

Development of a Medical Animation on
Acetaminophen Metabolism and Hepatotoxicity

BY

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PROJECT RESEARCH

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Abstract

Although acetaminophen (APAP) is a common ingredient in many prescription and over-the-counter medications, an overdose of APAP has the potential to cause chemical-driven liver damage (hepatotoxicity). A visual representation of APAP metabolization and its relationship to hepatotoxicity could be useful in the education of healthcare providers. This project planned and created a medical animation using an adapted professional medical animation workflow. The animation was designed to inspire healthcare providers to learn about the APAP metabolic pathway while providing them a warning of what happens during an overdose. By visually conveying this information to the viewer, this animation serves as a visual reinforcement of the recommended APAP dosage amounts and the need to prevent serious APAP overdose.

I. Introduction

a. Overview

Acetaminophen, or APAP, is the active ingredient in widely used over-the-counter and prescription medications. Many healthcare providers consider APAP a safe and effective way to relieve pain and reduce fever (Tylenol[®], 1999). Both of these functions are complex and are not entirely understood. Even what happens when APAP is metabolized remains uncertain. In 2009, a Food & Drug Administration (FDA) panel recommended a reduction in how much APAP should be consumed and provided new usage guidelines and warnings intended to protect the public from overdose situations. There is a fine balance between the maximum recommended dose of APAP and an unintentional overdose amount. Very serious side effects can occur if the recommended dose is exceeded. If too much APAP is consumed, the build up of potentially hazardous metabolite byproducts can lead to liver damage (Gunawan & Kaplowitz, 2007). During this project, further research was done in order to find a way to visually demonstrate these dangers of APAP overdose to an audience of healthcare providers.

Medical animations on anatomical, cellular and molecular topics have been created by other researchers and professional companies. Molecular animations often show a mechanism of disease (MOD) or a mechanism of action (MOA). A MOD demonstrates a pathophysiology while a MOA could show certain treatments of the problem. MOA animations can be a powerful way to communicate complicated subjects to those in the pharmaceutical industry (Kermani, 2009). Professional animation workflows for creating medical animations have been established by various companies and agencies. The professional workflow has many steps, such as pre-production, design, production, and post-production, which are completed by a team of people with specific roles.

b. Purpose

How can the APAP metabolic pathway and its potential for hepatotoxicity be visually explained to an audience of healthcare providers? In order to visualize the hepatotoxic effects of an APAP overdose, could a short medical animation be created that represents the APAP metabolic process? To develop such an animation, can the production roles and steps from a professional medical animation workflow be consolidated and done by one researcher rather than a team of people? These research questions of why and how to create a medical animation on APAP metabolism and hepatotoxicity were addressed by research conducted during the course of the project.

II. Literature Review

This literature review provides a brief science overview of acetaminophen (APAP) metabolism and hepatotoxicity. The methods used to educate healthcare providers on overdose prevention depend on the needs of this audience. For the viewer to understand the problems associated with APAP overdose, planning was done on what kind of information would be most beneficial for them to know. The findings of this research were used later during the animation content development steps.

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

Metabolites of APAP are produced during metabolization. Although some of these metabolites are part of an effective way to relieve pain, others have effects that can be non-beneficial (Graham & Scott, 2005). N-acetyl-p-benzoquinone imine (NAPQI) is a reactive metabolite produced during metabolization. NAPQI is dangerous to cells and needs to be broken down further into inert metabolites that can 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. 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).

Hepatotoxicity is a negative effect to liver cells caused by chemical agents (Srivastava et al., 2010). Excess NAPQI is a hepatotoxic agent. Hepatotoxic conditions due to increased NAPQI can put stress on liver cells and increase the potential for damage. Harmful events due to APAP overdose include the reduction of a liver cell's ability to make ATP energy (Hinson, Roberts, and James, 2010). ATP is needed to drive normal cellular functions, and hepatocyte necrosis can result from a disruption of the ATP energy source.

APAP is widely studied as a drug that if taken in large enough quantities predictably results in liver damage (Gunawan & Kaplowitz, 2007; Larson, 2007). APAP hepatotoxicity causes most cases of acute liver failure, due to drug-induced liver disease. Research implies that potential APAP hepatotoxicity is normally prevented by the hepatocyte's natural 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 has recommended that APAP maximum dosages be lowered and those medications that combine APAP and other active ingredients, such as narcotics or cold medications 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.

Some startling statistics regarding APAP usage were identified in a study by Stumpf et al. (2007). Patients do not always know all the facts about their medication or the amount of active ingredient it contains. Only 2% of the patients surveyed could identify how much APAP is a maximum dose while 15% were able to tell which prescription medications also contained acetaminophen as a secondary active ingredient. The majority of patients were unaware that liver damage may occur if they exceeded the recommended maximum dose. 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). Further education of those patients and their medical providers may help prevent APAP misuse.

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 typically cause hepatic damage and failure. 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 can end up with liver damage. The current FDA usage guidelines may be sufficient if there is greater understanding of how APAP should be used in each situation.

The risk of APAP overdose can be reduced but when too much has already been taken, what can 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 the overdose (Tylenol[®], 1999). Therefore, it is important to know when and how much APAP has been taken. Instilling a sense of urgency in healthcare providers to respond quickly 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) assert "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". These statements clearly support increasing awareness in many areas so as to prevent APAP overdose.

New learning tools, such as medical animation, could be used for education. McGill (2008) provided examples of researchers who are combining scientific information with the latest in animation techniques to create medical animations. Many studies have looked at how medical animations are being used as learning tools for cellular and molecular topics. One such study by McClean et al. (2005) examined students who were learning about DNA and RNA. The students who had viewed molecular animations were found to retain more knowledge than those who had access only to traditional methods of learning. The majority of subjects also stated that they preferred learning with the provided animation. Extending the use of medical animation depends on the general acceptance of animations as teaching tools. An increase in the use of medical animations also increases the development of technologies for medical animation production.

III. Project Methods

The project involved the planning and creation of a medical animation on the metabolization of APAP and the associated risk of hepatotoxic damage. The methods used followed a professional medical animation workflow and were adjusted as project work progressed and better options were found. The intermediate steps of project development have been documented including background research, software usage and visual examples from the final animation. This methods section is not necessarily a step-by-step tutorial on medical animation creation but rather a guide to what was done during the project. There are many ways to carry out each step depending on the needs of the project and the resources available. The major project steps were pre-production, design, production and post-production. A breakdown of these steps is summarized below in Table 1.

Table 1: Summary of Steps

PRE-PRODUCTION	DESIGN	PRODUCTION	POST-PRODUCTION
Content Development	Mood Boards	Shot List	Animation Full Render
Science Reference Deck	Model Book	3D Scene Set-Up	Compositing
Script (VO and Action)	Concept Art	3D Animatic	Motion Graphic Labels
Storyboards	3D Modeling	3D Character Animation	Visual Post Effects
Animated Storyboards	Textures and Lighting	3D Camera Animation	VO Recording
		3D Effects	Music
		Rough Cuts	Final Composite Rendering

a. Project Pre-Production

Pre-production laid the groundwork for subsequent aspects of the project. Because the project emphasized scientifically accurate content, these steps were significantly important and accounted for much of the project timeline. Content development, script development, and storyboarding were the steps done during pre-production.

i. Content Development

The scope of how much content was to be covered by the animation was decided upon early in the project. Without adequate planning, the project could have quickly become too expansive to show in a short animation format. Identifying the level of detail and amount of content to be covered helped form a story. Content discussed in the literature review was distilled into what could be presented in a few minutes. The most valuable source of content information came directly from

the Tylenol[®] PPI. What is known about the APAP MOA and metabolism was summarized in the PPI. The names and percentage amounts of the APAP metabolites were also listed there. As story details were found, they were added to a science reference deck, Appendix A. The science reference deck consolidated information that was to be incorporated into model design and animation action. This deck organized facts such as size, alternate names and word pronunciation of story elements.

Molecules and the proteins involved in the story were the main characters for the animation. Character references were gathered from the Protein Data Bank (PDB) (<http://www.rcsb.org>) and PubChem (<http://pubchem.ncbi.nlm.nih.gov/>). A reference number from these sources identified each structure and these numbers were added to the science reference deck. 3D structures of the enzymes cytochrome P450 and glutathione transferase were located on the PDB. Multiple versions of these proteins were available on the PDB but many were of different sub-types and not relevant to the APAP story. The 3D PDB files were downloaded as a .pdb file type. APAP, NAPQI, GSH, NAC, and the 5 metabolites of APAP were located on PubChem. The 3D PubChem structures were downloaded as .sdf files. These 3D structure files were saved for later use in the development of 3D models.

The hepatocyte was identified as the main cellular character. In the liver, hepatocytes are grouped in lobules. The liver lobule was therefore added to the list of models to be created. The liver and stomach as organs were important as story elements and to provide an environment. A representation of a bottle of Tylenol[®] and tablets of APAP were also to be characters of the story. Image research found examples of how these characters have been represented by other researchers. The source or location of reference images was noted for future reference.

ii. Script Development

Before beginning the script, a bullet point outline was developed. This outline contained the names of all characters and a basic layout of the story flow. The outline was then expanded into a full script, Appendix B. The script consisted of columns with various details of the animation. One column contained animation notes that were a written description of the actions or movements in that portion of the animation. Another column contained the accompanying narration called the voice over (VO). At about 100 words per minute, the VO was used to help with timing and provided an estimated total animation length. The final script was 260 words in length, indicating that the animation would be approximately 2.5-minutes long. This length was determined to be appropriate for the project's goal yet still contained enough content to create an interesting

animation. The VO verbally reinforced important content points to be demonstrated with animation. An additional column of the script listed onscreen text to be shown during each story section. The VO was eventually recorded as an audio file that was incorporated into the final animation. Details of this process are provided in the sound editing section.

iii. Storyboarding

Storyboards are a basic visualization of the story and helped with animation pacing. They also gave an approximation of the anticipated visual flow of the animation. Very rough thumbnail sketches were done in conjunction with script development so that the visuals were kept in line with the story. After the script was “locked”, final storyboard images were drawn in pencil and scanned for modification in the computer. Storyboard images were created in a widescreen format to match the desired aspect ratio for the animation. An individual storyboard image was created for approximately every sentence of the script. Arrows were added to some images to indicate the direction of motion for the characters. Labels of on-screen text were added to the images. The storyboard images were added into a deck with the script and were often referred to as project production progressed.

Animated storyboards combined the static storyboard images with the recorded VO audio. Apple iMovie was chosen for this purpose due to ease of adding or updating elements. Image and audio files were imported into iMovie and dragged to the timeline where they could be rearranged. The waveform of the VO audio file was made visible in the timeline so that the image display length could be adjusted to match the VO timing. A screenshot of the animated storyboard process is shown in Figure 1. A movie file of the animated storyboards was saved. Viewing the movie indicated content and story flow problems such as potentially confusing transitions between scenes or environments. An area in particular that required revision was an abrupt scene change to a molecular level of magnification. Initially, the scene with the tablets was followed directly with a scene showing molecules of APAP inside a cell. The script was rewritten to explain how a tablet enters the stomach and is absorbed into the blood, which would then bring APAP to the hepatocytes in the liver. The storyboard images for this new sequence of events were drawn to include intermediate views of the stomach, gastrointestinal cells, and the liver lobule. These changes were easier to incorporate at this stage than after production had begun.

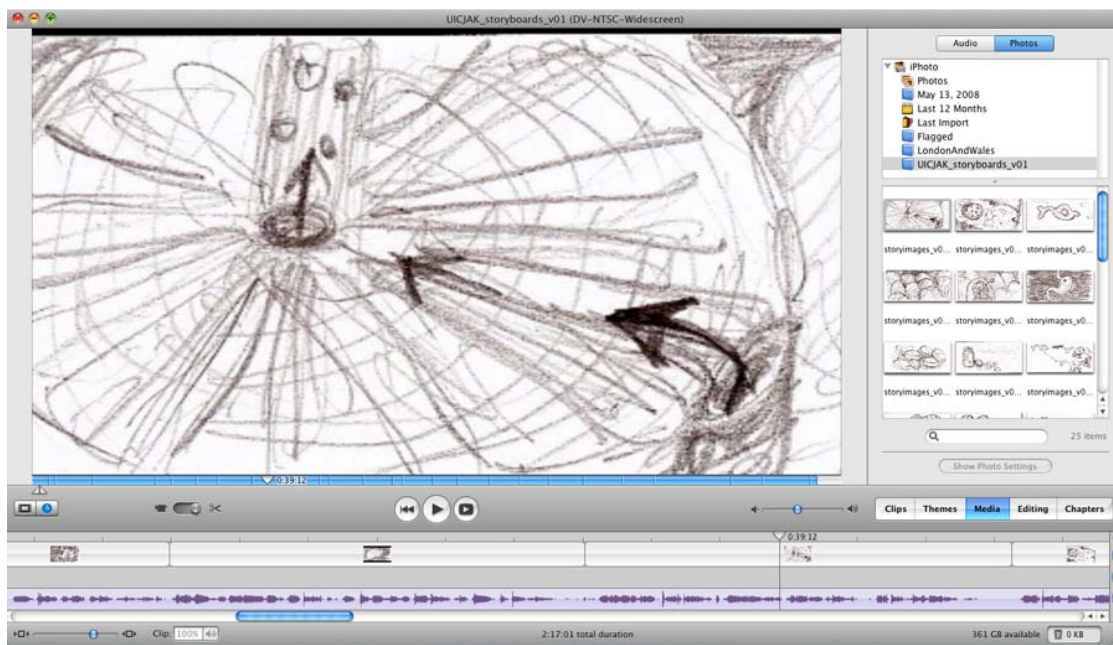


Figure 1. *Animated storyboards*

b. Project Design

The steps of project design prepared the visual elements for inclusion in the final animation. From mood boards and concept art to modeling, textures and lighting, these steps brought the project into 3D by providing the characters and scenes with a specific look.

i. Concept Art

Mood boards were the first step in creating a visual look for the animation. Various images and photos were used to inspire a color palette and the environmental feeling for the scenes and characters of the animation. A total of 9 mood boards were created and assembled into a deck, examples are shown in Appendix C. Reference photographs were found of the Tylenol[®] bottle, tablets, and liver tissue. Some mood boards were exclusively for look and feel and included images of honeycombs, chalky candies, gummy bears, and APAP metabolic pathway diagrams. Reference images for the liver lobule consisted of scanning electron micrographs (SEM) of real hepatocytes and photos of the arrangement of honeycombs. The mood boards deck had written descriptions of how the images related to the anticipated scenes and characters.

Concept art consists of illustrations specifically created for the animation that illustrate the environments or characters following the established look and feel of the mood boards. A storyboard sketch was used as the base drawing. 2D software, including Adobe[®] Photoshop[®] and Autodesk[®] Sketchbook Pro, was used to paint color on the image in layers that could further be edited. Style comps were created for 3 major scenes of the animation: the liver lobule (Figure 2), the

hepatocyte (Figure 3), and the intracellular molecular environment (Figure 4). The coloring of the liver lobule (Figure 2) reflected the mood board images of healthy colors. The hepatocyte concept art (Figure 3) showed internal organelles and the nucleus. The coloring of these elements and the molecules was purely artistic. The bright color palette used for the molecules was based on images in the mood boards of colorful candies. These vivid colors helped to keep the elements discernable from one another. Two exceptions to the vibrant color scheme were APAP and NAPQI. A white color was used for APAP that reflected the original APAP tablets. This white color was changed to grey for NAPQI to hint of its role as the “dangerous” metabolite. Damage to the intracellular structures and the hepatocyte was shown with an animated desaturation of the brightly colored elements. This color shift was used to suggest that the desaturated grey NAPQI molecules had caused the damage. As NAPQI was converted into inert metabolites, they were given friendly colors to indicate that they were no longer damaging. The smooth endoplasmic reticulum had been identified as the main site of APAP metabolism and the background color of the molecular environment in Figure 4 reflected its coloring. This was color cue was to help orientate the viewer as to where they were during animation scene changes.

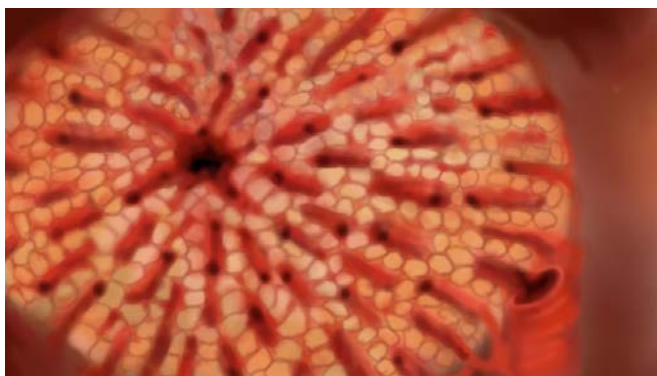


Figure 2. *Concept art - Liver lobule*

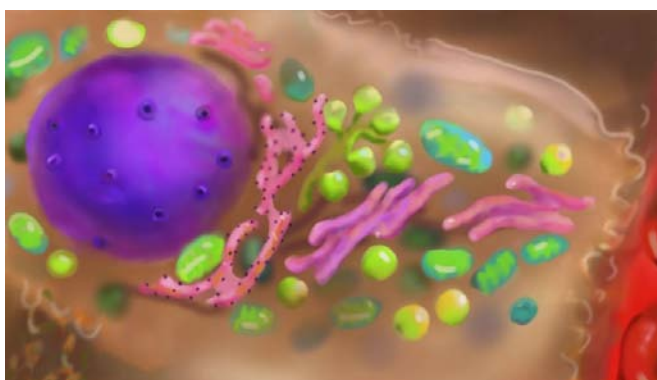


Figure 3. *Concept art -Hepatocyte*

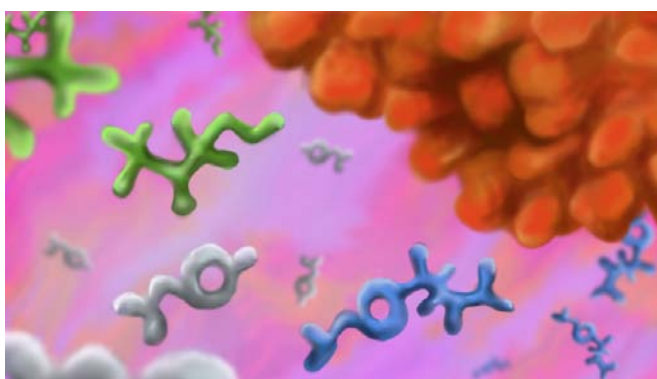


Figure 4. *Concept art - Intracellular environment*

ii. 3D Modeling

Characters that had been illustrated in storyboard images and concept art were developed into 3D models. A preliminary model book was assembled with model sketches and default renders of the individual models that were to be created or modified from existing models. Example pages from this deck are shown in Appendix D. The PDB and PubChem numbers were added to the deck pages for reference of the original 3D file. The deck was referred to during modeling and animation to ensure all needed models were completed.

Molecule files in a PDB file format were directly imported into Maya[®] with the mMaya plugin. Files from PubChem first needed to be converted into PDB files. The UCSF Chimera molecular visualization program (<http://www.cgl.ucsf.edu/chimera/>) was used to open the PubChem .sdf files and save them in a PDB file type that could then be used with Molecular Maya (mMaya) (<http://www.molecularmovies.com/toolkit/index.html>). Once the files were imported into Maya, the surface mesh settings for each model needed individual adjustments to the resolution, smoothness, threshold, and blobby radius. Figure 5 demonstrates the settings used for the metabolite models. When the desired look was achieved, the surface was converted into a polygon surface and the model was saved as an .obj file. Examples of PubChem molecules created are shown in Figure 6, while a PDB model is shown in Figure 7.

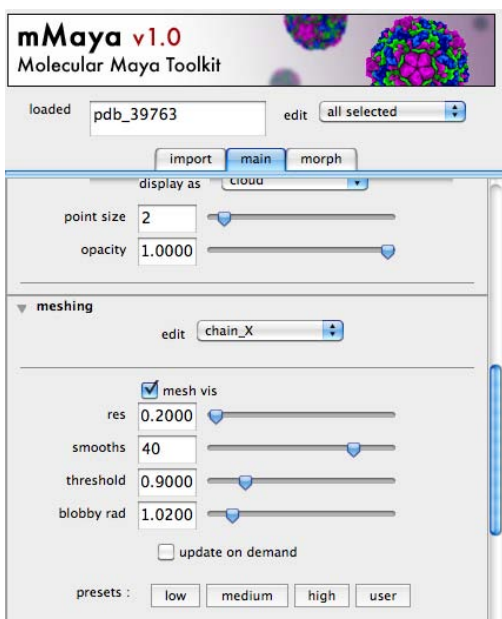


Figure 5. mMaya mesh settings

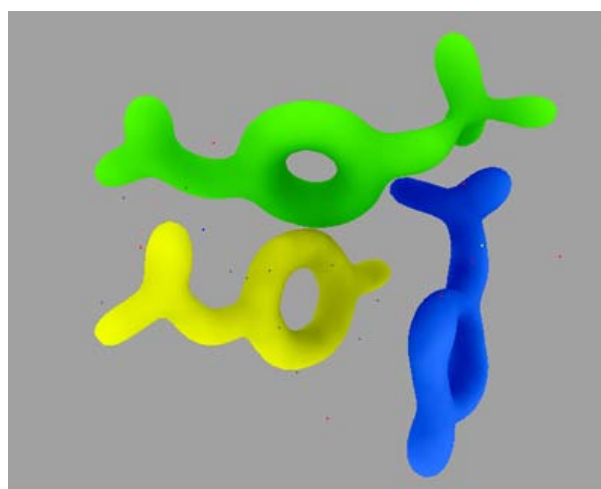


Figure 6. PubChem models - APAP and metabolites

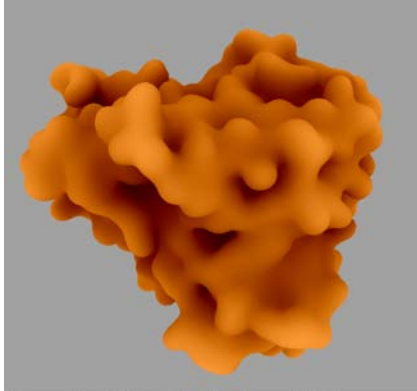


Figure 7. PDB model - *Cytochrome P450 enzyme*

Various modeling techniques were used for the other non-molecular models. The modeling process for the Golgi apparatus is shown in Figure 8. For that model, several basic cube shapes were created and a face was removed from each cube (Figure 8, a). A bridge modifier was used to connect the shapes and to add new geometry to the model (Figure 8, b). When all the holes were connected into one shape, the model was exported to Mudbox[®] for final sculpting and smoothing (Figure 8, c).

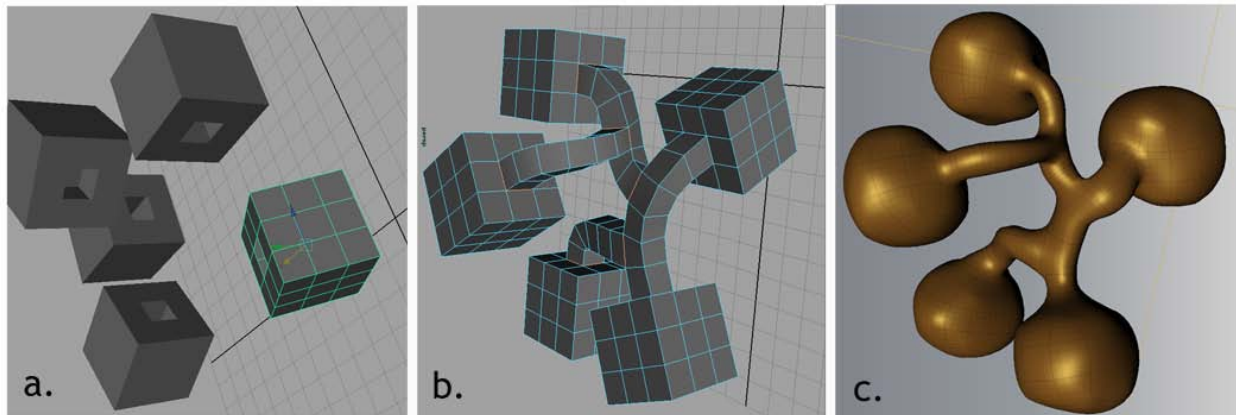


Figure 8. *Modeling the Golgi apparatus*

Other models specifically created for the project included an APAP bottle, APAP tablets, liver lobule, and the hepatocyte. The liver lobule and hepatocyte surface were modeled from basic polygon shapes. Mudbox[®] sculpting was used to add surface detail to the models which were then imported into Maya[®] as a new .obj file. The profile of the APAP bottle was drawn with a spline tool. This profile was revolved to create a 3D shape of the bottle. The tablets were modified from a cylinder shape by adding a groove down the center and beveling the edges. The liver and stomach models were purchased 3D assets that were modified slightly in Mudbox[®] in order to blend with the style of the newly created models.

iii. Texture and Lighting

The 3D models were textured to resemble the concept art. Texture development involved trial and error of creating and correctly placing surface textures, called shaders in Maya[®]. The APAP tablets, molecules, and proteins were textured with basic Lambert shaders that had a dull surface appearance. The APAP molecule was colored white to match that of the chalky tablet. To resemble the concept art, NAPQI was colored grey and various bright colors were chosen for the remaining metabolite shaders. Rendering was tested at this point to see how different render passes could be composited to provide additional surface texture. The addition of an ambient occlusion layer helped to give the molecules a chalky surface.

The surface of the liver lobule model was painted with the brush tool in Mudbox[®]. That initial painted color map was exported from Mudbox[®] as a TIFF image. Photoshop[®] was used to add additional detail to the flat image of a healthy liver lobule (Figure 9, a). A version of the map was also painted with grey and deeply saturated brown colors to indicate severe hepatocyte damage of the lobule (Figure 9, b). The painted surface map images were saved as .png files. Each map was placed on a lobule model in the color channel of a shader. The shader was given a slightly glossy Blinn surface. The glossiness helped give the model an appearance of wet tissue.

The APAP bottle and cap were textured with a basic Blinn shader. The bottle required a label. The process of applying a cylindrical UV map to correctly orientate the label image is shown in Figure 10. The ground plane underneath the bottle and tablets used an image as a texture. A photo of a paper cloth was used in the color channel of the shader. The placement of the image was repeated to cover the entire ground plane surface.

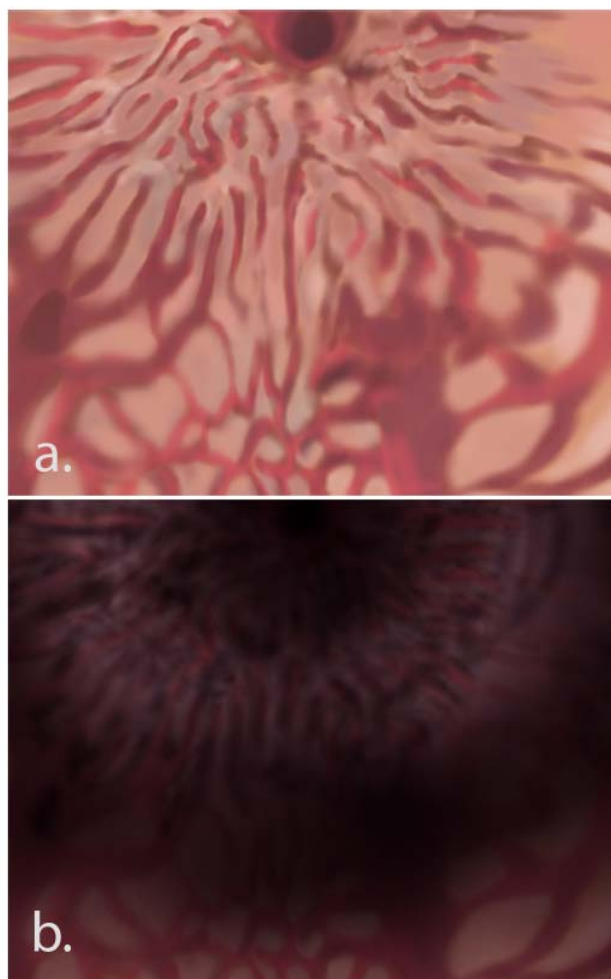


Figure 9. *Liver lobule texture map*
a. *Healthy lobule*, b. *Damaged lobule*

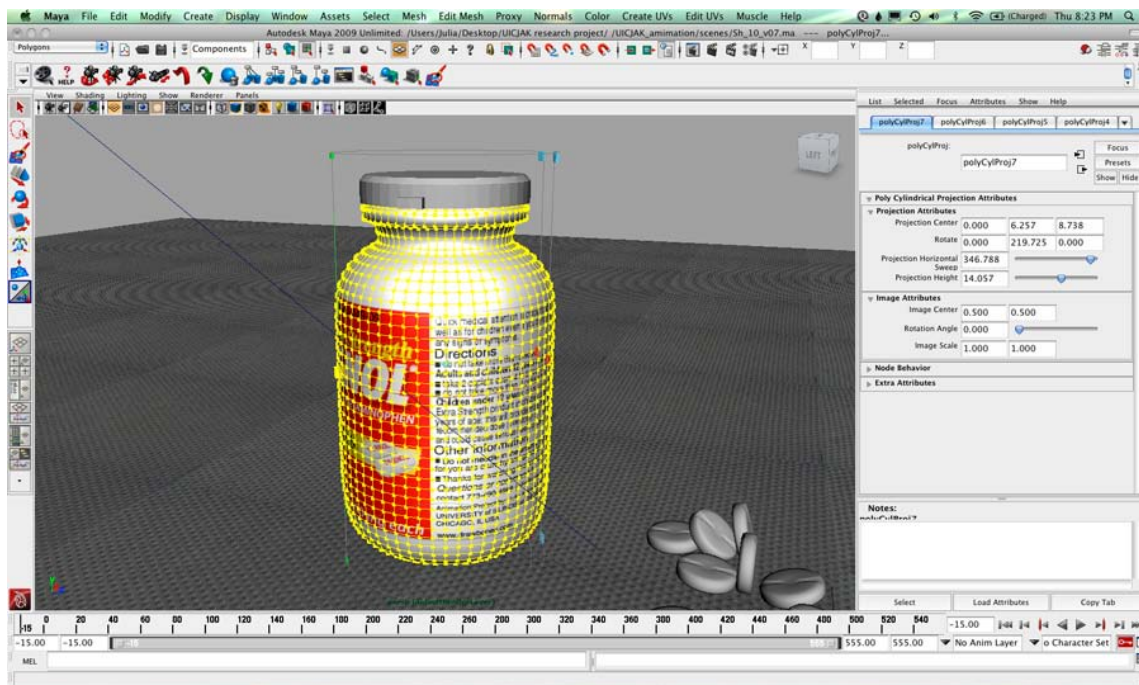


Figure 10. APAP bottle label map placement

Preliminary lighting of the characters was tested as scenes were set up. It was determined that the APAP bottle scene would need a 3-point light set-up with shadows enabled for the realistic look that was desired. The other scenes of the animation were to be less realistic and the lighting was kept more basic. An ambient light source and an additional directional light were sufficient for most scenes. Shadows for the molecules and other models were not directly created with 3D lighting. Rendering of those shadows was done with a separate ambient occlusion layer to be applied during compositing. An ambient occlusion layer gave the appearance of subtle shadows.

c. Project Production

The production stage of the project took all the prepared visual elements and turned them into a 3D animation. A spreadsheet shot list was created to track elements to be added to each scene and to define the shot timing. The shot list divided the entire animation into individual camera shots according to the script VO and a description of what was to be animated. The length of shots in the 2D animatic provided the number of frames required for the animation. Multiplying the shot length in seconds by 30 frames per second gave the number of frames required per scene. 15 frames were added to both ends of the shot to allow for transitions between scenes. Each shot was assigned a shot number. The shot number was used in the naming convention of all files associated with each shot.

i. 3D Animatic

The 3D animatic was created by populating each scene with 3D elements according to their arrangement in the storyboard images and concept art. The animated storyboards were used as a timing reference to fine-tune the motion of the characters. The high-resolution 3D models in some shots were temporarily substituted with low-resolution 3D models (Figure 11). This was done to save on computer processing and animation rendering time. Default gray colors were applied to the models at this stage. The accuracy of the characters was 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 to increase clarity. The framing of the scenes was blocked out using 3D cameras in Maya[®]. The scenes were previewed as Maya[®] playblast animations. The playblast animations were stored as movie files and were composited together with the VO audio track to create the 3D animatic for review. After viewing the 3D animatic, any necessary timing and motion changes were incorporated to better align the visuals to the VO.

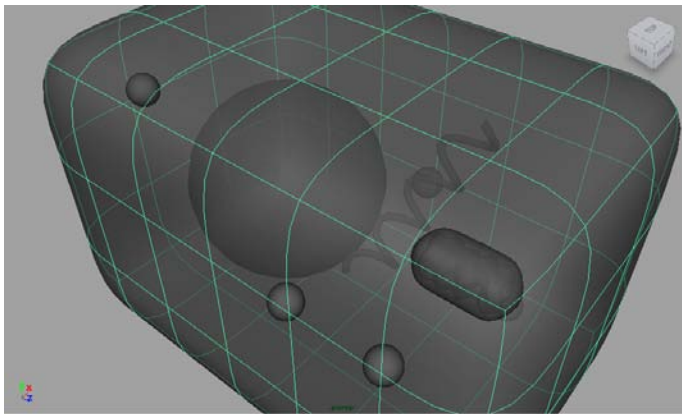


Figure 11. *Low-resolution hepatocyte model*

ii. Animation

Movements of characters, cameras and scene elements were refined. Low-resolution models were replaced with the final high-resolution models. Once animation of a 3D scene was “locked” the scene was colored, shaded and lit with the lighting that had been developed during the design steps. The concept art was used as a guide for the look and feel. Render tests were done to ensure scenes were rendering properly and looked as expected. As test renders were made, they were added to the compositing file in order to view the animation as a rough cut. When a final rough cut was approved, scenes were prepared for final rendering by deleting excess models and adjusting render settings. Removal of excess geometry from the scene shortened render time. The Maya[®] render

settings were checked to ensure that only the correct frame range of the scene would be rendered by the desired camera.

d. Project Post-Production

Post-production included the final steps of assembling the animation. Rendering and compositing turned the grey models of the 3D animatic and rough cuts into a final animation. The final animation file was rendered from After Effects® and converted into various file formats, such as .mov and .avi, so as to be playable on different computer systems.

i. Rendering

Each frame of the animation was rendered as a separate image in order to prevent loss of work if the entire sequence did not render correctly. Rendering was also done in passes so that post effects could be applied during compositing. The native Maya® file format .iff was used as the image file extension format. Maya® was set to automatically render a batch of frames while adding the shot number, layer name, and frame number to each file. The main pass for each shot were a color shader pass (Figure 12, a), ambient occlusion pass (Figure 12, b), and a depth pass (Figure 12, c). The depth pass render settings had to be calibrated individually for each shot based on the distance of the models in the scene from the camera. A static image of a sphere with a surface bump shader was rendered for use as a mottled background in the intracellular scenes. The render time of an individual frame for most render layers was a few seconds. The ambient occlusion pass had a render time of 1-3 minutes per frame and was rendered last in case any animation changes were needed. Rendering all layers for each shot took many hours so rendering was planned for night or when the computer was not otherwise in use.

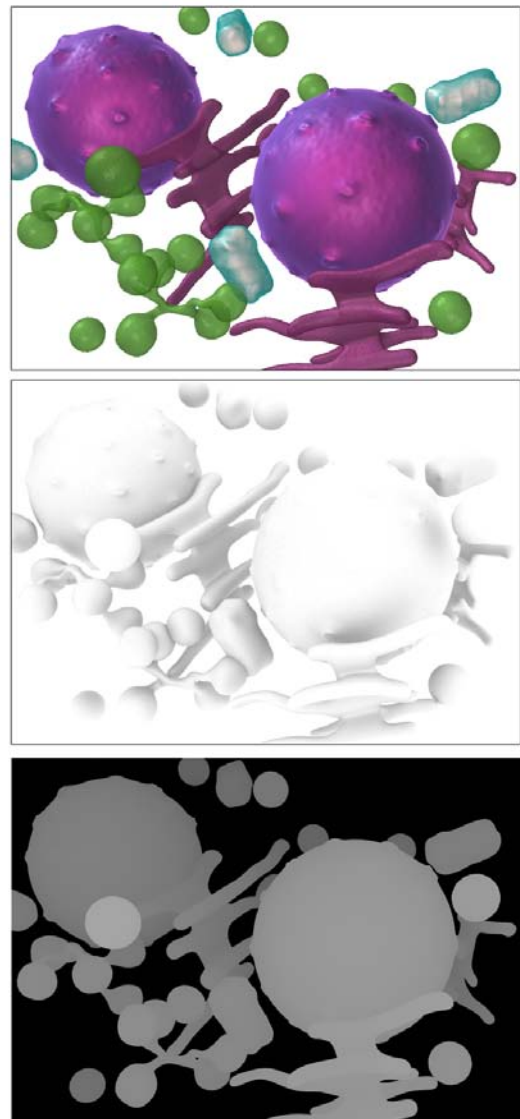


Figure 12. Render passes
a. Color pass, b. Ambient occlusion pass, c. Depth pass

ii. Compositing

Compositing brought together the various individually rendered image files. The After Effects® composite used for the 3D animatic and rough cuts was again used as a base for the final composited animation. The image sequences for each pass were imported into layers in After Effects® and pre-composited into the appropriate shots. Simple motion graphic labels were added. The depth pass was used in an adjustment layer with a lens blur effect so that far background and extreme foreground objects appeared out of focus. The ambient occlusion layer was set to multiply which gave a shadowy effect to the models. The rendered still image was added as the mottled background for the molecular shots. A solid black layer with a feathered subtraction mask was added above the background layer to darken the edges and vignette the scene. Other post-effects, such as glows, were added to slightly highlight the molecules. Figure 13 shows an example of the compositing process for a molecular scene. The individual pre-composited scene layers were placed in the main timeline and transitional adjustments were made to fade between scenes. Examples of composited screen shots from the final animation are shown in Figure 14.

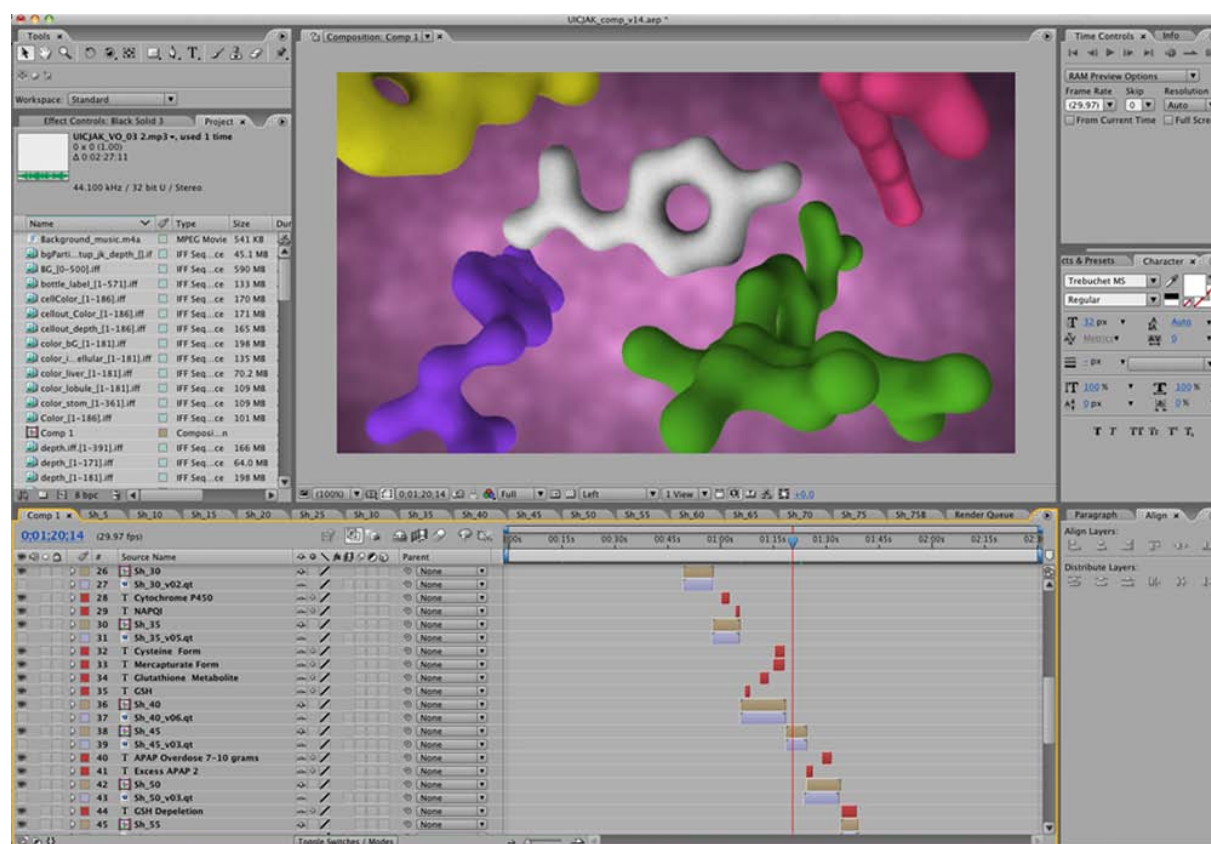


Figure 13. *Compositing the animation*

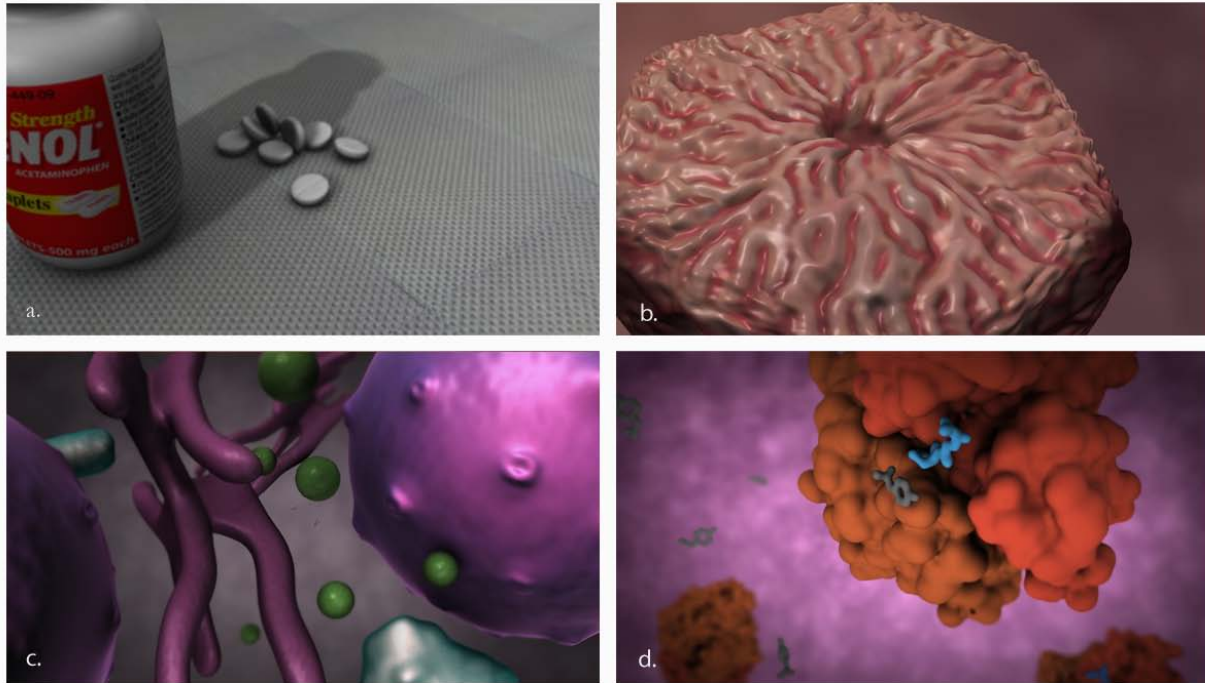


Figure 14. *Compositing animation screenshots. a. APAP bottle and tablets, b. Healthy liver lobule, c. Hepatocyte interior, d. Intracellular environment*

iii. Sound Editing

The VO script was recorded with an external microphone connected to the computer. Garage Band was set to record a voice audio file, such as for a podcast. The VO script was recorded in short segments according to the shot list. The recording process and the waveforms of the VO audio file are visible in Figure 15. The audio segments were previewed and adjustments to the pacing

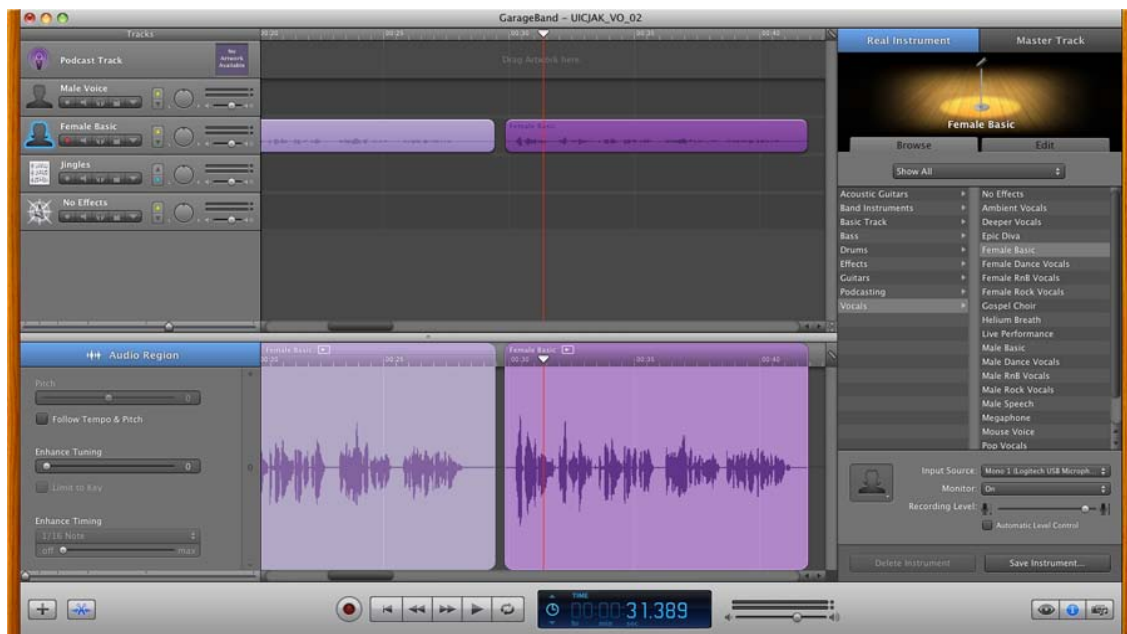


Figure 15. *Voice over recording*

and pronunciation were made until each track sounded consistent. The individual segments of recorded audio were aligned in the Garage Band timeline and saved as one audio file. This audio file was imported into After Effects during the compositing step. A basic music track from the Garage Band library was selected for background music. The music track was not as long as the animation so it was copied and repeated several times to provide music for the entire animation.

e. Project Management

Overall, project development was helped by the use of organizational and project management software. An application called Papers (<http://mekentosj.com/papers/>) was used during the literature review and content development to organize reference articles and PDFs. The search feature of Papers also led to the discovery of additional content assets. A web browser plug-in called Zotero (<http://www.zotero.org/>) was used to track and save the location of online resources and images. A summary of the references was uploaded to RefWorks (<http://refworks.com/>) in order to apply inline citations and populate the reference page in the appropriate format. OpenProj (<http://openproj.org/>), an open source project management application was used to create and update the project timeline (Table 2). This timeline was set to show how upcoming steps were reliant on the completion of previous steps. Background research and project organization benefited from the use of these tools.

A website for the project was created at www.drawbones.com/UICJAK as a place to share the project and animation development with project advisors, reviewers and other researchers. The most current version of storyboards, mood boards, concept art, and script were added to the project website. Videos of the animated storyboards, 3D animatic, and rough cuts were uploaded to YouTube (<http://www.youtube.com/>). Web links to the YouTube video were embedded in the project website so as to provide one location to review the most current project material.

Table 2: Timeline

		Name	Duration	Start	Finish	Predeces...
1		Julia's Research Project	155 days	12/21/0...	7/23/10 5:00 PM	
2		Pre-Production	100 days	12/21/0...	5/7/10 5:00 PM	
3		Proposal Draft	16 days	12/21/09...	1/11/10 5:00 PM	
4		Proposal Draft Advisor Review 1	5 days	1/11/10...	1/15/10 5:00 PM	3
5		Proposal Revisions 1	19.125...	1/12/10...	2/8/10 9:00 AM	3
6		Proposal Advisor Review 2	2 days	2/9/10 8:...	2/10/10 5:00 PM	5
7		Proposal Revisions 2	18 days	2/11/10...	3/8/10 5:00 PM	6
8		Proposal Advisor Final Review	2 days	3/9/10 8:...	3/10/10 5:00 PM	7
9		Proposal Final Revisions	1.25 days	3/11/10...	3/12/10 10:00 AM	8
10		Proposal Full Committee Review	33.75 d...	3/12/10...	4/28/10 5:00 PM	9
11		Script Development	11.75 d...	3/12/10...	3/29/10 5:00 PM	9
15		Science Reference Deck	36.75 d...	3/12/10...	5/3/10 5:00 PM	7
12		Script Revisions	18 days	3/30/10...	4/22/10 5:00 PM	11
13		Mood Boards	5 days	4/12/10...	4/16/10 5:00 PM	12
14		Storyboard Development	3 days	4/23/10...	4/27/10 5:00 PM	12
16		Advisor Storyboard & Script Revi...	2 days	4/28/10...	4/29/10 5:00 PM	14
17		Storyboard revisions	5 days	4/28/10...	5/4/10 5:00 PM	14
18		Voiceover Recording	1 day	5/7/10 8:...	5/7/10 5:00 PM	17
19		Design	35.5 days	4/26/10...	6/14/10 5:00 PM	
20		Model Sketches	6 days	4/26/10...	5/4/10 1:00 PM	14
26		Animated Storyboards	11 days	4/28/10...	5/12/10 5:00 PM	14
23		Models Development	14 days	4/28/10...	5/18/10 1:00 PM	14
24		Model Book, Storyboards, Script...	5 days	5/5/10 8:...	5/11/10 5:00 PM	17;20;26
21		Style Comp Development	17.5 days	5/10/10...	6/2/10 5:00 PM	20;13
22		Style Comp Advisor Review	2 days	6/3/10 8:...	6/4/10 5:00 PM	21
25		Textures Development	8 days	6/3/10 8:...	6/14/10 5:00 PM	21;23
27		PRODUCTION	33 days	5/10/10...	6/23/10 5:00 PM	
28		Shot List	3 days	5/10/10...	5/12/10 5:00 PM	17
29		3D Scene Set Up	12 days	5/20/10...	6/4/10 5:00 PM	26;28
30		3D Animatic	12 days	5/20/10...	6/4/10 5:00 PM	29
31		3D Animatic Advisor Review	3 days	6/7/10 8:...	6/9/10 5:00 PM	30
32		Animation Finalization	10 days	6/7/10 8:...	6/18/10 5:00 PM	30
33		Rough Cut 1 (Some renders)	5 days	6/7/10 8:...	6/11/10 5:00 PM	29;30
34		Rough Cut 1 Advisor Review	3 days	6/14/10...	6/16/10 5:00 PM	33
35		Lighting 1st. Pass and Testing	5 days	6/14/10...	6/18/10 5:00 PM	33
36		3D effects development	5 days	6/14/10...	6/18/10 5:00 PM	33
37		Render Final - Full Resolution	3 days	6/21/10...	6/23/10 5:00 PM	36
38		POST-PRODUCTION	30 days	6/14/10...	7/23/10 5:00 PM	
39		Motion Graphics	10 days	6/14/10...	6/25/10 5:00 PM	33
40		Post Visual Effects Development	5 days	6/14/10...	6/18/10 5:00 PM	33
41		Music & Sound Effects Developm...	5 days	6/14/10...	6/18/10 5:00 PM	33
45		Final Paper	10 days	6/14/10...	6/25/10 5:00 PM	33
42		Render out of After Effects	3 days	6/21/10...	6/23/10 5:00 PM	40
46		Prepare final presentation	10 days	6/28/10...	7/9/10 5:00 PM	39;40;4...
44		Project Advisor Sign Off	5 days	6/30/10...	7/6/10 5:00 PM	37;45
43		Final presentation	2 days	7/22/10...	7/23/10 5:00 PM	44

f. Hardware & Software Resources

This is a summary of the specific hardware and software used during the project. A MacBook Pro computer (Apple Inc., Cupertino, CA) was used for the majority of the work. 2D artwork elements, such as storyboards and concept art, were hand-drawn, digitally scanned then modified in SketchBook Pro 2009 (Autodesk® Inc., San Rafael, CA) and/or Adobe® Photoshop (Adobe Systems, San Jose, CA). The voice over script was digitally recorded with Garage Band (Apple Inc., Cupertino, CA). Animated storyboards were created with iMovie (Apple Inc., Cupertino, CA). The primary 3D software was Maya® 2009 (Autodesk® Inc., San Rafael, CA). Molecular structures were imported with Molecular Maya, mMaya (<http://www.molecularmovies.com/toolkit/index.html>). The UCSF Chimera molecular visualization program (<http://www.cgl.ucsf.edu/chimera/>) was used to convert PubChem files to PDB files. Mudbox® 2009 (AutoDesk® Inc., San Rafael, CA) was used for the sculpting and painting of many 3D models. Adobe® After Effects® (Adobe Systems, San Jose, CA) was used to composite the individual files into the final animation. Certain post-effects and visual treatments also were done in Adobe® After Effects®.

IV. Summary and Discussion

Planning a professional medical animation normally requires that project roles be assigned to separate individuals. Depending on the type of animation, these roles may include: medical writers, science content strategists, project producers, art directors, 2D artists, modelers, animators, texture and lighting specialists, motion graphic artists, and composers. These individuals form a team that works together to complete an entire animation. The roles for this project were consolidated and done by one researcher. The alteration to the professional workflow sometimes was an improvement. For example, since the art director was the same person who had performed the background research and written the script, there was no need for separate briefing meetings on the science of the story. Other combinations worked well such as having the compositor also do the lighting and plan how the scenes were rendered. Combining roles for this project resulted in the completion of an entire medical animation by a single researcher.

Although the workflow and breakdown of roles for this project was different than a professional workflow, the steps used to complete the animation remained similar. The major steps of the project were pre-production, design, production, and post-production. Pre-production determined the science story to be shown. Even with a full-length movie, it would not be possible to show every detail of the story. The type and amount of content visualized by the animation was designed with the needs of an audience of healthcare providers in mind. Extensive background research provided a level of detail appropriate for this audience. A main source of project content was the Tylenol[®] PPI which described the absorption and breakdown of APAP into metabolites. As the topic for the project, APAP metabolism and hepatotoxicity provided an interesting visual story with many scenarios and molecular characters. The content also centered on the current FDA recommendations for overdose prevention. The animation was presented in a scientifically accurate manner with certain liberties taken for storytelling purposes and to consolidate the content into a few minutes of animation. For example, not all of the enzymes that were responsible for production of metabolites were shown. A science reference deck, script and storyboards were created during the pre-production process.

The design of how to show the metabolic pathways and sites of action was the next step in the creation of the animation. Mood boards were assembled early in the design process to provide visual inspiration for the characters. Scenes were planned to gradually bring the viewer from a gross level to a molecular level of magnification, and from the easily recognizable to the more unknown. Concept art was created for the liver lobule, hepatocyte and intracellular environments. The pill

bottle and tablets were shown at the beginning of the animation to give the viewer a familiar point of reference. APAP absorption and delivery to the liver was introduced with a depiction of the entire stomach and liver. Viewer focus was then shifted to a microscopic level by first showing the liver lobule and then zooming in to an individual hepatocyte. The VO indicated the site of APAP metabolism as the smooth endoplasmic reticulum. The animation then visually cut to a nanometer level of magnification to show where molecules and enzymatic proteins are located and interact. The characters listed in the science reference deck were required as 3D models. A model book was assembled as a reference for the look and design of these models. PubChem or PDB files were used for the molecular characters, while the other elements were created from scratch or adapted from purchased models. These models were textured and lit to resemble the concept art. Design steps gave the animation a vibrant look and feel.

Production steps carried out the design envisioned for the content. Maya[®] was used as the 3D software for the animation. The production workflow of Maya[®] is different from other 3D software, although some aspects such as modeling and key frame animation were very similar. The animation dynamically presented APAP metabolism as interaction between 3D models. This was in contrast to the diagrammatic representations of pathways shown in many references. Maya[®] was chosen as the 3D software for animation production specifically so that the mMaya plug-in could be used. The use of mMaya gave accurate 3D shape to the molecules of APAP, metabolites, and various metabolic enzymes. By bringing the story to life in this way, an engaging display of APAP metabolism was created by production of the animation.

During post-production, adaptation of some steps was needed. These adaptations were based on limited access to computer resources. For example, only relatively basic shaders and lighting were used since there was not access to the additional computers that would be required to render the animation with a complex shader and lighting network. Although not necessary for the completion of this project, additional machines could have been used to decrease render time and allow for the inclusion of more elaborate effects. The steps of post-production were done last to complete the final animation.

V. Conclusion

Healthcare providers, including pharmacists and pharmacy technicians, work to prevent patient misuse of medications. In light of the 2009 FDA recommendations and warnings on APAP usage, these healthcare providers may benefit from an increased understanding of the processes involved in APAP metabolism and chemical-driven liver damage. An increased knowledge of these processes by healthcare providers may help decrease the occurrences of APAP overdose in patients.

A research question, identified at the beginning of this project, was how could the APAP metabolic pathway be visualized for an audience of healthcare providers. This problem was addressed with the design of a short medical animation on the topic. By designing and developing this medical animation, a new way to visually represent the process of APAP metabolism and effects of hepatotoxicity was created. The review of literature supported the validity of medical animation. Although the animation was not user tested, the research done during the project provided content that is relevant to healthcare providers.

The roles and the development steps of a professional medical animation workflow were adapted into a new set of methods. Since one researcher was able to complete all animation steps of pre-production, design, production, and post-production, the professional medical animation development process was successfully consolidated. The methods used during this project for animation development were explained and examples presented so as to encourage other researchers to create their own medical animations on new topics.

Further development of accurate medical animations depends on the creation, adaptation, and use of new medical animation tools. One of these new tools is the Maya[®] plug-in, Molecular Maya, called mMaya, which provides the ability to directly import accurate molecular structures directly into the commercial 3D program. The use of mMaya, is a new step in the development of medical animations. Before mMaya was developed, other steps were required to make use of PDB molecular structures in medical animations. Other researchers may choose to only work with 3D software that is familiar, but experimentation with new tools such as mMaya is important. Expanding the development and use of medical animations may lead to further improvements in technologies specifically designed for their creation.

VI. Appendices





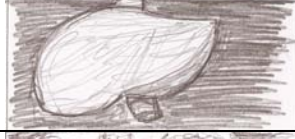
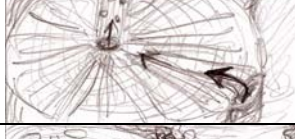


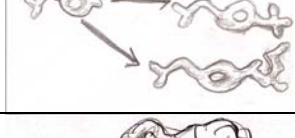


Appendix A: Science Reference Deck

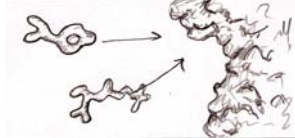



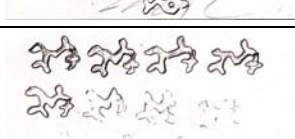
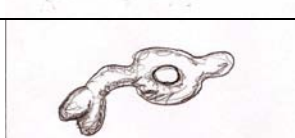





This science reference deck was created during content development and contains additional science information and sources of molecular data used during animation development.

Character Name (molecular level)	PDB/ PubChem	Also known as/ Type	Size/Weight	Pronunciation	Notes
Acetaminophen	CID_1983	APAP, paracetamol, Tylenol®	151.17 g/mol	acet-amin-o-phen ə-ˌsɛ-tə-ˈmi-nə-fən, ,a-sə-tə-	
Acetaminophen cysteine	CID_83997	APAP metabolite	254.31 g/mol	cys-teine 'sis-tə-, ɛn	
Acetaminophen glucuronide	CID_83944	APAP metabolite	327.29 g/mol	gluc-uro-nide glü- 'kyur-ə-, nɪd	
Acetaminophen sulfate	CID_83939	APAP metabolite	231.23 g/mol	sul-fate 'səl-, fāt	
Acetaminophen glutathione	CID_83998	APAP metabolite	327.29 g/mol	glu-ta-thi-one ,glüt- ə-'thī-, ðn	
Acetaminophen mercapturate	CID_539698	APAP metabolite	312.34 g/mol	mer-cap-TUR-ate	
NAC	CID_12035	N-acetylcysteine, overdose antidote	163.19 g/mol	ace-tyl-cys-te-ine ə-ˌsɛt-'l-'sis-tə-, ɛn	
Cytochrome P450	2J0D	Enzyme, CYP2E1, CYP1A2, CYP3A4	Length [Å] a = 67.25 b = 210.71 c = 161.25	cy-to-chrome 'sīt- ə-, krōm	
Glutathione	CID_124886	GSH, tripeptide, cofactor	307.32 g/mol	glu-ta-thi-one ,glüt- ə-'thī-, ðn	
Glutathione transferase	1EOH	Enzyme, protein, polypeptide	Length [Å] a = 82.97 b = 84.02 c = 236.97	glu-ta-thi-one ,glüt- ə-'thī-, ðn	
NAPQI	CID_39763	N-acetyl-p-benzoquinoneimine, APAP bioactive metabolite	149.15 g/mol		
COX	1PRH, 4COX	Enzyme, Cyclooxygenase	Length [Å] a = 179.80 b = 133.60 c = 118.40		Not used in the animation

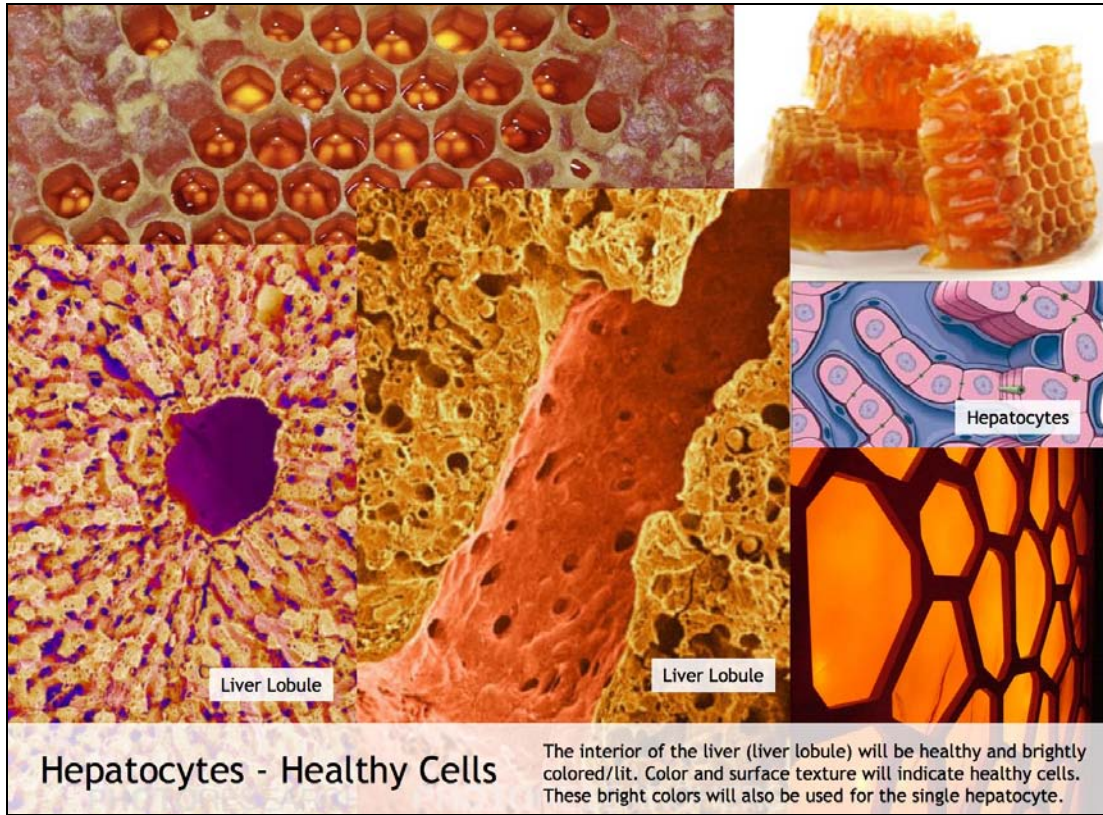
Character Name (cellular/systems level)					
Liver	N/A	Organ			
Hepatocyte	N/A	Cell		he-pa-to-cyte hi-'pat-ə-, sīt	
Smooth endoplasmic reticulum (ER)	N/A	Organelle		en-do-plas-mic ,en-də-'plaz-mik re-tic-u-lum ri-'tik-yə-ləm	
Golgi apparatus	N/A	Organelle			

Appendix B: Script, Storyboards, VO, Text on Screen, Notes

Storyboard Sketches	VO - Word Count 260	Text on Screen	Animation Notes
	Acetaminophen or APAP is a widely used medication with analgesic and antipyretic properties.	Acetaminophen APAP	Fade in. Shown is a bottle of APAP and tablets of APAP with a neutral background.
	The FDA recommends a maximum dose of 4 grams of APAP per day. Consuming more APAP than recommended can potentially cause severe liver damage.	Maximum APAP dose 4 grams per day	Camera pushes in to show what 4 grams of active ingredient looks like (eight 500mg tablets = 4grams).
	When APAP is taken orally...		Cut to a single APAP tablet moving downward in the stomach. The stomach will be simple and no other stomach contents will be shown. A visual effect shows the tablet dissipating to individual particles representing APAP molecules.
	...it absorbs rapidly in the upper GI tract. APAP enters the bloodstream and is carried to sites of action.		Picture-in-picture is faded on and shows villi surface of GI tract. Picture-in-picture cross fades to show APAP passing through the surface of the villi.
	The liver metabolizes APAP and produces metabolites required for function.	Liver	Stomach fades off and liver fades on.
	Many metabolic pathways occur in the liver to rid excess APAP and other substances from the body.	Liver Lobule	Cut to interior of liver. Healthy hepatocytes are arranged in a symmetrical pattern. Blood cells are flowing along arrow path.
	APAP is metabolized in the hepatocyte's smooth endoplasmic reticulum.	Hepatocyte	Cut to single hepatocyte that nearly fills the screen. Simple cellular contents are shown including; nucleus, endoplasmic reticulum, golgi, mitochondria etc.
	The majority of APAP...	APAP	Cut to a simple intracellular space environment, the same color of the smooth endoplasmic reticulum. The APAP molecule structure is shown. More molecules will be seen in the background throughout all molecular shots.
	...is conjugated by enzymes into inert sulfate and glucuronide metabolites.	APAP Sulfate APAP Glucuronide	Camera move to show scene wider. Labels appear with the 2 metabolites.
	An enzyme, cytochrome P450, converts the remaining APAP...	APAP Cytochrome P450	Cut to focus on Cytochrome P450 as it drifts into view. APAP enters the active site of the enzyme.
	...to NAPQI.	NAPQI	NAPQI exits the enzyme.

Storyboard Sketches (cont.)	VO - (cont.)	Text on Screen	Animation Notes (cont.)
	NAPQI can be combined with GSH...	NAPQI GSH	Cut to another enzyme. Both NAPQI and GSH enter the active site.
	...to create an intermediate glutathione metabolite. Further conjugation results in mercapturate and cysteine forms.	APAP Glutathione APAP Mercapturate APAP Cysteine	APAP Glutathione exit the enzyme. Same arrow and label treatment is used for these 2 end product metabolites.
	Inert metabolic end products are harmlessly eliminated in the urine.		Camera drifts to frame up the end products. These metabolites are shown moving away from center and off frame. Fade to black.
	The situation changes if an excessive amount of APAP enters the system. An overdose of 7-10 grams of APAP in one day...	Excess APAP	Fade in to slightly different (color) cellular environment. More APAP molecules are seen. Some in background convert to the first 2 metabolites. Most convert to NAPQI.
	...quickly exhausts the GSH available for NAPQI deactivation.	APAP overdose 7-10grams	GSH molecules are shown but there are not enough to pair with all the NAPQI.
	NAPQI is toxic to cellular proteins and nucleic acids.	NAPQI	Cut to show single NAPQI.
	Damage to intracellular structures causes irreversible harm to the hepatocyte.		Cut to NAPQI moving away from the area to structures nearby which lose color and look ill.
	Spreading hepatocyte destruction can lead to hepatic failure and patient death.	-Hepatocyte Destruction -Hepatic Failure -Patient Death	Cross fade to liver lobule now with obvious damage. Show 3 bullet points in time to VO. Blow out to white.
	There are ways to avoid such consequences. N-acetylcysteine, called NAC is the antidote for APAP overdose.	NAC	Fade in from white to ambiguous cellular environment. NAC pathway is shown with 3D molecules. Excess NAPQI is in the environment.
	If NAC is given in time, it converts to GSH for deactivation of excess NAPQI before hepatotoxicity can occur.	NAPQI GSH	NAPQI is converted by the enzyme into the metabolite.
	Increasing general awareness of appropriate APAP usage could help prevent overdoses from occurring.	Prevent APAP Overdose	Cut to pill bottle of APAP and tablets. Same scene as the beginning. Screen fades to black. The end!

Appendix C: Mood Board Examples

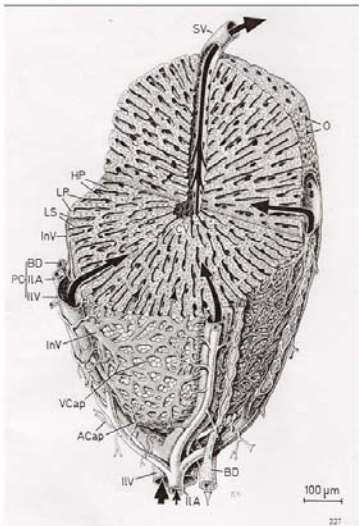


Appendix C: Mood Board Examples cont.

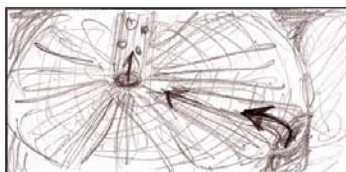


Appendix D: Model Book Examples

Acetaminophen Metabolism and Hepatotoxicity



This is a reference image that will be used to create the model. The drawing below is from the storyboard where the model will be used.



Liver Lobule

Julia Klein

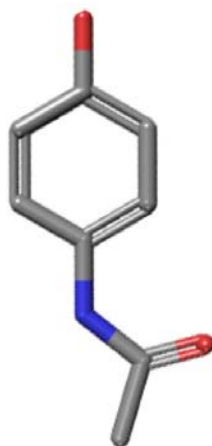
Model Notes:

The liver lobule model will be created as a base shape in Maya and then sculpted in Zbrush or Mudbox.

Acetaminophen Metabolism and Hepatotoxicity



APAP

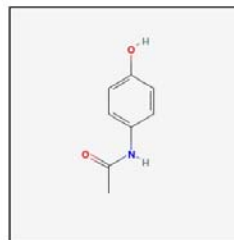


Julia Klein

Model Notes:

The Molecular Maya plug-in (<http://www.molecularmovies.com/toolkit/index.html>) will be used to create a molecular surface.

Structure Reference:
PubChem CID_1983



VII. References

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