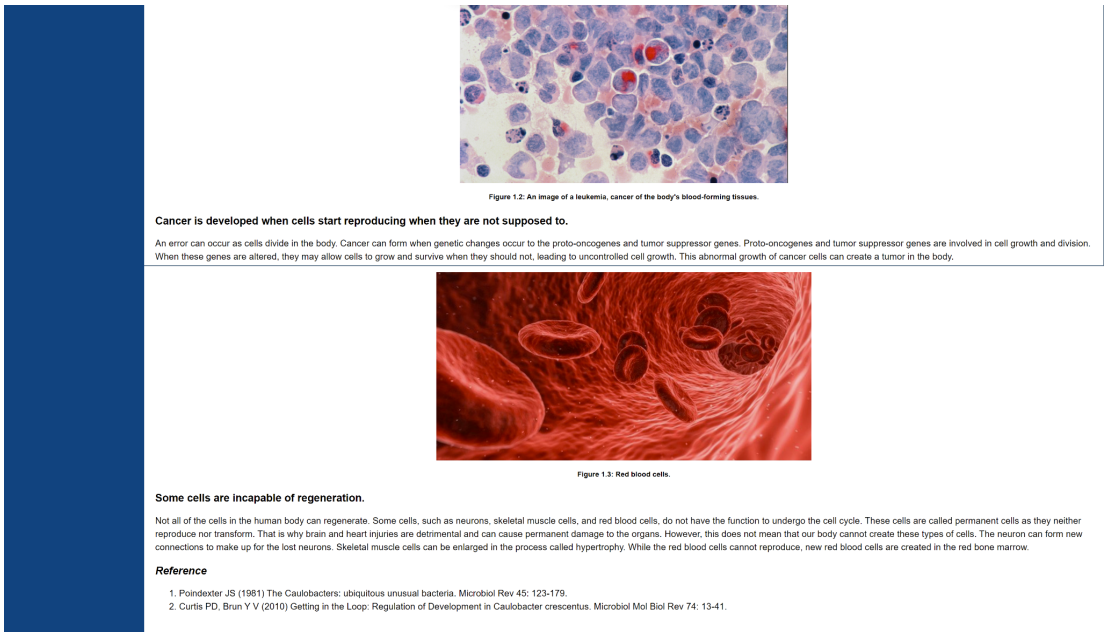

Figure 25: Interesting Cell Cycle Facts Page (2)

The second to last page on the website is the “Visualization” page. This page houses all the interactive mathematical models generated with data from Professor Tyson’s lab. Users who are visual learners or interested in seeing how cells grow and divide can find plenty of useful information on this page. Once a user navigates to the Visualization page, they can choose between the PleC and PopZ model types. These model types represent the two groups of cell division methods. After the user selects their desired model type, they can select one or more cell species to see a visualization of how those types of cells grow and divide. Figure 26 shows the visualization being run after the DivK and DivK-P cell species were selected as part of the PleC model group.

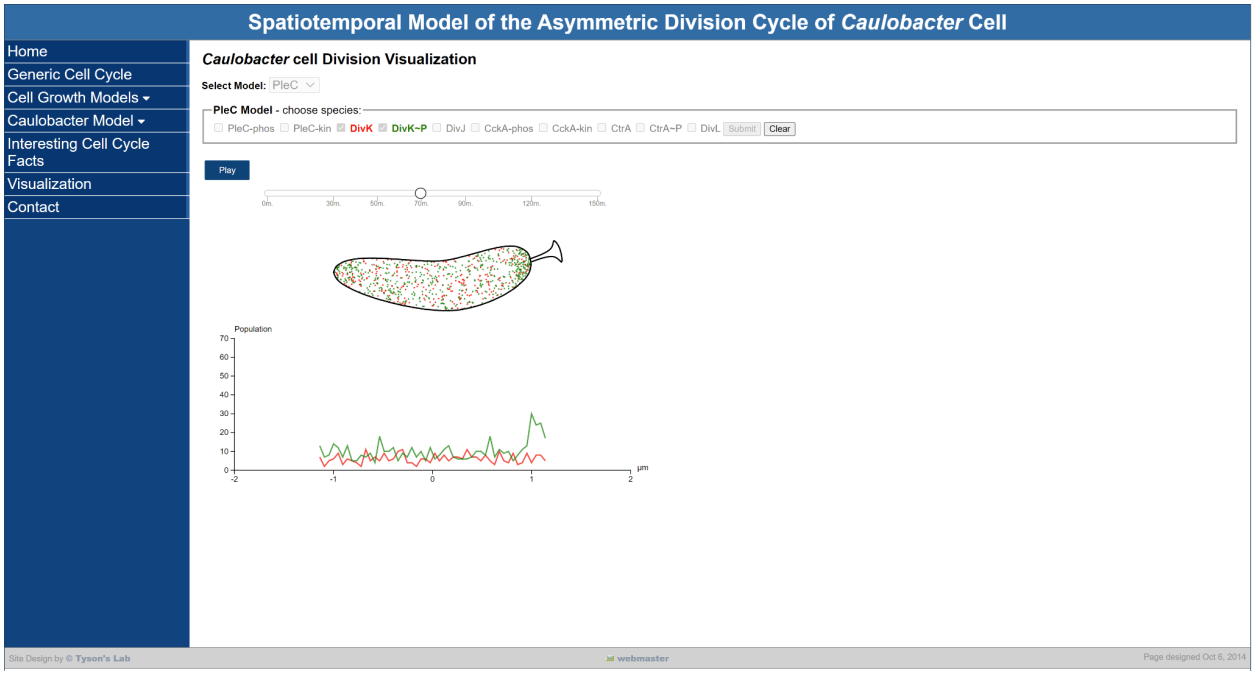

Figure 26: Visualization Page

The final page on the website, located at the bottom of the navigation bar, is the “Contact” page. This page contains links to Professor Tyson’s lab website and Professor Cao’s computational biology lab website. There is also the address for Professor Tyson’s office, his phone number, fax and email address. Figure 27 shows the “Contact” page.

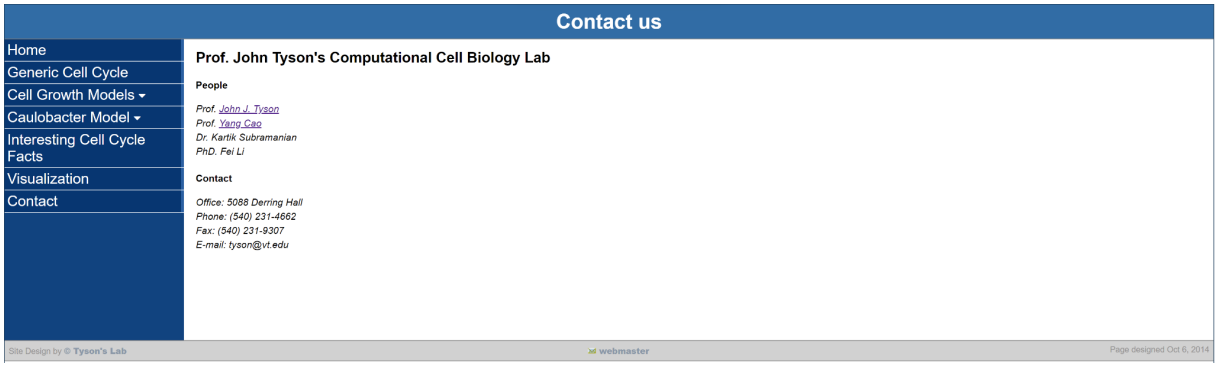

Figure 27: Contact Page

8.0 Developer's Manual

8.1 Inventory of all files

Tables 2-5 detail all the files in our project repository.

Table 2 describes all of the HTML files in our repository. These files are the basis for the webpages that make up the Cell Cycle Visualization site.

Filename	Description	Files Referenced
Index.HTML	Contains code for "Home" page. Gives users introductory information on the cell cycle	Animal Cell vs Plant Cell Graphic.jpg stages-of-mitosis-gif.gif stages_of_meiosis_chart.png
FrogEggModel.HTML	Contains code for "Frog Egg Model" page. Contains information on recent frog egg cell research	Poro_Nuclear_Ovoc-eII_Xenopus.jpg 202101_African_clawed_frog.png
BuddingYeastCell.HTML	Contains code for "Budding Yeast Cell Model" page. Includes recent budding yeast research findings	buddingyeast.jpg
FissionYeastCell.HTML	Contains code for "Fission Yeast Cell Model" page. Based on fission yeast cell research from USC	fission_yeast.jpg fission_cycle.png
GenericCellCycle.HTML	Contains code for "Generic Cell Cycle" page. Explains each cell cycle phase with text and graphics.	Cell_Cycle_Graphic_1.jpg
Caulobacter.HTML	Contains code for "Caulobacter Information" page. Includes text and graphic describing recent Caulobacter cell research	CCGraph/CC_circle.png
TemporalModules.HTML	Contains code for "Temporal Modules" page. Includes research information and graphics for Bistable Histidine Kinase and Plec and DivL Localization modules.	CCGraph/21.png, CCGraph/22.png CCGraph/23A.png, CCGraph/23.png CCGraph/24.png, CCGraph/25.png CCGraph/26.png, CCGraph/31.png CCGraph/32.png, CCGraph/3e1.png CCGraph/3e2.png, CCGraph/3e3.png CCGraph/33.png, CCGraph/34.png CCGraph/37.png, CCGraph/39.png,
SpatialModules.HTML	Contains code for "Spatial Modules" page. Includes research information and graphics for PopZ and Chromosome Segregation modules	CCGraph/51.png, CCGraph/52.png CCGraph/4e1.png, CCGraph/4e2.png CCGraph/53.png, CCGraph/55.png CCGraph/56.png, CCGraph/58.png CCGraph/59.png, CCGraph/61.png CCGraph/3e1.png, CCGraph/6e1.png CCGraph/62.png, CCGraph/63.png CCGraph/64.png, CCGraph/65.png
InterestingFacts.HTML	Contains code for "Interesting Cell Cycle Facts" page. Mostly text and images.	human_cell.jpg tumor_cell.jpg blood_cell.jpg
Visualization.HTML	Contains code for "Visualization" page. Uses drawPleC.js and drawPopZ.js to create interactive cell cycle visualizations	drawPleC.js drawPopZ.js
Contact.HTML	Contains code for "Contact" page. Includes links to learn more about Professor Cao and Professor Tyson	None

Table 2: HTML File Chart

Table 3 describes all the JavaScript (.js) files contained in the website directory.

Filename	Purpose
D3/d3.js	Defines necessary D3 functions and properties
drawPleC.js	Defines functions to create PleC mathematical model
drawPopZ.js	Defines functions to create PopZ mathematical model
All .js files in CCData directory	These files are used to generate graphs used for cell visualizations

Table 3: JavaScript File Chart

Table 4 describes all the Cascading Style Sheets (CSS) files in the website repository. The main use of CSS files is to create custom HTML tags and customize the design of the website.

Filename	Page Where it is Used
buddingYeast.css	BuddingYeastCell.html, Caulobacter.html, Contact.html, FissionYeast.html, index.html
Style.css	GenericCellCycle.html, index.html, BuddingYeastCell.html, SpatialModules.html, TemporalModules.html, Visualization.html
Text_only.css	BuddingYeastCell.html, Caulobacter.html, Contact.html, FissionYeastCell.html, GenericCellCycle.html

Table 4: Cascading Style Sheets (CSS) File Chart

The first objective for maintaining the website is to make sure all HTML, JavaScript, CSS, and resource files, such as images and GIFs, remain in the directory even if the website continues to grow. Removing one or more of these files can ruin the formatting of the website or lead to webpages being unreachable. The necessary components to generate the mathematical cell models on the "Visualization" page are the drawPleC.js and drawPopZ.js files as well as the contents of the d3 directory.

8.2 Using Cell Visualizations

The drawPleC.js and drawPopZ.js JavaScript frameworks are used to create interactive cell cycle visualizations for one or more of the user-chosen cell species on the "Visualization" page. Cell visualizations are rendered by the user first choosing between the PopZ and PleC models. The PopZ model contains the species PopZ-p, PopZ-m, mRNA, and Gene. The PleC model contains the species PleC-phos, PleC-kin, DivK, DivK-P, DivJ, CckA-phos, CckA-kin, CtrA, CtrA-P, and DivL. Once the user chooses their desired model, they can select one or more species and the data for each will be color coordinated and overlaid in the cell visualization. The user can speed up or jump to different parts of the animated visualization using the scroll bar and the visualization can be stopped or started using the play/pause button. Figure 28 shows the cell visualization generated when the user selects the mRNA and Gene species. The webpage will recognize that the user selected multiple species and will label each one with different color text so the cell visualization is easy to understand. In this instance, mRNA is in red and Gene is green.

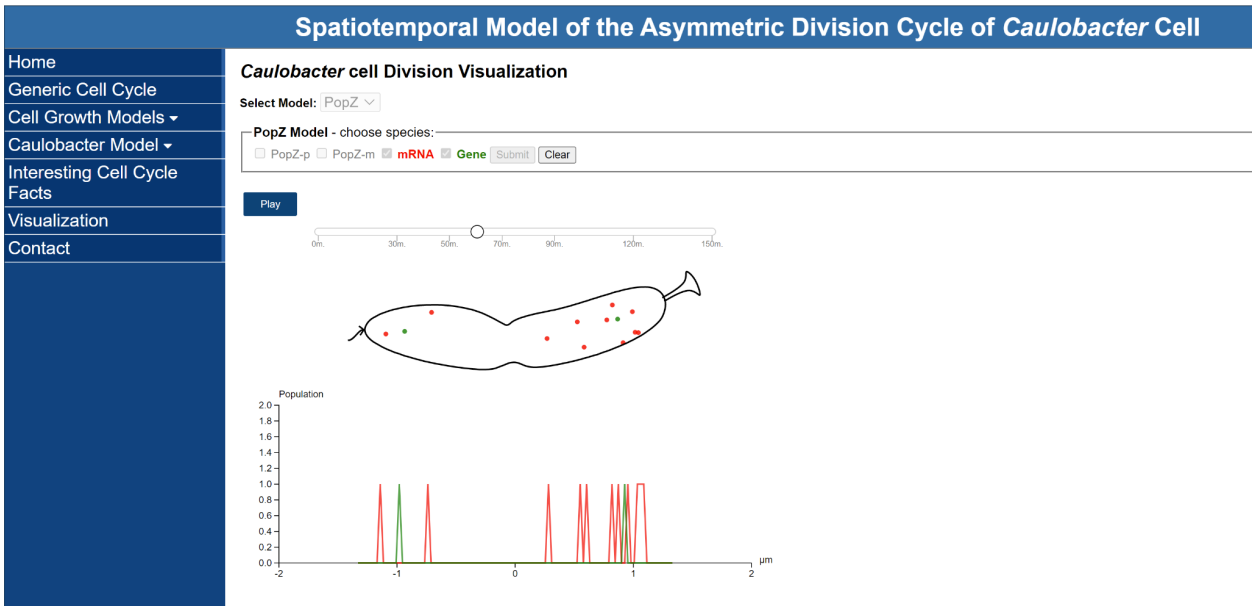

Figure 28: mRNA and Gene Cell Species Visualization

9.0 Lessons Learned

Our team learned that it is important to portray technical information in a clear, concise manner. Technical information may contain jargon and technical terms that make it difficult to understand. We found that it is important to explain any important information and use visualizations to engage the audience. As our team worked with creating mathematical models, we learned that choosing engaging, informative graphics can convey a lot of information in an easy to understand way.

Also, our team learned that dividing topics in different subsections makes it easier to organize information. Dividing the website into different webpages made it easier to focus on each individual page. It was easier to design the webpages when the topic was simple to understand.

Our team learned that it is important to think about the audience and the purpose of our project. Thinking about the needs of each member of our audience was helpful when we were designing our webpages. Our team designed the website based on how the audience would use the website. Listing out the purpose and audience of each webpage helped us design our website.

9.1 Timeline and Schedule

The timeline of our time working on this project was split into 5 phases. Each of these phases is defined by what parts of the website each of us were working on and our most recent meeting with Professor Cao to get his feedback. Figure 29 is a graphical representation of our project timeline and the work we did during each phase of the project.

Phase 1 1st Week of February	Phase 2 3rd Week of February	Phase 3 2nd Week of March	Phase 4 1st Week of April	Phase 5 End of April
- 1st Meeting with client - Understand website files - Collect background info	- Design website layout - Review each other's information - Assign web pages to work on	- 2nd meeting with client - Implement Dr. Cao's feedback - Create cell cycle model pages	- Add links for further learning - Condense research info into two pages	- Final client meeting - Test math models - Improve website design

Figure 29: Phases of the Project Timeline

During each of the project phases, Cesar was the project leader and divided the work so each team member was working on a different part of the website. Our group met with our client, Professor Cao, three times during the semester. After each meeting, we worked on implementing his feedback and we gained a clearer understanding of his vision for the final website. Figure 30 shows each of the meetings we had with Professor Cao and the feedback we received.

Meeting 1 February 4th	• Include content for general public & younger students • Use up to date research information • Order pages from simplest to most complex
Meeting 2 March 18	• Add links for further learning • Create separate pages for Cell Cycle Models • Add detailed Generic Cell Cycle page
Meeting 3 April 22	• Include all Cell Cycle visualizations on one page • Test all mathematical models • Include reference section for each page

Figure 30: Client Feedback Chart

9.2 Challenges

The challenges we've faced as a team have centered around information collection, understanding the original website files, and addressing the needs of all the user groups for the website. One challenge that our team faced was finding reliable information for our website. As each of our members lacked sufficient knowledge about the cell cycles and bioinformatics, we had to research and find reliable information to create the webpages.

Another challenge was learning about the legacy code we received from our client. Our team had to learn about how the existing code of the website works and learn about technologies used in the code. We had to learn about the front end technologies such as HTML/CSS and D3 for the mathematical models.

Also, creating webpages based on our intended audience was challenging. As our website has three primary audiences – younger students, the general public, and experienced users – we had to design each webpage with a particular audience in mind. For each portion of our audience, we had to be creative and address the audience's needs when using the website.

10.0 Future Work

As the website continues to grow and evolve, new information should be added with the goal of covering new concepts while keeping the site organized and easy to navigate. Incorporating more mathematical models, such as the ones implemented on the Visualizations page, would be a great way to extend the functionality of the website. DrawPleC.js and DrawPopZ.js are JavaScript files that generate the current interactive models and can be used as a reference for creating new mathematical models.

The content on the existing pages is up to date and accurate, but those pages can be improved by adding additional resources, such as videos, animations, and links to external sites. The Spatial and Temporal Modules pages contain research information collected from Professor Tyson's lab. Any information from new research findings should be added to these pages. A page dedicated to giving users background information on Professor Tyson's lab and how his research is conducted would be a useful addition to the website.

Future work can be done on improving the website UI. Our main goal as a team was to collect useful information and display it in an organized manner. This meant we did not focus as much time as we would have liked on the UI and design of the website. Future teams can work on improving the color scheme to highlight important sections of the website. Also, the consistency of the website can be improved to provide users with a uniform experience across all webpages.

The UX of the website can be improved to provide users an easier time navigating through the website. The navigation menu can make it easier to navigate through the website. A search bar would be a helpful addition for users that want to find a specific section or topic without having to look through multiple pages. Additionally, a future team can include accessibility features for people with disabilities. Auditory features can be included to aid people with hearing-related disabilities. Each of the images on the website includes a caption and description, but the website is not currently optimized for the visually impaired.

11.0 Acknowledgements

Dr. Young Cao: Client
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Email: tyson@vt.edu

Dr. Edward Fox: Professor
Email: fox@vt.edu

Ryan Wood: GTA
Email: ryanw23@vt.edu

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