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Breaking Down Silos: Systems Mapping in Cellular Biology

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Abstract

Cellular biology is well established as a basic biological science, but the complexity of the cell often results in having to approach content piece by piece, compartmentalizing course material as "silos". Students often struggle with finding common themes or linking together topics, both within a single class or across subjects. Here we approach protein trafficking from a systems thinking perspective, where educators can shape student capacity to map relationships between cellular structures and processes. Students develop collaboration skills while improving their understanding of complex, multi-faceted cellular interactions. We introduce how to generate a slice-of-the-system map to connect relationships between key aspects of cellular processes. Additionally, students find common themes in a model system and map specific mechanisms in cellular biology, ultimately breaking down the silos to better understand the inner workings of an intricate cellular system.

Keywords: systems thinking, protein trafficking, vesicular transport, cellular biology, system mapping, group work, collaboration, active learning

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INTRODUCTION

Systems thinking is an approach to investigate factors, interactions, steps in a process and other interconnected sets of elements that are organized to contribute to a possible outcome (Meadows 2008). The benefits of systems thinking have long been documented as beneficial in understanding in-depth mechanisms, but the approach, specifically in biology where educators have largely relied on textbook information and structure in their delivery, is still foreign (Momsen et al. 2022).

In cellular biology, the complexity of the cell often results in having to approach content piece by piece, compartmentalizing course material as "silos". However, in this piece-by-piece instructional format, students often struggle with identifying common themes, linking together topics over time, applying material in a broader context and visualizing the process as a whole. Here we introduce a "slice-of-the-system" mapping method for isolating the protein trafficking process (the slice) of the cellular system to introduce systems thinking, a process that provides students with the capacity to map relationships between cellular structures, processes and organization, and analyze how different cellular systems interact (Momsen et al. 2022), while developing collaboration skills and promoting active learning. Systems thinking and the slice-of-the-system mapping framework provided in this publication can be introduced as early as secondary school through strategic scaffolding and thoughtful pedagogical practices.

We have used this process to introduce a wide variety of topics from public health and epidemiology practices to cellular biology. It has also been used to provide transparency and identify new strategies to strengthen existing processes within an organization with variable success. No matter the topic, it is imperative that students don't feel overwhelmed. Therefore, supporting material (in the form of a video or lesson) pairs well with this activity.

In our experience, this activity takes 2-3 class periods of instruction and guidance, plus independent student time outside of the classroom over the span of approximately two weeks. Systems mapping is used as an approach to link concepts or topics together, so prior to introducing the activity, the content required to create the systems map should have previously been introduced. The set-up for this activity and the cost is minimal. However, slice-of-the-system format may be foreign to most students, as it is fundamentally different in design from that of a common flow chart and may be daunting. It is therefore recommended that substantial time (in class and outside of class) be allotted for this activity.

On day 1, once the activity has been introduced, it is recommended that the instructor guides students through an example such as provided in Figure 1 – which is a basic outline of a slice-of-the-system map. Then, construct a small map together as a class, such as a slice-of-the-system map of a pizza delivery process (Figure 3, Appendix A). It is recommended that instructors guide the map building process with probing questions but not build the map for students. For example, to identify actors in the process (Figure 3, green boxes), you may wish to ask, "Who is involved in the pizza delivery process?". Or to identify key steps in the process (Figure 3, yellow boxes) and key players/sticking points (Figure 3, pink clouds) that may be missing, ask "What would happen if the traffic was bad?" or "Does the person who takes the order need to know the menu in detail? How would you ensure they did?". This provides students with a demonstration on how to think through a process, modify their map in real time, and introduces the slice-of-the-system format while promoting student-driven outcomes. Once students have created a map together with the instructor's guidance, it is recommended that instructors review the format and components of the map with students. Upon completion of this example, students can be organized into teams and be provided with the materials so that they may begin creating their map. In the activity described within this paper, students are instructed to make a protein trafficking map. It is imperative that you provide students with time to work on their map in class on day 1 while the example and thought process of slice-of-the-system mapping is fresh. We encourage students to continue to work on their map outside of class prior to their next class together. Designating an entire second class to map building with instructor guidance in a team-by-team setting is beneficial as each team may approach their map slightly differently. We often encourage students to use outside resources to aid in their mapping process, specifically for Part 2 of the activity.

If time permits, an optional step to this activity is to provide students with opportunities to share and collect peer feedback. This can be done in the classroom or in a digital environment. In the digital environment, teams can post their maps on a discussion board and peers can comment with questions and suggestions. In the classroom, provide students with sticky notes (perhaps in a different color that hasn't been used), and circle the room, leaving feedback or thought-provoking questions on the provided sticky notes. Each team can collect these notes and use them to modify their map before final submission.

STUDENT OUTLINE

Objectives

Map relationships between organelles, cellular structures and processes.
Apply current knowledge and understanding of steps of the protein trafficking process in a broader view.
Identify the role of key proteins in protein trafficking.
Build critical consciousness.
Develop collaboration skills with peers.

Introduction

Protein trafficking is extremely complex with several families of proteins participating in the process as cargo proteins are transported from organelle to organelle through vesicles. Cells bind and aggregate cargo proteins in a source compartment, form vesicles from the membrane of that source compartment, transport the vesicles to a target compartment, and fuse incoming vesicles to that target compartment's membrane to deliver the cargo protein to that target compartment. Without some kind of scaffold and proteins to help, a cargo protein would not reach its correct final destination.

This activity introduces you to how each family of proteins participates in the process, where they are introduced and why each step is needed. It will also enable you to map how different types of cargo proteins move from compartment to compartment and what they need for directional transport. Once the general mechanics of the process are understood, it is much easier to identify what specific proteins from a particular family are doing.

For this activity, you will break down the process of routine transport by creating a systems map of the vesicular transport stages of the protein trafficking process.

Methods

Part A: Construct a Slice-of-the-System Map

Your slice-of-the-system map should demonstrate the process of protein trafficking. Your map should be clearly organized and labeled with appropriate actors, action steps, key players/sticking points, and outcome. A simple illustration of how to format your system map is provided in Figure 1. The initial steps of protein synthesis, starting with the nucleus, have been provided in Figure 2.

To begin, we will create a system map together in class of an unrelated, but fun topic. This example will introduce you to the slice-of-the-system format that is expected for this activity.

Each team is provided with the following items to create your map: 1 piece of white poster board, packs of sticky notes (yellow, blue, green, orange, pink), 1 black permanent marker, 1 role of painter's tape. It should be noted that for the protein trafficking map, your actors (green) will be organelles or cellular locations and key points (pink) will be key protein families (listed below, see part B in these instructions).

Starting after the cargo protein has been synthesized (i.e. at the end of Figure 2), work together as a team to continue creating your system map of the vesicular transport stages using the supplies provided. You will have to add additional actors and steps as you build your version of the protein trafficking system.

If you would rather create a digital version of your map, you are welcome to do so using a flowchart creator of your choice, such as Lucidchart (Lucidchart Software Inc.), Google Slides (Google LLC), Google Drawings (Google LLC), Microsoft PowerPoint (Microsoft Corporation) or Canva (Canva Pty Ltd.). If you choose to create a map digitally, please share your final image with your instructor as a shareable link that can be viewed by anyone.

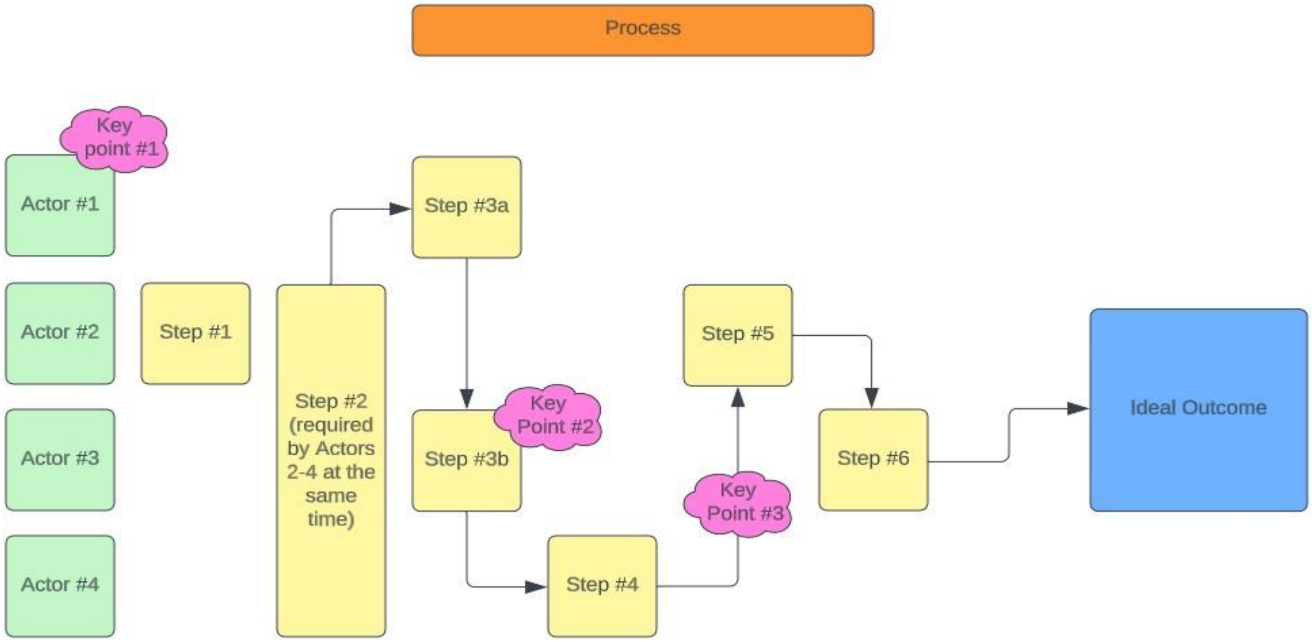

Figure 1: Slice-of-the-system map of a process (orange). Actors (green) are aligned on the left side in rows. The steps of the process (yellow) are placed in the row for the actor(s) that are involved. Some steps may be shared across actors. The final outcome (blue) is the ideal outcome for the process. Key players/sticking points (pink) are placed anywhere on the map where issues could arise or where steps could potentially be blocked, disrupting the process from reaching its outcome. Arrows may be used to illustrate the directional flow of the process.

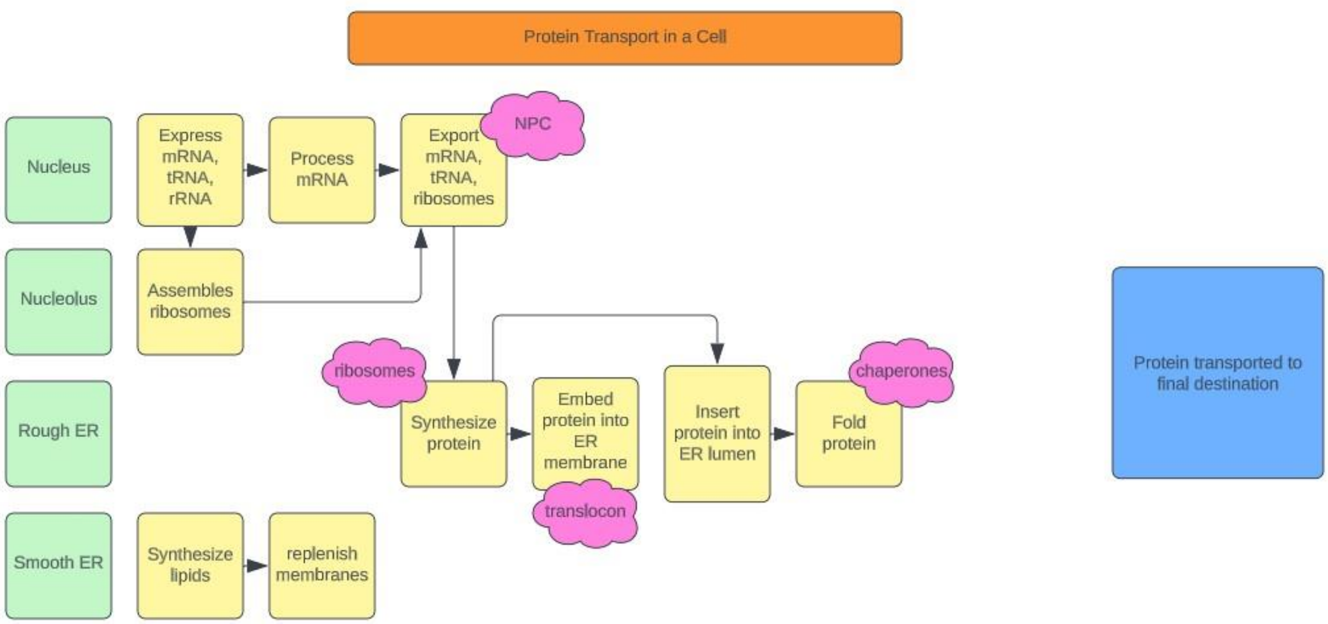

Figure 2: Slice-of-the-system map of the beginning of protein transport to be used as a starting point in creating student maps. Actors (green) are aligned on the left side in rows. The steps of the process (yellow) are placed in the row for the actor(s) that are involved. The outcome (blue) is the ideal outcome for the process. Key players/sticking points (pink) are placed anywhere on the map where issues could arise or where steps could potentially be blocked, disrupting the process from reaching its outcome.

Part B: A Break in the System

Once you have created your slice-of-the-system map for protein trafficking, each team is tasked with hypothesizing what would happen if one key player in the protein trafficking process was non-functional. For this part, you will use the list of main classes of proteins (bulleted in the List of Molecule Families below) to complete two items:

1. Using your default slice-of-the-system map, mark:
    a. The step where a member of each main family joins in the process.
    b. The step where the member of each main family leaves or stops acting.
    c. The specific trigger or event that causes each main family member to join the vesicle, leave the vesicle, or to act on the vesicle in some way.
2. Specific proteins (*italicized*) are listed under each main protein family. You will be assigned one specific protein to focus on. In a separate section (not on your map), in paragraph form, use scientific writing format with appropriate reference to discuss the following:
    a. What would happen if your specific protein was non-functional in the cell?
    b. Hypothesize the potential outcome(s) of the protein trafficking pathway for this scenario. Are there fail-safe mechanisms to reduce the severity of the outcome?

<u>List of Molecule Families</u>

- Adapters
- Arf/Sar
- Cargo
    - *Cathepsin A (acidic carboxypeptidase C; breaks down endocytosed proteins)*
    - *Transferrin (the carrier protein that binds iron released by digestion in the gut and transports it in blood to cells)*
    - *Trypsin (digestive enzyme secreted by pancreatic gland cells after a meal)*
- Cargo Receptors
    - *Mannose-6-phosphate receptor*
    - *Transferrin cargo receptor*
    - *Trypsin cargo receptor*
- Coat Proteins
    - *Clathrin - responsible for transporting vesicles in both directions between trans-Golgi network, endosomes, lysosomes, and trans-Golgi membrane*
    - *COP-I – located in vesicles that bud from ERGIC or Golgi, go backwards to return cargo to the ER*
    - *COP-II – located in vesicles that carry proteins from the ER to ERGIC/Golgi; forward along the secretory pathway*
- Dynamin
- Motor proteins
- Rab proteins (prenylated side chains anchor these proteins to the cytoplasmic side of membranes).
    - *Rab1 – on Golgi complex*
    - *Rab2A – on ER, cis-Golgi network*
    - *Rab3A – on secretory and synaptic vesicles, required for membrane repair*
    - *Rab5A – on plasma membranes, clathrin-coated vesicles and early endosomes*
    - *Rab6A – on Golgi and trans-Golgi network*
    - *Rab9A – on late endosomes, trans-Golgi network*
    - *Rab11A – on recycling endosomes, exocytotic vesicles*
    - *Rab14 – on early endosomes*
    - *Rab26 – on acidified vesicles and lysosomes*
- Rab-GAP
- Tether proteins
- t-SNAREs
- v-SNAREs

Summary

As we have learned in class, proteins require specific signals, carriers, and cytoskeletal components to reach their destination. Over the next two weeks, you will compile the mechanisms in which proteins are synthesized and transported through a cell and create a slice-of-the-system map of the cellular protein trafficking process. Upon completion of this exercise, each team will have created a slice-of-the-system map that begins with RNA synthesis and encompasses all the possible directions in which proteins are transported.

Grading Rubric

Part 1 – Slice of the System Map (0-10 points)
Is the map complete? Does the map flow in logical order? Does the map make sense?

Part 2 – A Break in the System (0-10 points)
Were all questions addressed with thoughtful discussion? Was effort shown? Do the answers read logical?

MATERIALS

This exercise can be introduced face-to-face or in the digital environment. Below is a list of supplies required for each of these modalities.

Hands-on, Face-to-Face Environment

In this modality, students work in teams (3-4 students) to create their systems map together. The instructor will require a computer and projector to project instructions, 1 piece of poster board (white or light color), 1 roll of painters' tape, 1 black permanent marker, sticky notes (square shaped) in blue, orange, yellow and green (1 pack of each color), and sticky notes (circular, cloud or star shaped is best) in hot pink or purple (1 pack) for building the slice-of-the-system map. Students require printed instructions (1 per student), poster board (white or light color, 1 per team), painters' tape (1 roll per team), black permanent marker (1 per team), sticky notes (square shaped) in blue, orange, yellow and green (1 pack of each color per team), and sticky notes (circular, cloud or star shaped is best) in hot pink or purple (1 pack per team).

The Digital Environment

In this modality, students may work individually or in teams to create their systems map. The instructor will require a computer and projector to project instructions and present the example slice-of-the-system map, a flow chart creator of choice, such as Lucidchart (Lucidchart Software Inc.), Google Slides (Google LLC), Google Drawings (Google LLC), Microsoft PowerPoint (Microsoft Corporation) or Canva (Canva Pty Ltd.) for building the slice-of-the-system map, and webinar software (if presenting remotely to students). Students require a computer, flow chart creator and instructions for the activity.

NOTES FOR THE INSTRUCTOR

It should be noted that the specific activity presented in this publication is best suited after vesicular transport has been introduced in class. Additionally, all master proteins should be discussed at some level with students. From experience, it has been beneficial to provide chapter readings from the assigned textbook, lesson slides, and extra videos to aid in student understanding of the topic prior to introducing this mapping activity. Students cannot be expected to map any process without first being taught the different cellular compartments involved and how proteins are processed and move through the secretory pathway.

To promote peer collaboration, this activity is best practiced in a team/group setting of 3-4 students and can be accomplished in both the face-to-face and digital classroom environments. It is extremely simple to set up, with minimal preparation ahead of time. To save time and to aid in a smooth transition from the instructional component of the activity to teamwork, it is recommended that students be assigned to teams/groups prior to the first day in which the activity is introduced.

There is no one way to create a slice-of-the-system map. Some use the X-axis as a measure over time, while others use arrows to show directional flow of the process. We have also found that students respond favorably to the learning process if they are shown ahead of time that the process in creating a systems map is very organic, and that the map may change drastically as new variables are added. It is therefore highly recommended that when introducing this method of systems mapping to students, that a small topic be mapped as a class. Detailed instructions on how to introduce systems mapping with a fun topic on the pizza delivery process has been provided in Appendix A.

There are multiple ways in which students can complete question 1 of part 2. Many students will provide different colored sticky notes (or objects in the digital environment) that depicts where the major families of proteins enter and leave the system. For example, if a protein is required as a vesicle forms (e.g. dynamin), there may be a green sticky note (or circle) on the map at that step. Once the vesicle is completely formed and moves to its next step, a red sticky note (or hexagonal symbol) may depict that the protein is no longer required. Red and green arrows are also a popular symbol of choice for this part of the assignment.

Having completed the exercise in both modalities, we have found that when space or resources are limited, or if the classroom is not set up so that students can work at tables in small groups, the digital environment is more favorable. However, we have found that students enjoy the hands-on aspect to this activity, providing opportunities in the classroom to engage in peer discussions without the stress of having to use technology. It should be noted that the digital environment allows for students to keep a digital copy as a convenient size, versus having to carry around a large poster board or take a picture of the poster board map they have created. The poster board format is favorable for opportunities for teams to circle the room and provide feedback to other teams.

It is not recommended that students be required to use one specific digital tool or program as this may isolate student engagement for a variety of reasons. It is recommended that instructors be mindful of inclusive opportunities for students, including limiting the cost to participate. As with many digital tools and programs, free versions are available, but they often have limitations. In this publication, Lucidchart (Lucidchart Software Inc.) was used to create the example maps provided (Figures 1-3) but tools such as Google Slides (Google LLC), Google Drawings (Google LLC), Microsoft PowerPoint (Microsoft Corporation) or Canva (Canva Pty Ltd.) (to name a few) could be utilized. If you choose to use a digital tool such as Lucidchart, the free version limits students to a set number of items on a single chart. However, we have learned that if students share the chart with their teammates, each student in the shared chart has that same set number of items to add, which can be combined additively in the shared chart, therefore increasing the total limit.

Adopting new strategies for the classroom is often met with hesitation or, more realistically, the fear of failure. In our experience, we have found that approaching a new idea with honesty by informing students that the activity is new and therefore may not run as planned, and providing students with an opportunity to provide constructive feedback has allowed us to improve the activity over time. Additionally, for a complex activity such as systems mapping, using formative assessment with quality feedback has been recognized as an effective way to promote student motivation and learning (Bierer et al. 2008, Carrillo-de-la-Peña et al. 2009, Evans et al. 2014) with minimal to no impact to their grade. The process of creating the map and working with peers may be graded on a scale, but it is highly recommended that the final maps created by students are not assigned a grade or are only graded for completion. This practice reduces the student anxiety that may exist over a complex and often foreign concept (Cardozo et al. 2020, Wang 2023). We have provided the disclosure that we have used when introducing the activity for the first time, and a short list of questions that have been used to collect student feedback in Appendix B.

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About the Authors

Amanda Martyn is a Visiting Professor of Biology at Wake Forest University. With a Ph.D. in Molecular Biology from the University of Guelph (Guelph, ON, Canada) and post-doctoral fellowships at Western University (London, ON, Canada) and Duke University (Durham, NC, USA), Amanda has focused her research interests on using animal models to study the cellular stress response and molecular mechanisms of behavior, including post-partum depression, Alzheimer's disease and post-traumatic stress disorder. Amanda as dedicated almost two decades to teaching at the high school, undergraduate and graduate levels, bringing thoughtful pedagogical practices to the classroom and laboratory in order to stimulate student interest and excitement of topics in cellular and molecular biology, genetics, epidemiology, public health and forensic science.

Candice Chambers serves as Teacher Development Specialist at the North Carolina School of Science and Mathematics, providing professional development and instructional support for teachers. She has taught a variety of courses focusing on applications in forensics and health sciences. In addition to teaching, Candice has engaged in curriculum development, piloted new instructional technologies in the classroom, supported school-wide professional growth initiatives, and scaffolded new advising opportunities for students in distance education. She has also participated as a fellow with the 2017 Grand Challenges cohort for 100Kin10, the Education Policy Fellowship Program with the NC Public School Forum, and with NCSLA as a Science Leadership Fellow. Candice holds an MA in Anthropology from North Carolina State University, a BS in Anthropology from the University of Tennessee at Chattanooga, and a Certificate in Core Public Health Concepts from the University of North Carolina at Chapel Hill.

Dan Johnson has been a Teaching Professor of Biology at Wake Forest University since 1998. He teaches in the first-year sequence for majors, cell and molecular biology, disease biology, and cancer biology. From 1998 to 2021 he coordinated the undergraduate biology laboratory program. Currently his research focuses on using computational linguistics and data science methods to track students' development as scientific writers in large-enrollment courses.

APPENDIX A

Detailed Instructions on How to Introduce Systems Mapping in the Classroom

Start by explaining the goal of the activity, which is to map the process of vesicular transport (or the system of your choice). Introduce the format of slice-of-the-system mapping and explain each of the components (colored boxes, Figure 1) and layout to students.

Explain to students that a slice-of-the system map is like a swimming pool with swim lanes. Each of the actors have their own swim lanes and are lined up in a column on the left-hand side.

- The Process (orange box/sticky note) - This is basically the title of the process that will be mapped. There should only be one on a single slice-of-the-system map).
- Steps in the Process (yellow boxes/sticky notes) - Each step should be aligned in the swim lane of the actor that performs that step.
- Desired Outcome (blue box/sticky note) - The outcome is always a best-case scenario. This is important to note, because the goal of this activity is not only to map the process, but then to identify key players in the process that when not functioning normally, could result in a break in the system.
- Key Players/Sticking Points (pink shaped flags/sticky notes) - Anywhere on the map can be flagged as a key player or sticking point. These should be labeled clearly with the key player action or an issue that could arise if the step in the system fails.

Go over a fun and relatable example with students, creating a map together so that students can see how the map is built in real time. We have used the Pizza Delivery Process (Figure 3).

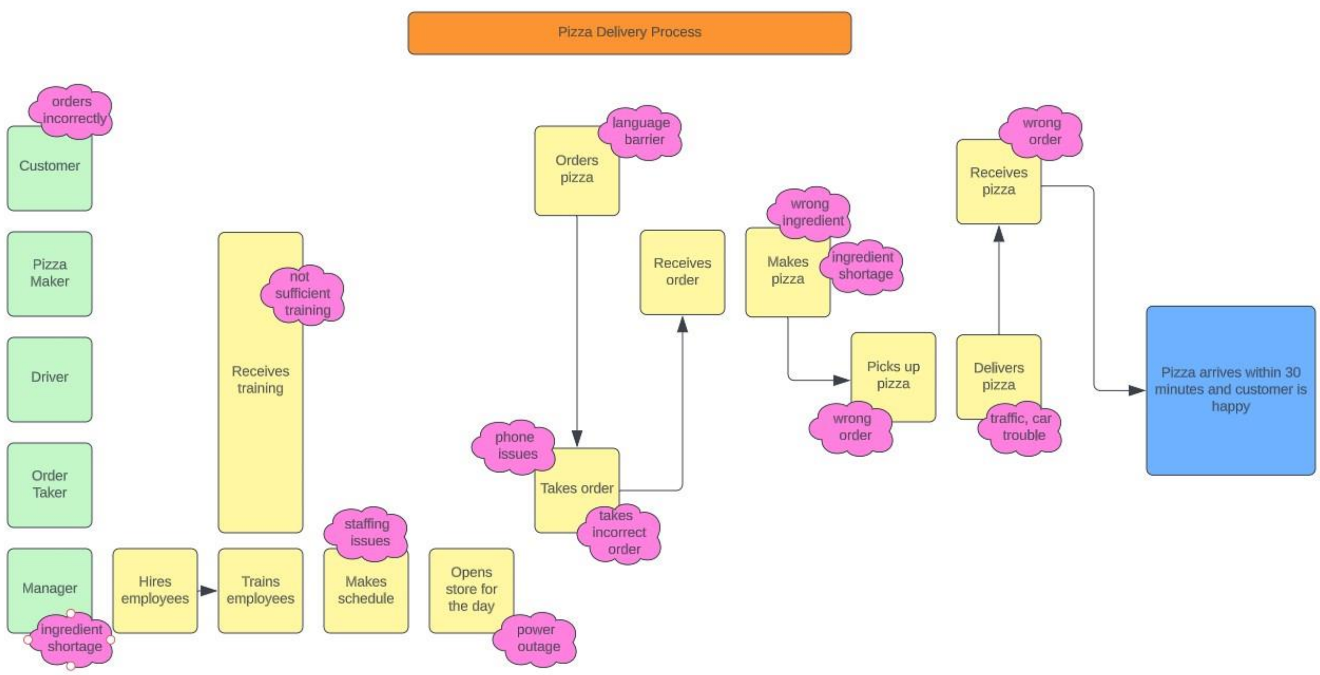

Figure 3: Slice-of-the-system map of the pizza delivery process. This map is an example of an entertaining and relatable topic that was completed together in class to demonstrate to students the format and thought process of systems mapping.

You may wish to give students a starting template to keep them on track. For example, if you want students to start post-translational, then to prevent students from starting with gene transcription, or even further back in the process (i.e. DNA replication) give them the pre-translational part of the map as an example or starting point (Figure 2).

This activity will take 2-3 class periods to complete. On the first day, introduce the concept of slice-of-the-system mapping, go through an example together (like Figure 3), then break students into teams and have them create their shared document, using your starting template (Figure 2, for example), or hand out the crafting items to have students create hard copies of their map. On day 2, students should complete their own map in their assigned teams. Encourage students to use outside resources to aid in their mapping process, specifically for Part 2. An optional task, which could be performed on day 3 or in the digital environment, have students circle around the classroom and, using additional sticky notes (perhaps in a different color that hasn’t been used), provide feedback to teams on their maps before final submission.

APPENDIX B

Disclosure to Students

You may wish to provide your students with a disclosure about this being the first time the activity is being attempted. Here we provide a short statement that we have used previously.

"Slice-of-the-system mapping has been implemented in a few courses I have taught previously, but I've never actually implemented this approach before in this specific manner. While I hope this will be a fun and informative exercise, with anything new, there may be hurdles to overcome. Together we have the power to make this a useful activity in breaking down the silos and putting weekly material together. I ask that you communicate with me if you feel it is not working for you or your team. I will take your feedback into consideration upon grading. Also, since this is the first time in this endeavor, this case study will be graded on effort only, not on how correct it is. I will also provide you with an answer key and with my version of the slice-of-the-system map. Let's see what we can do!"

Student Feedback

Please take a moment to answer the following questions with constructive feedback.

1. What did you like about this case study and why? What did you not like? Why not?

2. What could be done IN CLASS to improve this case study?

3. What could be included in the written case study instructions to improve this case study?

4. Did this case study help you and your team in understanding the process of protein trafficking as a whole? Please provide details where it did (if it did) and where it did not (if it did not).

5. Would you recommend this case study be used in the future? Why or why not?