# Development of a Medical Animation on Acetaminophen Metabolism and Hepatotoxicity

Research Project Proposal

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This research project will be submitted in partial fulfillment of the requirement for the
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## Abstract

This project will plan and create an animation on acetaminophen (APAP) metabolization with the intent of demonstrating its relationship to chemical-driven liver damage (hepatotoxicity). APAP is a common ingredient in many prescription and over-the-counter (OTC) medications. Recently the Food and Drug Administration (FDA) recommended that the maximum daily dose of APAP be lowered due to the potential to cause liver damage (Food & Drug Administration, 2009). The goal of this project is to visually inspire interest in APAP metabolism while warning the viewer of the potential consequences to the liver of APAP misuse. Healthcare professionals could benefit from being more aware of how the medication works. Since the project focuses mainly on the creation of an animation, only informal testing will be done. The success of the project will be measured by completion of an animation that would instill viewer curiosity while serving as a visual reinforcement of the recommended APAP dosage amounts. The information conveyed to healthcare professionals through this animation may help prevent serious APAP overdose.

## Overview

The topic of this project and proposed animation is acetaminophen (APAP). As an active ingredient of many over-the-counter and prescription medications, APAP is widely used and considered safe by most health care providers. The medicinal functions of APAP are to relieve pain and reduce fever (Tylenol, 1999). Both of these functions are complex and are not entirely understood. Even how the medication is metabolized remains uncertain. This project will not focus on these functional properties but instead concentrate on APAP metabolization and subsequent consequences to the body if too much is taken. In 2009 a panel of the FDA recommended reducing how much APAP should be taken and gave usage warnings intended to protect the public. Since very serous side effects can occur if the recommended dose is exceeded, awareness of what happens when APAP is metabolized should be brought to the attention of medical professionals (Larson et al., 2005). This animation will visually introduce APAP metabolization, illustrating how overuse may lead to related liver failure. An animation such as this could be used to educate and alert pharmacists, pharmacy technicians and other health care professionals on the potential dangers of APAP overuse. Understanding the science of APAP may help protect those who can benefit from its functional properties.

There are various categories of medical animation such as gross anatomical, cellular and molecular. Molecular animations can show a mechanism of disease (MOD) or a mechanism of action (MOA). MODs demonstrate a pathophysiology while MOAs show how certain treatments can be used. MOA animations can be a powerful way to communicate complicated subjects to those in the

pharmaceutical industry (Kermani, 2009). This project will create a combination MOA/MOD animation intended as a purely educational piece for an audience of health care professionals.

Extending the use of animation technology will depend on the general acceptance of animations as teaching tools. A consequence of the resultant increase in adoption will be increasing animation development. McGill (2008) provided examples of other researchers who are combining scientific information and the latest in animation technology to create medical animations. There have been many studies on how medical animations teaching cellular and molecular topics are being used as learning tools. One such study by McClean et al. (2005) examined students learning DNA and RNA topics. They found that students who had viewed molecular animations retained more knowledge than those who only had access to traditional methods of learning. The majority of subjects also stated that they preferred learning with the animation.

Expanding the use of medical animations may lead to further improvements in technologies specifically designed for their creation. An example of a new technology is the recently released plug-in for molecular visualization called mMaya (http://www.molecularmovies.com/toolkit/index.html). The mMaya plug-in provides the ability to directly import molecular structures into the Maya® 3D program. Further improvements of how animations can be created depend on development and usage of these new tools. It is the intent of this project to make use of mMaya to accurately show how molecules of APAP interact with various enzymes and cellular receptors.

## Literature Review

This literature review will provide a brief scientific overview of acetaminophen (APAP) metabolism and hepatotoxicity. Tylenol® product information and research study findings will be examined and used for content development of the animation. How and why to educate healthcare professionals on overdose prevention will depend on the needs of this audience. For them to understand the problems associated with APAP, planning is needed of what information should be presented to them.

APAP approved usages are antipyretic (fever reducer) and analgesic (pain reliever) (Tylenol®, 1999). The analgesic mechanism of action (MOA) of APAP is unlike anti-inflammatory drugs used for similar conditions such as ibuprofen and aspirin. Anti-inflammatories prevent formation of prostaglandins that lead to inflammation (Graham & Scott, 2005). The MOA of APAP is unique. The main analgesic function of APAP is not anti-inflammatory but instead APAP decreases pain signal transmission (Aronoff, Oates and Boutaud, 2006). APAP is different because it is a weak inhibitor of prostaglandin synthesis (Botting, 2000). Tylenol® Professional Product Information (1999) describes the accepted MOA for APAP analgesia as inhibition of the nitric oxide and neurotransmitters receptor pathways. Interruption of these pathways in nerve cells can elevate the pain threshold. In order for this interruption to occur, APAP must first be metabolized.

APAP metabolization produces metabolites. Although some of these metabolites are part of an effective way to relieve pain, others effects can be non-beneficial (Graham & Scott, 2005). One reactive metabolite produced is N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is dangerous to cells and needs to be broken down further in order to be disposed of by the liver (Tan, New, & Chan, 2008). This liver disposal system is in place as a way for the body to regulate not only what it consumes but also how it removes waste products. Further metabolism of NAPQI can cause problems since the reactive metabolite can trigger a series of cellular events that can ultimately lead to toxic liver damage (Srivastava et al., 2010).

A negative effect to liver cells caused by chemical agents is called hepatotoxicity (Srivastava et al., 2010). NAPQI can be a hepatotoxic agent. Hepatotoxic conditions due to increased NAPQI put liver cells under stress and higher potential for damage. The damaging events of APAP overdose include the reduction of a liver cell's ability to make ATP energy (Hinson, Roberts, and James, 2010). As a result, liver cells can be damaged by necrosis due to the lack of ATP that is needed to drive normal cellular functions.

APAP is widely studied as a drug that if taken in large enough quantities predictably results in liver damage (Gunawan & Kaplowitz, 2007; Larson, 2007). Most cases of acute liver failure, due to drug-induced liver disease, are caused by APAP hepatotoxicity. Research implies that potential APAP hepatotoxicity is normally prevented by the liver cell's ability to warn other cells of the danger by

activation of certain genes within the cells (Coople et al., 2008). Expression of these genes results in cellular defense against the reactive APAP metabolites. Martin-Murphy, Hold and Ju (2009) suggest that these warning signals are measurable indicators of how APAP is affecting the body and may give a potential target for overdose treatment.

How much APAP is too much? The current FDA recommended maximum dose of APAP is 4 grams per day (Tylenol, 1999). Depending on the health status of the individual, dosage in excess of this maximum may be difficult for the body to safely metabolize. A panel of the FDA recently recommended that APAP maximum dosages be lowered and those medications that combine APAP and other active ingredients, such narcotics or cold medication should be limited or removed from the market (Food & Drug Administration, 2009). These recommendations are currently pending approval. Compromises are being determined so that overdoses can be prevented and those who need APAP can still have access to it.

A study by Stumpf et al. (2007) identified some startling statistics regarding usage. Patients do not always know all the facts about their medication or how much active ingredient it contains. Only 2% of the patients surveyed could identify how much APAP is a maximum dose while only 15% were able to tell which prescription medications also contained acetaminophen as a secondary active ingredient. The majority of patients were unaware that their liver may be damaged if they took too much. Based on those results, patients seem to be at great risk of unintentionally overusing APAP simply due to lack of knowledge about what they are taking. Studies such as this support the FDA panel recommendations to lower APAP dosage (Food & Drug Administration, 2009). Is there really a need to lower the dosage amounts or could further education be needed?

There is an amount of APAP that will cause ill effects. An extensive medical literature search by Dart and Bailey (2007) determined that the current recommended maximum amount does not cause hepatic failure and death. In their estimation, most patients have trouble identifying how much APAP they have taken, thus they may mistakenly consume more than the recommended dose. As a result, patients ended up with liver damage. The current FDA usage guidelines may be sufficient if there is greater understanding of how much APAP should be used in each situation.

The risk of APAP overdose can be minimized but when too much has already been taken, what should be done? Larson (2007) describes 3 factors that may minimize the development of tragic results. These factors are: quick identification of the APAP overdose situation; appropriate response of healthcare providers to the patient's urgent condition; and prompt treatment to halt the spread of damage before it becomes irreversible. Treatment for APAP overdose involves the administration of N-acetylcysteine immediately after overdose (Tylenol®, 1999). Therefore, it is important to know when and how much APAP the patient has taken. Instilling a sense of urgency in healthcare providers to respond with overdose treatment is critical.

Healthcare providers could certainly benefit from learning more about how APAP works but what exactly is important for them to know? Gunawan and Kaplowitz (2007) asserts that "The understanding of the mechanism of drug-induced liver injury is of great importance and may lead to prevention and better treatments". This statement highlights the potential benefits of increasing understanding of APAP. The same conclusion was made by Martin-Murphy, Holt, and Ju (2009) as "Elucidation of the underlying mechanism(s) is necessary for identifying predisposing factors and developing strategies in the treatment and prevention of (drug-induced liver injury) DILI". In addition, healthcare providers could benefit from further instruction on APAP usage. Larson et al. (2005) confirmed that "Education of patients, physicians, and pharmacies to limit high-risk use settings is recommended". All this research clearly points to increasing awareness in many areas so as to prevent APAP overdose. New learning tools, such as this medical animation and its resultant visual impact, would help this process.

## Project Methods

The project involves the planning and creation of a medical animation on the metabolization of acetaminophen with the associated risk of hepatotoxic liver damage. This methods section describes the anticipated steps of the project, which will follow a professional medical animation workflow. All steps of project development will be documented including background research, software usage, and potential pitfalls encountered. A science reference deck will be attached as an appendix to the final paper. This deck will contain more specific details and the exact sequence of action for the animation. The project methods will be adjusted as work progresses. The major project steps are pre-production, design, production and post-production.

## Project Pre-Production

Pre-Production lays the groundwork for subsequent aspects of the project. Because the project will emphasize scientifically accurate content, these steps are significantly important. The science reference deck will be created to organize details such as character sizes, amounts and image references.

### Content Development

The scope of how much content to cover must be decided upon early in the project. Without adequate planning, the project could quickly become too expansive. Identifying the level of detail to be shown will help form the story. Content discussed in the literature review will be distilled into what can be presented in a few minutes of animation.

Cells and molecules involved in the story will be the characters of the animation. Structural references of these molecules will be gathered from 3D data on the Protein Data Bank (PDB) (http://www.rcsb.org) and PubChem (http://pubchem.ncbi.nlm.nih.gov/). The accuracy of the characters

may be marginally adjusted in order to tell a coherent and relevant story. The relative size and speed of character movement and the density of the cellular and molecular environments are examples of alterations required for increased clarity. The molecular structures of APAP, reactive metabolites, chemical messengers, certain enzymes, and cell receptors will be referenced as molecular characters. The hepatocytes and lymphocytes are to be cellular characters. Other tissues or systems to be included as environments are the blood vessels, bile ducts, liver, and the interior of the intestines where absorption occurs.

### Script Development

Before writing the script, a bullet point outline will be developed. This outline will contain the names of the characters and a basic layout of the story flow. The script, consisting of 2 written columns, will cover more details of the animation. One column of the script will be a description of the actions for each portion or scene of the animation, the other column will contain the accompanying narration or voice over (VO). At about a 100 words per minute, the VO will help with animation timing and will verbally reinforce important content points that will be demonstrated. The script will annotate where the content information came from. The VO will be recorded as a working audio file.

### Storyboard Development

Storyboards, a basic visualization of the story, will provide timing and give a visual approximation of the anticipated flow of the animation. For this project, they will be loosely sketched out and scanned for modification in the computer. They will be created only in black and white or grayscale. The number of individual storyboard images will be determined as the script is developed. Animated storyboards or 2D animatic will combine the static storyboards images with the VO audio. Viewing of the 2D animatic may indicate content or story flow problems to be addressed with script rewrites and/or storyboard image revisions. Changes will be easier to make at this stage than after more time has been invested.

## Project Design

The design steps of the project will include visual aspects of the animation. These steps will bring the project into 3D by preparing models for animation.

### Concept Art

Concept art will consist of mood boards and style comps creating a look and color palette for the scenes of the animation. Mood boards will be of various images and photos inspiring a color palette and environmental feelings of the scenes. Written descriptions will be made of how the mood board elements apply to the scenes and characters. Style comps will be pieces of art created specifically for the animation and will illustrate some of the environments where characters interact to establish a look and feel. These style comps will be done in color for each major scene of the animation.

### 3D Modeling

Characters, illustrated in storyboards and style comps, will be developed further into 3D models. Some molecules will be directly imported from the PDB (http://www.rcsb.org) into the 3D program whereas cells, tissue, and other environmental elements will need to be created from scratch. Various modeling techniques will be used.

### Texture Development

The 3D elements will need to be textured to resemble the concept art. Texture development will involve trial and error of creating and correctly placing the textures, called shaders, on the models. Preliminary testing will be made of how the 3D lights will be applied to the characters and scenes.

## Project Production

The production stage will turn visual elements into a 3D animation. A spreadsheet shot list will be created to track individual elements to be added to each scene.

### 3D Animatic

The 3D animatic will develop the movement of character models and scene elements. The 2D animatic will be used as a reference for timing. A shot list will be written as a spreadsheet breaking the entire animation into camera shots along with the VO and a description of what will be animated. Temporary low-resolution 3D models may be used to save on computer processing and rendering time. The scenes will be blocked out using cameras in the 3D program. The scenes will be rendered as playblast animations that will have no colors or textures applied. These playblast animations will be composited into a movie for review.

### Animation

Animation development will gradually create a more final animation. Movements of characters, cameras and scene elements will be refined. The 3D scenes will be colored, shaded and lit with 3D lighting. The concept art will be used as a guide. Render tests will be done to insure scenes are rendering properly and look as expected. As these tests are made, they will be added to the composited animatic file in order to view the animation as a rough cut. Scenes will be prepared for final rendering.

## Project Post-Production

Post-production includes the finals steps of the project. The final animation will be converted into various file formats playable on different computer systems.

### Rendering

Each frame of the animation will be rendered as a separate image in order to prevent loss of work if the entire sequence does not render correctly. Rendering will also be done in layers to simplify compositing. Examples of layers are a separate background or highlights for certain post effects. Rendering of each

shot is expected to take many hours so render time will be planned for night and other times when the computer is not otherwise in use. Additional machines may be used to decrease render time.

### Compositing

Compositing the animation will bring the various rendered 3D image files and layers together into the final video. During compositing, simple motion graphics and labels will be added. Other post-effects such as glows to indicate activation of molecules may be added.

### Sound Editing

VO audio files will be combined with the final animation. Basic music and sound effects will be applied if time allows. The final animation files will then be rendered out of the post-effects program.

## Summary of Steps

| PRE-PRODUCTION | DESIGN | PRODUCTION | POST-PRODUCTION |
|---|---|---|---|
| Content Development | Mood Boards | Shot List | Render Full Resolution |
| Science Ref. Deck | Model Sketches | 3D Scene Set Up | Motion Graphics |
| Script (VO and action) | Concept Art | 3D Animatic | Post Visual Effects |
| Storyboards | 3D Modeling | 3D Character Animation | Music & Sound Effects |
| Voiceover Recording | Textures | 3D Camera Animation | Finalize Animation |
| Animated Storyboards | | Rough Cuts | |
| | | Lighting | |
| | | 3D Effects | |

## Discussion

The project will create a stand-alone animation that presents concepts of acetaminophen metabolism related liver damage. Background research will support the level of detail appropriate for the intended audience of healthcare professionals. The goal is to create a complete, useful animated video on the APAP metabolic production of byproducts. If too much of the medication is consumed, a build up of potentially hazardous metabolite byproducts could lead to liver damage (Gunawan & Kaplowitz, 2007). There is a fine balance between the medicinal amount of APAP and an unintentional overdose situation. Bringing attention of the viewer to the science involved in APAP metabolism may lead to an understanding of how an overdose could potentially damage the liver.

The steps used to plan and create the animation will be adapted from the workflow of similar projects of professional medical media companies. Individual roles normally completed by a team of people at an agency will be consolidated so that one person can complete the project. The final animation will provide a complete story that may not be quite as polished as a true professional workflow. There

will be further discussion and explanation into how workflow could be improved with more resources. Due to the limited scope of the project, some steps will not be fully completed. For example, the VO script will not be professionally recorded, and the final renders will not nearly be as elaborate or as large in frame size. Even with these simplifications, the animation should be potentially useful to the viewer.

The main focus of this project will be to do research to identify the key elements involved and present them in a scientifically accurate manner. Background information and current data along with concerns brought up with the recent FDA recommendations will be addressed. Even in a full-length movie it would not be possible to show every detail of the story, therefore this project will also determine which elements should be shown in the animation. The animation is expected to provide the viewer important information on the consequences of metabolic breakdown of APAP.

## Conclusion

This project will be an exploration of what is involved in creating a medical animation project. Part of this project involves learning the Maya® software. Potential pitfalls are likely. The limited amount of time available to complete the project will be the greatest issue. Also since only one person will be performing all steps, there may be some areas that are too difficult thus requiring simplification. Even with those problems areas, it is anticipated that the project can be completed. Conclusions about what would make the process easier (e.g. more time and more people) will be gathered from the results.

## Project Management

### Hardware & Software Resources

The specific hardware and software used for the final animation will be fully documented as the project progresses. The following is a short summary of what is anticipated for use. A MacBook Pro computer (Apple Inc., Cupertino, CA) will be used for the majority of the work. Various 2D artwork elements, such as storyboards and concept art, will be hand drawn, digitally scanned then modified in Adobe® Photoshop® (Adobe Systems, San Jose, CA). The voice over script will be digitally recorded with an external microphone and Garage Band (Apple Inc., Cupertino, CA). Animated storyboards involve compositing the storyboards images in iPhoto and/or iMovie (Apple Inc., Cupertino, CA). The primary 3D software will be Maya® (Autodesk® Inc., San Rafael, CA). Maya® will be used for all the 3D aspects of the project including modeling, animatic, animation and certain effects. Molecular structures will be imported into Maya with the mMaya plug-in (http://www.molecularmovies.com/toolkit/index.html). Adobe® After Effects® (Adobe Systems, San Jose, CA) will be used to composite the individual files into the final animation. Certain post-effects and visual treatments will also use Adobe® After Effects®.

### Technical and Creative Assistance

Support in creating this project has been offered by individuals at Eveo inc. (www.eveo.com San Francisco, CA). People offering assistance include; storyboard, 3D and motion graphic artists, medical writers, producers, creative and art directors. They will provide technical, creative, and project management advice but the primary project investigator will do all actual project work.

## Timeline

| | |
|---|---|
| Summer 2009 | **DONE**- Project topic chosen |
| | **DONE**- Preliminary research began |
| Fall 2009 | **DONE**- Project committee members selected |
| | **DONE**- Project timeline revised |
| Jan 2010 | **DONE**- Draft project proposal |
| | **DONE**- Spring 2010 class registration **DONE**- Department waiver approval |
| | **DONE**- Name added to pending graduation list, spring 2010 |
| February | Approval of proposal by project committee |
| | **DONE**- Scott D. to review and comment first |
| | **DONE**- Suggested improvements made |
| March | **DONE**- Submission to committee |
| | Develop Animation Script |
| | Draw Storyboards |
| | Work on Concept Art |
| | Record VO script |
| | Animated Storyboards -Composite recorded VO script with storyboards |
| | Plan models |
| | -Determine which models could be PDB or PubChem or must be created |
| April- June | Animatic Animation in Maya® |
| | -Maya® animation of animatic |
| | -After Effects® compositing of animatic |
| | Animation in Maya |
| | -Shaders developed |
| | -Scenes set up in Maya® |
| | -Character and element motions animated |
| | Finalize animation |
| | -Render scenes |
| | -Composite animation |
| May- Summer | Finalize research paper |
| | - Change language of proposal to be in past tense |
| | - Rewrite sections with results as needed |
| | Preparation project for presentation |
| | - Submit and have approval of required department forms |
| | - Create PowerPoint presentation |
| | - Arrange defense date before deadline |
| | - Book travel to Chicago after date is finalized |
| | Defense of project in Chicago with all committee members present |
| | Submit written project research paper |
| Aug 10th | Deadline for completion of degree requirements for Summer 2010 |
| | CELEBRATE! |

## Appendix

The science reference deck will be attached as an appendix to the final paper. This science reference deck will be created during content development and will contain the additional science information used during animation development.

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