Antibody drug discovery: From Idea to Biotherapeutic Molecule

By

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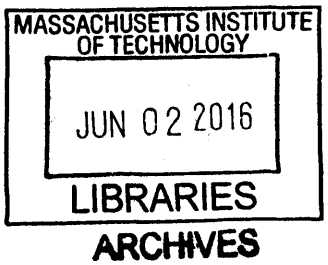

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Abstract:

Graybel (a fictitious name used for privacy reasons) is a large developer of pharmaceuticals. Graybel'[] Antibody Protein Engineering Group (APEG) is responsible for early stage drug development of biotherapeutic molecules. Part of this responsibility is delivering high quality molecules while meeting tight deadlines. Across the industry there is constant pressure to decrease timelines, while at the same time the complexity of molecules is increasing. In order to meet this challenge, APEG must be highly adaptable. Unfortunately, unanticipated biology, long project lead times, unpredictable workflows and inadequate workflow tracking systems make it difficult to precisely determine what causes delays. This uncertainty, combined with the inability to quickly pilot changes to process or methodology, makes each potential change both risky and costly. The goal of this project was to provide APEG with two things: the knowledge needed to build a robust workflow tracking system and simulations that would assist in finding root causes of issues and allow for low-cost piloting of potential solutions. Combined, a workflow tracking database and decision tool would greatly reduce the risk associated with implementing changes, allowing APEG to adapt to meet increasingly difficult industry standards.

Multiple avenues were used to collect the data needed on APEG'[]workflow. The primary []ource of data is interviews, with both management and experienced bench workers. These interviews provided data on workflow paths and estimates for workflow stage durations that could not be found elsewhere. In addition, they provided a way for APEG members to be involved in the project. Additional data was gathered from rudimentary systems that are used to track workflow within some functional groups. This data was then used to create detailed process maps, and simulations. Once validated, simulation results were analyzed and experimented with to determine current bottlenecks, potential future issues and possible fixes for these problems. In addition, a new metric was introduced for quantitatively evaluating the difficulty of a project called the Technology Readiness Level (TRL). Essential project decisions were identified, and recommendations made to track those issues. Bottlenecks were identified through queue analysis. Potential changes to fix these and other issues were piloted to determine effect. Future states, both with and without these changes, were simulated to determine potential problems. From this, causes of current and potential future delay were identified and recommendations developed. Recommendations included staffing changes, cross training, real-life piloting and developing a deeper understanding of certain processes.

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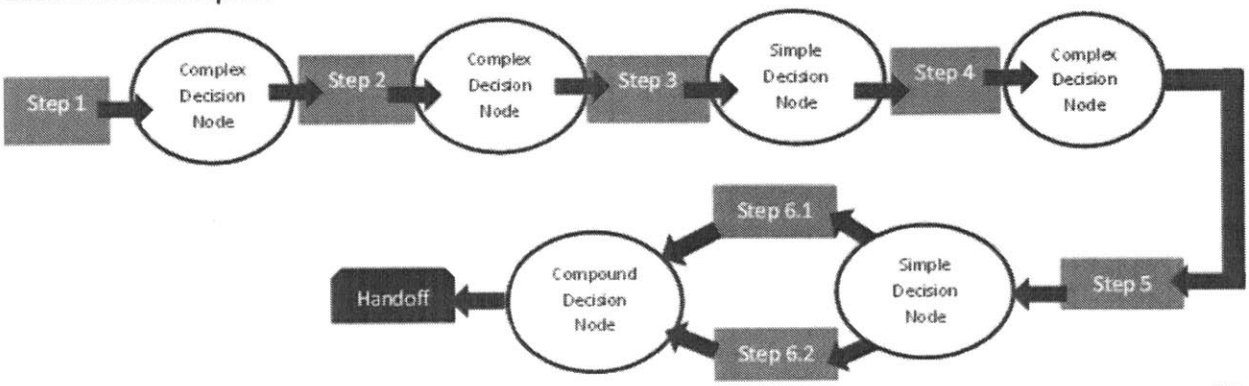
Section B.3: Group B2



Chapter 1: Introduction

Project Overview

The goal of this project is to provide pharma company Graybel's (name disguised) Antibody Protein Engineering Group (APEG) with tools to reduce their drug development timelines while maintaining quality by improving their processes. Drug discovery is a complex, experimental process with inherent rework and churning that cannot be avoided. APEG is responsible for antibody based drug discovery, which has two development paths called In-Vivo and In-Vitro. In-Vivo development is conducted utilizing the immune reactions of animals, and In-Vitro development is entirely laboratory based. Both of these methods are utilized by APEG. APEG is divided into 7 functional groups, which for the purposes of this thesis will be called Groups A, B1, B2, C, D, E and F. Groups A-E will be extensively analyzed; Group F will not, due to its small size and the extremely technical processes that it is responsible for.

A number of challenges were encountered while analyzing APEG's processes. APEG's process is complex and extremely interconnected. At a high level, flow is generally linear, but this is very deceptive. A given project will backtrack multiple times throughout its development cycle, transitioning between groups and churning within those groups. This is partially due to the aforementioned inherent variability of experimental drug discovery and partially due to artificial variability due to APEG's processes and Graybel's overall organization. Combined, these introduce extreme variability into APEGs development timelines that is difficult to predict. This is compounded by APEG's fractured understanding of its processes. Executives within APEG understand things at a high level, but are missing details. Bench workers (the scientific equivalent of front-line workers) understand the details of their own process, but may miss the bigger picture, and do not understand the details of other group's processes. Management within APEG's groups is in between the two, but focused within their own group. As a result, there is no one who understands the entire picture at both the high and detail levels for all groups. There is a general lack of workflow tracking data that makes obtaining this understanding nearly impossible. Bench workers are torn between competing metrics for success for APEG and other Graybel Groups involved in the project, which makes it difficult to determine where improvements should occur and heavily influences APEG's project load. In addition, there are emergent automation opportunities which may be beneficial to APEG's processes but they require extensive capital investment and may not be fully utilized by APEG scientists, making it difficult to determine which are worthwhile. On top of all this, APEG had undergone restructuring during the last year, which has resulted in the formation of new groups and the fusing of old groups. Many of these new groups have not yet fully established their processes and have no history, which makes analyzing them difficult.

Extensive process mapping was done in order to gain an understanding of APEGs process. Bench workers, management and executives representing all groups within APEG were interviewed for 2-3 hours each to build these process maps. These interviews served multiple purposes: (i) anecdotal information gathering; (ii) involving APEG members with the process to obtain buy-in; and (iii) obtaining understanding of the process at multiple levels. Interviews concerned workflow paths, step durations, identification of decision points and gathering of documented historical data, which was only available for Groups A and E. The resulting data was then analyzed and used to estimate duration of process

steps. Process Maps were then created and contributors were re-interviewed to ensure accuracy. Typically this resulted in 2-3 revisions of the process map, with a final product that all group members agreed upon. Process maps were built at three levels; Level 1, the executive level, was meant to represent an overall, generally linear interpretation of the process that an executive would have. Level 2, or management level, mapped the general steps within each group, as management would see them. Level 3, the bench level, was the most complex and represented actual bench work done.

During interviews, it became clear that APEG needed a formalized framework for evaluating and communicating individual project complexity as project complexity heavily influenced project set duration and repetition likelihood. Interviews identified three characteristics that contributed to complexity: (i) disease complexity; (ii) solution complexity; and (iii) solution platform complexity. A framework was developed based on these three characteristics, called the Technology Readiness Level (TRL) framework. The framework consisted of 3 axes, each one dedicated to the aforementioned characteristics. Complexity was indicated numerically from 1-3, with 1 being easy and 3 being hard, for each axe. 'Easy', 'Medium' and 'Hard' were defined by the amount and quality of existing prior work applicable to the project. This then gives cumulative TRL values from 3-9, with 8-9 being hard, 5-7 being medium and 3-4 being easy. This gave a defined method for evaluating overall project difficulty as well as a built-in method of breaking down that complexity into informative components. This could then be used to evaluate APEG's capacity and improve internal and external communication.

Simulations based upon the process map and TRL levels were then built. The process maps were used to build workflow paths and determine step duration. The previously discussed TRL determined the outcomes of decisions and duration of steps which were often dependent on project difficulty. The simulation modeled rework and churning as part of these decisions; a potential outcome was often "return to previous step." Thorough the simulation building, additional interviews were conducted when necessary to obtain estimates of needed values. Some values had to be determined empirically through simulation experimentation. Simulations were then validated iteratively through comparison to historical and anecdotal data and additional interviews. Due to limited data for some groups, perfect accuracy could not always be achieved.

Once the simulations were validated, analysis and experimentation were conducted to identify bottlenecks and potential solutions. This identified bottlenecks of varying severity in four groups, one of which would greatly benefit from additional personnel or automation. Further experimentation was then conducted with TRL variations, testing a total of 9 potential variations. The first three were the slight variations on the current situation, designed to determine simulation sensitivity to TRL variables. Then extreme TRLs were tested, to ensure that the simulation reacted appropriately and give an idea of the responsivity that should be expected for the last three TRLs. The last three TRLs were designed to test potential future TRLs. These TRLs revealed another bottleneck in Group E, which is currently being hidden by Group E utilizing extreme effort to maintain production times. Potential future TRLs were also tested with potential improvements, to ascertain potential future impact of those changes.

Overall, the project delivered 3 recommendations to APEG along with the simulations themselves. First, implantation of the TRL framework, which is a flexible, qualitative and nuanced method for evaluating

project difficulty with a number of potential applications. In addition, it can be used to communicate nuanced understandings of project difficulty in an easy to understand manner. Second, recommendations on what data should be tracked in order to best understand their processes. Finally, recommendations on process changes that could potentially benefit their work and accompanying information on where to watch for developing problems.

APEG Background and Project Objective

Graybel[1] is one of the world's leading pharmaceutical companies. Within Graybel is the Antibody Protein Engineering Group (APEG), an R&D group located in the U.S.. In order to understand Graybel and APEG's motivations, goals, and operations it is important to understand drug discovery and Biotherapeutics. Drug discovery is a complex, costly process. APEG is responsible for supporting early drug-discovery; from idea to pre-clinical validation. Within the organization, they are positioned as shown in Figure 1.

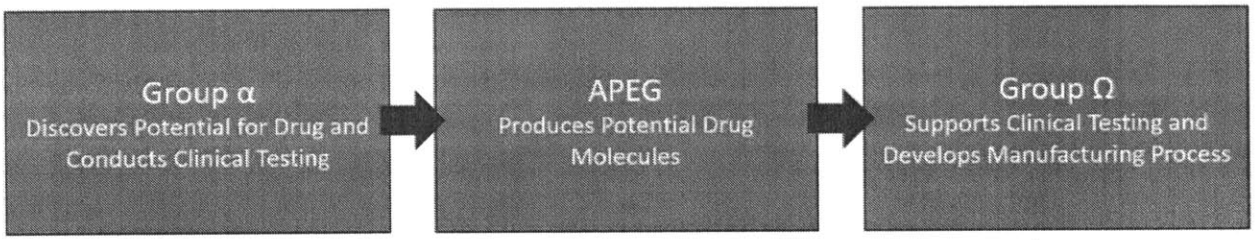


Figure 1: APEG's Position within Graybel

As an R&D group, APEG's process is highly variable and prone to change and customization to meet project specific needs. The projects that they are responsible for are increasing in complexity and difficulty. Consequently, in spite of their highly intelligent, experienced workforce, it is becoming increasingly challenging to maintain and improve project completion times. APEG's goal is to shorten their cycle times without negatively impacting quality or greatly increasing cost. Paul, et al. suggests four methods for shortening drug discovery R&D cycle time.

1. Use cycle time (i.e. how long it would take to develop the drug) as part of the decision to develop a drug
2. Identify the critical chain of project tasks and adapt as needed
3. Improve processes
4. Reduce wait times
   (Paul, et al., 2010)

It is the goal of this project to assist all of these methods through the creation of process maps and simulations. Process maps will be used to identify critical tasks and how they connect, and then used as the basis of the simulations. The simulations themselves will allow APEG to independently test the potential impact of future changes. Finally, the simulations will be used to identify bottlenecks and recommend methods for fixing them.

[1] Name obscured for confidentiality

Scientific Background

Generic Drug Discovery

There are three stages of drug development: (i) Drug Discovery; (ii) Pre-Clinical; and (iii) Clinical (See Figure 2). This project concerns the first.

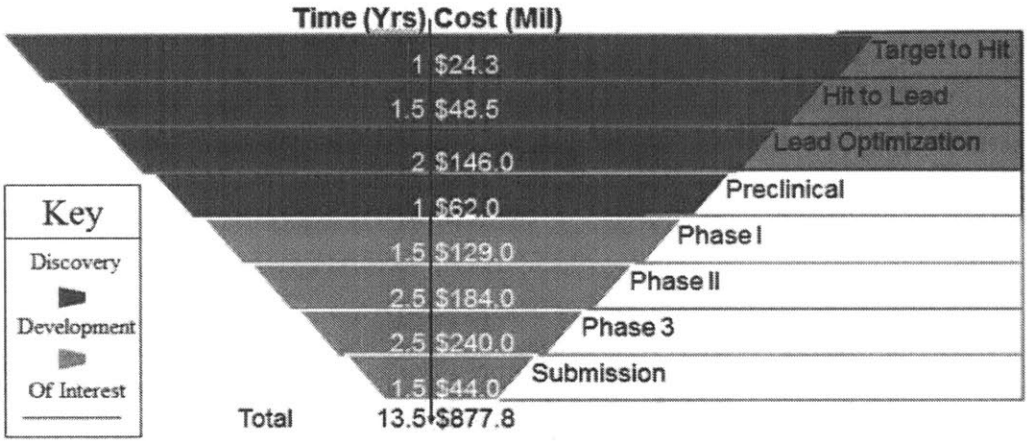


Figure 2: Overview of Drug Discovery Process (Paul, et al., 2010)

Drug discovery consists of three stages. Prior to the process start, a potential molecular target associated with the disease is identified, generally by academia or internally within the organization. During this pre-step, , the target is evaluated in multiple in-vitro and in-vivo experimental laboratory systems designed to confirm the association of the target with the disease (Kumar & Gopinath, 2013) Step 1 of drug discovery is Target to Hit, the first section in Figure 2. Hits are molecules that meet the basic requirements to potentially treat the disease, such as chemically reacting to the target in favorable ways. The second step is Lead Identification, the second section in Figure 2. This stage consists of taking a wide array of potential treatment molecules or "Hit□" and putting them through repeated tests to narrow down the number of potential molecules. For example, finding the molecules that bind most strongly to the target. Step 3 is Lead Optimization, the third section in the above figure. This involves iteratively engineering the molecules to improve their properties, most often potency in models of the disease. At the end of these three stages, a drug candidate is selected. This is the best molecules to potentially treat the disease. This is also done through iterative testing, some of which is done in animal models of the disease. After a candidate is selected, Preclinical trails can begin. (Kumar & Gopinath, 2013) There are multiple approaches to developing molecular entities, from small-molecule or medicinal chemistry to large molecules. . Certain methods are more suitable for certain target types than others. (Hughes, Rees, Kalindjian, & Philpott, 2011)

Drug development as a whole is significantly impacted by the cla□□c trade off of doing thing□ the 'right' way or doing things as quickly as possible. The drug development industry is highly motivated to shorten drug development times, and much emphasis is placed on being the first treatment to market. Additionally, it is impossible to determine if a potential drug will be a successful treatment until the completion of human trials. A molecule that successfully treats a disease in a laboratory setting and in animal models can easily experience complications when used in humans that make it non-viable.

Success in the lab and animal models increases the probability that a potential drug will be successful in humans, but does not guarantee it. Consequently, some companies evaluate success based on the number of molecules that proceed from one step to the next, rather than level of success from tests performed within that step. (Paul, et al., 2010) For example, say that a molecule that reaches the end of drug development has a 50% chance of successfully working in humans. Producing more molecules results in a higher chance that a treatment will be successful in clinical trials. With a 50% success rate for each individual molecule, 3 molecules would have an 88% chance of producing a viable drug. As a result, some individuals within the industry view quantity as a more significant factor in eventual success in human trials than tests in animal models and laboratory settings. It is therefore common to use time and quantity of molecules as metrics of successes within the industry. It is important to note that quality estimations provided by testing are still important; increasing the number of molecules to 3 while decreasing the individual molecule success chance could negatively impact overall success rates. If individual molecule success is reduced to 25% due to decreasing testing times negatively impacting quality of tests, having three molecules would only return a 58% success rate. In order to achieve an 87% success rate, 7 molecules would be needed. Thus, developing methods to improve molecule quantity and development times without affecting the quality analysis provided through testing is extremely important.

Antibody Drug Development

One approach is development of biotherapeutic molecules, which is APEG's specialization. One of the most common biotherapeutic molecules is immune-system-produced antibodies. Antibodies are thought to be less toxic than chemically synthesized small molecules, but due to their relatively large size and the resulting inability to penetrate cells, they are typically used to modulate the activity of cell surface and secreted disease associated targets. In other words, issues that can be treated from outside a cell. (Hughes, Rees, Kalindjian, & Philpott, 2011) There are two primary methods currently in use for antibody discovery. The first, In-Vivo, relies on targeted immune system reaction. An animal analog, typically a mouse, is injected with the target molecule. Once the animal's immune system reacts appropriately to the target, it is culled and its antibody repertoire extracted. Subsequently, the repertoire of molecules tested and lead molecules selected. It is important to note that this process produces non-human molecules, which must then be "humanized" to yield a biotherapeutic drug for use in humans. (Nelson, 2000) The other method, In-Vitro, does not involve any animals. Instead, they begin with a naive[2], pre-built, human-based library of tens of millions of antibody molecules. These molecules are run through a series of tests, each test reducing the number of potential molecules. Eventually, these tests determine the lead molecules. (Stowell & Dzik, 2003) In-vivo and In-vitro methods are compared in Figure 3. Lead Optimization for these two methods follows essentially the same process once the in-vivo molecules have been humanized.

[2] Naive in this case means the humans who donated antibodies to the library who have not been specifically exposed to the target protein

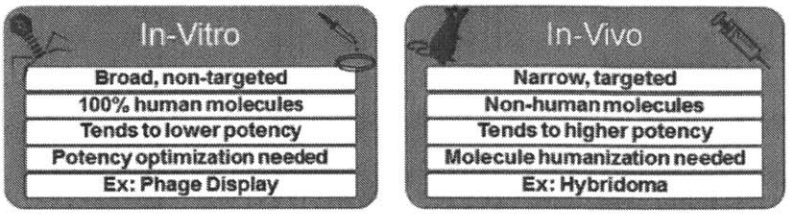


Figure 3: Advantages and Disadvantages of In-Vitro (Nelson, 2000) and In-Vivo (Stowell & Dzik, 2003) Drug Development

APEG and Graybel operate within a complex, changing market that requires carefully balancing adaptability, cost and long lead times. Graybel has many different potential methods of developing drugs; Biotherapeutic antibodies are APEG'□niche within the organi□ation. Antibodies, in general, have two methods of development- In Vivo and In-Vitro, each with its own unique benefits and challenges. APEG is responsible for both of these, as well as optimization of its molecules.

Chapter 2: Process Analysis Challenges

When trying to improve its processes, APEG faces a variety of challenges. Their process is highly complex, with steps connecting through a complex web of decisions. This makes it difficult to separate the inherent variability of drug discovery from the artificial variability introduced by APEG's process. There is currently minimal workflow tracking, and varying understanding of APEG's process at different levels of the organization. Balancing the competing objectives of quality, time and customization is increasingly difficult. Accountability and ownership by groups with different motivations leads to inconsistent direction and mixed signals. Emergent automation has the potential to be revolutionary, but is difficult to evaluate and implement. Recent management changes and restructurings have resulted in some very new groups who are not yet fully accustomed to their roles.

Complex, Interconnected Process

APEG's molecule development is a complex, highly interconnected process. A deceptively simple map of APEG's overall process can be found in Appendix A.0, where it is discussed in detail, and is reproduced below in Figure 4.

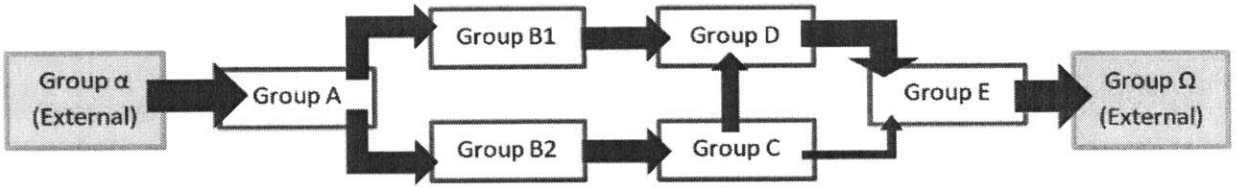


Figure 4: High-Level Overview of APEGs Process

The general process flow is as follows:

1. An external group (Group α) initializes a project
2. Group A begins the project
3. Group B1 or B2 (or, in rare cases, both B groups) then take over
4. Any work done by Group B2 proceeds to Group C
5. Any work done by Group B1 and some (estimated at 70%) of Group C's work proceeds to Group D
6. All work done in Group D and the remaining work at Group C proceed to Group E
7. Work done within Group E is passed to an the external group responsible for the next stages in the development process (Group Ω)

However, the process is much more complex in practice. Each substep within a group may fail, and some of those failures will send the project back to a previous group instead of simple internal backtracking. For example, it is possible, though somewhat unlikely, for something to fail in Group E and send the project all the way back to Group A. Moreover, a project could progress down the B1 path, fail, and then be sent to B2. Additionally, while throughout this paper a project will be referred to as a singular entity, in reality a project may be comprised of a number (between 1-10,000 depending on project stage) of

individual molecules, each of which may occupy a certain stage, and only some of which may fail a given step. In other words, a project may have molecules with Groups C, D and E at the same time, or virtually any other combination. In addition to this, Group A occupies a specific niche within the organization which makes it particularly mission critical. It may be called on at any time to assist any other group[3], in addition to its own work. Thus, delays in Group A can affect projects at any stage.

Additionally, APEG is responsible for a portfolio of projects and a percentage of projects are canceled each year. This can occur for many different reasons, among which are: (i) upper management strategic decisions; (ii) the project being deemed non-viable due to new scientific knowledge; and (iii) project success through a different discovery platform in another group (such as small molecules). These projects are replaced with new projects, so the total number of projects is fairly consistent.

Appendix A Sections 1-6 gives detailed (though still simplified) process maps for each group, as well as a description of the group itself and how it interacts with the rest of the organization.

Overall Process Understanding

In addition to these intricacies, presently there is no uniform, comprehensive and robust tracking system capturing the breadth of activates in place at APEG. A subset of groups have primitive databases to capture project workflows, tasks, and applied employee resources. In contrast, other groups do not directly capture and track specific tasks in their workflow; instead, tasks and time spent per task can only be inferred from high-level employee logs. These logs capture the relative amount of time devoted to any given project by person, and knowledge of which tasks a group or individual preforms can then be used to approximate amount of time spent on each project task for each person. This methodology is, however, inconsistent at best, unreliable, and analysis is time consuming.

Fortunately, APEG is composed of intelligent, highly experienced scientists. As a result, most groups have very good tribal knowledge of their own processes, and the majority of managers have informally analyzed their group's processes in some way in the last 3 years. There is a wealth of anecdotal information available. Unfortunately, anecdotal evidence has a few well-documented issues. Generally, it is considered the least reliable type of information. (Riffenburgh, 1999) Some believe that it is nearly useless, due to the effects of potential bias, assumed causal links, and other idiosyncrasies of the person providing the anecdote. (Sicherer, 1999) To counteract the inherent unreliability of anecdotal evidence, information for this thesis was gathered from a wide variety of people at all levels within each group.

In addition, Groups A and E track workflow internally within Excel spreadsheets or databases. Unsurprisingly, these groups also had the most rigorous process understanding and the most time-sensitive tasks. Details on data available by group can be found in Appendix A.

Difficulty Determining Metrics for Success

In addition to data-based challenges, APEG's culture also presents complications. APEG personnel are highly intelligent, independent scientists who through their early academic scientific training are taught to find individual solutions to problems. As a result, they prefer and more easily implement changes to

[3] What it is responsible for when this occurs is consistent, but essential and cannot be done by another group

process or methodology that are developed based on concrete data, experimentation or developed themselves. Long project lead times, expensive projects and project attrition make piloting and experimenting with process changes extremely difficult. The lack of process data has already been discussed. This situation makes it difficult for personnel to support changes without empirically grounded, scientific data that endorses said proposed changes- which often cannot be obtained.

As previously discussed, Graybel follows industry standard and evaluates success based on the molecule quantity rather than test-based success levels. This method is reasonable for large milestones such as hit or candidate selection, but is much more difficult to apply to less significant steps. Consequently, there is some debate concerning the best method for evaluating these steps; quantity is certainly part of it, as there must be enough molecules for the selection milestones, but some additional evaluation metrics, mostly test dependent, have been proposed. The lack of workflow data that makes it difficult to evaluate proposed process changes also makes it difficult to determine which of these metrics is significant.

Accountability, Ownership and Competing Objectives

Another aspect of APEG and Graybel's culture that impacts potential process improvements is the overall attitude towards accountability and ownership. Any project within APEG has a project lead who is responsible for the project within APEG and coordinates with the project owner, Group α[4], represented by a Group α project leader. Group α may not be collocated with APEG, and may not be knowledgeable regarding the intricacies of APEG's work. The Group α Project leader, the APEG project leader, and both Group α and APEG management are responsible for all decisions made concerning their project. In terms of responsibility Group α is roughly analogous to a district manager, the project lead to a store manager and the various APEG subgroups departments within the store. This dynamic affects project process decisions in two significant ways: the implications of successful/unsuccessful projects and balancing the use of standard operating procedures (SOPs) and innovation. Traditionally, SOPs are used to define a set series of steps that take an expected input and produce an expected outcome. Within APEG, SOPs typically exist at the bench level. For example, a specific test type may have a multi-step SOP that is used to determine if the molecules tested are toxic to mice. An SOP at this level generally has an expected duration. SOPs may also exist at higher levels; an example of this is a series of tests and other steps that must be performed to ensure that a potential drug is potent enough. These higher-level SOPs within APEG are generally not codified, and are only semi-standard. These SOPs typically do not have an expected duration-there is simply too much variation in delivery times.

In drug development, project attrition is common. As a result, risk mitigation is considered very important to improve the chance of success, and a successful project that actually makes it to market (successfully passing all clinical trials and the FDA) is highly valued by Graybel, Group α and the project leaders. Hence, project leaders and Group α strive to have a high rate of success and be fast to market. In addition, Group α strives to have as innovative a treatment as possible—developing a

[4] Group α refers to the external group who owns a given project. Group α for project 1 may be different from project 2's Group α, etc.

transformational treatment for a disease will both benefit the patients, Graybel and likely benefit the career of the project

In comparison, APEG's subgroups desire to provide molecules that are of the highest possible quality, with reducing delivery[5] times a close second priority. The subgroups are motivated to have a high portion of all projects succeed, but are not vested in the success of specific projects. In order to reduce production times, APEG prefers to use bench-level SOPs—which also, as previously mentioned, mitigates potential problems and ensures a semi-standard quality level. Which SOP is used is a function of the target, project requirements and what stage within APEG the project is at. However, as each project's goal is to develop molecules for a unique target, some target-dependent customization is always required. Also, the innovative molecules desired by Group α often cannot be generated with SOPs and require extensively specialized molecules and tests. This is typically due to unusual or unique molecules or extreme project requirements. Some of these innovative molecules are common enough to have their own somewhat less developed SOPs, but many of them require fully customized methodologies. This high level of process customization has led to a general perception that APEG does not have SOPs in the traditional sense, because every molecule is different.

The ongoing conflict created by these competing priorities—quality, customization and speed, results in mixed messages from bench workers when the concept of process improvements is raised. Frequent responses were "we could improve the speed, but then we won't be able to customize" or "if we reduce customization, quality will be negatively impacted" or even, occasionally, "improving quality will extend delivery times". The consensus seems to be improving in one respect will be detrimental to another and upset the careful balance that APEG currently maintains. The impact of altering the current situation maintained with these tradeoffs is unknown, and generally theorized by bench workers to be detrimental. This is a trade-off between quality, time and customization is a specialized form of the project management triangle, which illustrates the relationships between scope, schedule and cost. Typically, only two of these three objectives can be achieved at one time (McGhee & McAliney, 2007). APEG prefers to focus on quality and speed, while Group α focuses on speed and customization.

Emergent Automation

Emergent technology has the potential to have a huge impact on APEG's process. In fact, a recent process change that introduced automation, an improved process and a new subgroup has reduced the production of test articles by 2-4 weeks. As this is done a minimum of 4 times per project, it has had a very significant impact. This change had three reasons that it was successfully implemented:

1. Group E, who was responsible for this process before it was automated, was unaffected by the respective change during the development and implementation phase. If something went wrong, they could resume ownership with little effort. The process is currently owned by the new Subgroup G.

[5] Delivery times may refer to the time it takes to deliver from one internal APEG group to the next or the total time it takes to deliver a project to Group Ω. The two meanings are somewhat interchangeable; change in the former guarantees change of the latter.

2. The change has very clear time benefits, and impacted early stages where any minor reduction in the quality of the test article produced is less critical.
3. The process is not something that is significantly impacted by customization. Customization, if needed, is done before the process starts. The process itself is consistent for each molecule.

This is not true of all potential process automations. Automation is expensive, and implementation can be risky. It is not uncommon for an automation machine to be bought and then not fully utilized, due to unforeseen issues making it unfeasible to fully implement. These issues include but are not limited to:

- Complex set ups or changeovers that take more time than is saved with the automation
- New changeover bottlenecks, where only one or two people are certified to implement customized process on the machine
- Machine down time, particularly for machines that do not have a backup
- Inability of post-automation steps to handle the increased workflow
- Personal preference

Compounding this issue is APEG's lack of an internal process development team devoted to implementing automation across the department. If automation (or any other process change) is being considered, it becomes the responsibility of an individual scientist, or small team, to investigate the possibility while maintaining their project load. Consequently, the level of investigation and experience of those evaluating automation is very variable; it is entirely possible that this has resulted in potentially successful changes being rejected. As a result, one of the biggest challenges facing APEG is whether or not to automate, and how to determine which process steps would benefit most from automation

Management Changes & Staff Restructuring

In addition to all of the above, APEG has recently undergone some organizational changes. The goal of these changes was to better align to core functionalities, but groups are currently experience typical "transitional" challenges. Group B2 and Group C used to be one group; they were split in the last year. Group B2's manager was also hired within this timeframe. Another subgroup, Group F, who primarily provides technical support for the other groups, used to be two groups and was fused within the same timeframe. As a result, both of these groups currently have processes that are in flux. Group B2 is somewhat stable, and will be analyzed in this report. Group F, on the other hand, will not. This is partially due to the recent changes made, and also due to the nature of Group F's work and the small size of the group. These changes are summarized in Figure 5, where each box represents a functional group within APEG, and the labels indicate the processes and group members[6] who are members of that functional group.

[6] Processes and those who preform them are inherently linked due to the expert knowledge needed to perform such tasks.

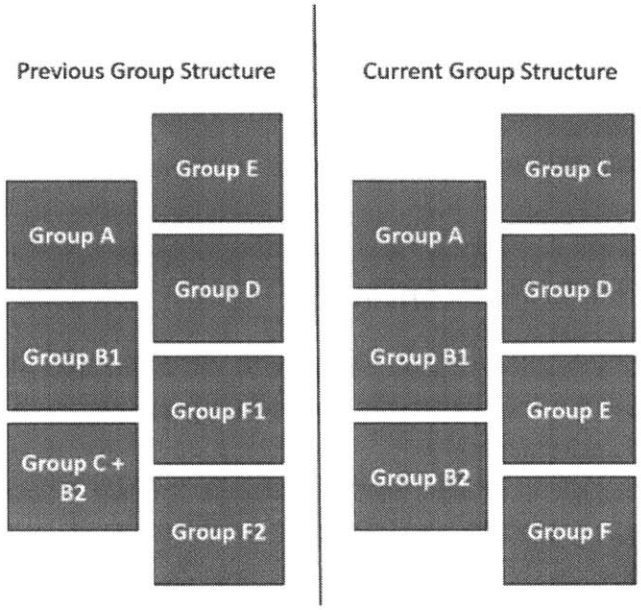


Figure 5: Organizational Changes in the Last Year

These challenges make it particularly difficult for APEG to implement process changes. It is very difficult to change complex processes without thorough workflow tracking data. Adding in the other complexities- competing objectives, management and staff changes, and the potential of automation to revolutionize everything- makes a difficult task seem nearly impossible. There are, however, ways to simplify and compartmentalize this process into something far less daunting.

Chapter 3: Solution Approach Methodology

The first step to analyzing a process is, of course, understanding the process. There is no better way to do this than through process mapping. Process mapping breaks a process down into discrete steps that can be understood as a series of interconnected units, rather than as a tangled web. Once the process is understood, one can begin to look for ways to improve the process. In processes with a fast turnaround time and low cost, this is typically done through piloting. Drug discovery, unfortunately, fits neither of these criteria. Instead, simulation was utilized. This provides a re-useable tool that can be used to evaluate the overall process and implement potential changes with little to no cost.

Process Mapping

One of APEG's weaknesses is the fragmented understanding, particularly at the bench level, of exactly what their end-to-end process entails, and the very specific responsibilities, workflows and tasks for each subgroup. A given bench worker is extremely knowledgeable about their own process and fairly knowledgeable about their group members', but may not have the same understanding of other groups' processes. As one progresses higher up the management chain, there is a progressively greater understanding of the overall process and at the same time a loss of detailed understanding of the complexities of each task involved. Lack of quantifiable data at the task level for each subgroup hinders the ability to address issues related to process improvements. No one person has complete, detailed knowledge for all processes in the department process, and there is no workflow management database to reference to facilitate the gathering of the relevant knowledge. Process mapping is an excellent tool with a long history of use in this sort of situation, as it is useful analytically and for communicating the current understanding of a process to group members. This is particularly significant as, historically, processes are the least understood and managed part of an organization. Additionally, the process of creating the map, independent of outcome, is extremely educational. In order to accurately map a process one must clearly understand the resource requirements, linkages and relationships of all process steps (Hunt, pp. 2-5).

Process mapping is primarily utilized for documenting, understanding and teaching processes, but it is also useful for change implementation, as it provides a holistic view of the interconnected process steps. In essence, a process map creates a shared understanding that can then be used to alter an existing process to better suit the organization and its needs. This is true both within the organization and externally with the organization's client. Often, potential process improvements become obvious as a map is developed. (Kesari, Chang, & Seddon, 2003) In general, there are four steps necessary to create a process map, shown in Figure 6. These four steps assume that the scope of the map has already been

determined.

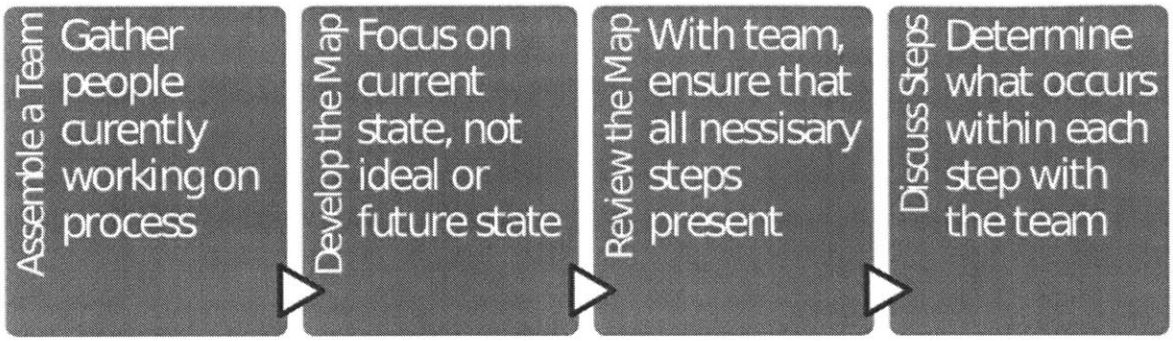


Figure 6: Steps to building a process map
(Graham, p. 150)

Graham recommends that process mapping begin with obtaining buy-in from management, which will greatly facilitate data-gathering. Once buy-in is obtained, the next step is to gather data. Ideally, this will first be done through observing individuals at work. When this is not possible, he recommends using recent data. Typically, this is not possible due to long process times or physical distance between process steps. The next step in data-gathering is to interview experienced workers, as they will have the best understanding of the process. This is essentially the Assemble a Team step in Figure 6. When doing this, it is important to focus on what is occurring at each step, not how it is being done. The attitude of the interviewer is extremely important; in this situation, it is easy for the interviewee to become defensive. It is important that the interviewer be genuine, good natured and focused on fact-finding (Graham, pp. 23-29). Once the data is gathered, it is time to Develop the Map. There are many different methods for doing this; all of them are acceptable. It is important that the map be both understandable and readable to the average layperson. Once the map is built, group members should Review the Map for accuracy and potential improvements. After the map is understood, the team should Discuss Steps to determine if more detail is needed or there are potential improvements (Graham, p. 183).

Madison recommends a similar approach. He also purports that obtaining buy in early is extremely important, and recommends involving people who work within the process both for obtaining buy-in and data gathering. He recognizes three levels of process mapping-macro, functional-activity and task-procedure. Macro charts are the highest level, and generally fairly easy to map. Functional-Activity charts are mid-level, and composed of general functions and activities as the name suggests. The most detailed level is task-procedure, and focuses on the minutia of a single step. Typically, these are used for training rather than analysis (Madison, 2005).

One common pitfall of mapping a process is over-specification of modeling; it is not necessary to fully model every step. While extensive knowledge of the process is recommended to build the map, the map itself must be carefully designed to ensure the optimal level of abstraction necessary to the process. (Kesari, Chang, & Seddon, 2003)

Due to the current situation within APEG, mapping their current process provides an additional benefit. As previously stated, APEG per□onnel generally believe that they don't have SOP□. In the words of

Steven Spear "[Proce[] Map[] and []milar tool[] are about execution of []tandard work… [they] give you a chance to innovate in a controlled manner, []o you won't introduce additional ri[]k into the product." Building process maps for APEG requires abstraction to the point that the customization done within APEG is mostly hidden behind 'black boxes'. In other words, the project based customization is at the Task-Procedure level, but generally does not impact the Functional-Activity or Macro levels. The contents on the 'black box' in thi[] ca[]e are unknown because of inherent variation at the bench-level in the process causing changes and adaptations in a wide variety of cases. For any given project, the content[] of the 'black boxe[]' are known. It i[] when trying to account for all project[], each with their own unique 'black box' content, that it become[] nece[]]ary to ob[]cure the exact detail[] for clarity'[]]ake. In other word[], a []tep may be []mply to "run te[]t[]." The specific tests run and the order that they are run in changes for every project and often cannot be predicted in advance. However, at this point in the process, some tests must be run. The bench work for this step is non-standard, but by taking a step back to the Functional-Activity level it is possible to find a standard step in a standard process. As a result, developing APEG process maps codifies APEG'[] high-level SOPs.

Modeling

One of the largest issues facing APEG is the combination of complex and diverse processes that they are responsible for executing. " The more different di[]cipline[] and []pecialtie[] that are involved, the harder it becomes to determine a priori exactly who []hould do what, when.. It i[]al[]o difficult, if not downright impo[]]ble, to predict the []y[]tem'[] behavior under the range of circumstances in which it must perform." (Spear, p. 105) This is one reason that piloting of changes is so common; another is to obtain buy-in from those who doubt that the potential improvement will be truly beneficial. (Hunt, p. 31) However, APEG has a high entry cost for piloting. If a pilot proves detrimental, it could have a huge negative impact on the projects it affects. As a result, APEG upper management must be certain that this will not happen before approving a pilot.

A viable alternative to piloting is simulation. Simulation data can be used to test and validate process changes at low cost. Additionally, the resulting data can be compared to current process data to determine the expected impact of the change; a proposed alteration may be rejected if it is successful but not successful enough to justify the cost. The resulting data can be both useful in determining the correct course of action and is potentially persuasive for those in doubt. (Detty & Yingling, 2000) Using simulations to aid in decision making reduces risk and assists strategic, tactical and operational management strategies. (Kellner, Madachy, & Raffo, 1999) The resulting quantitative data can also be used to develop metrics and associated goals to monitor implementation success. (Abdulmalek & Rajgopal, 2007) Additionally, simulation allows for the testing of a wide variety of hypotheses in a short period of time; this makes it much more likely that the optimal solution will be found. Simulation is so powerful precisely because of this flexibility. A wide variety of scenarios can be tested and analyzed in way that facilitates comparison between disparate strategies and the risk associated with implementation. (Alsudairi, 2015)

Kellner, Madachy and Raffo determined six primary reasons to utilize process simulation: strategic management, planning, control/ operational management, process improvement/technology adoption,

understanding, and training and learning (Kellner, Madachy, & Raffo, 1999). While all of these reasons are significant for APEG, the most important are processes improvement/ technology adoption and understanding at this point in time. Once better workflow tracking is implemented, strategic management, planning and control/operational management will become more significant. Due to APEGs highly individualistic methods, it is unlikely that training and learning would be emphasized.

Simulation is generally used to address three types of complexity (see Figure 7) which make use of analytical models difficult or impossible. APEG in particular possess complexity types 1 and 3 in abundance.

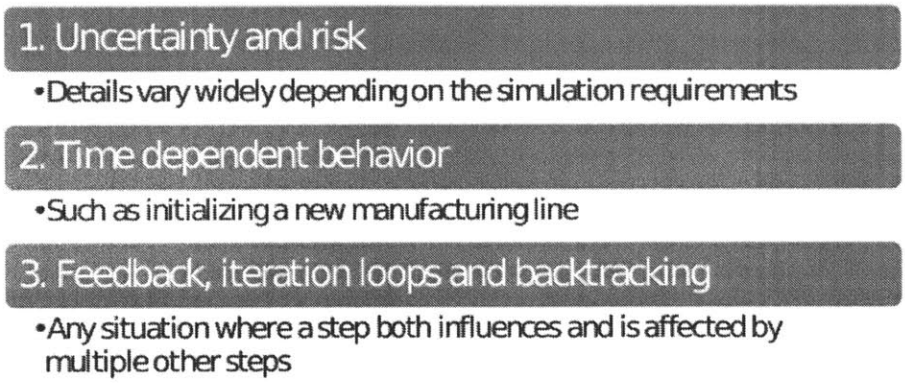


Figure 7: Motivational complexity types for simulation
(Kellner, Madachy, & Raffo, 1999)

There are, of course, downsides to process modeling. The most common is over analysis. It is not uncommon to build a model with data that is somewhat unreliable; in-depth analysis of the results is then somewhat useless. (Kesari, Chang, & Seddon, 2003) It is similar to the concept of significant figures, where one cannot assume greater accuracy in the results of calculation than was achieved when the contributing measurements were taken. As most data gathered for APEG is anecdotal, this is something that can potentially have a huge impact upon the reliability of the results.

When building a simulation, the first and most important step is to carefully determine the purpose of the model, what questions it should answer and what questions it is actually capable of answering[7]. It is particularly important to identify important processes and how they relate to each other. Key tasks, significant units, resources, workflows, iteration loops/backtracking/feedback and other interdependencies must be identified and accounted for. (Kellner, Madachy, & Raffo, 1999) A complete explanation of simulation development can be found in Figure 8.

[7] This may be affected by model type, modeling software, data reliability and availability and a host of other potential complications

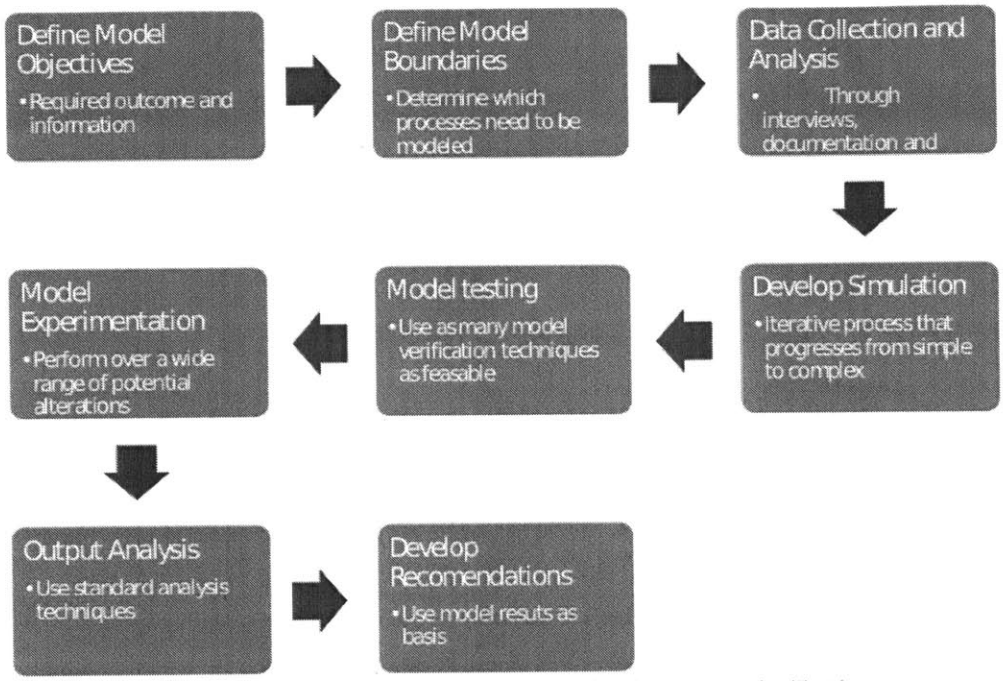


Figure 8: The stages of simulation development and utilization
(Hlupic & Robinson, 1998)

Once a simulation is 'complete' it must validated as much as possible. This can be done through model inspection and reviews, but data comparison is preferred where available. The model should also be calibrated to match real world expectations as much as possible. This calibration process often suggests metrics that would provide valuable real world data, in addition to improving the model itself. When the data to do this does not exist, there are a few potential strategies:

- Approximate conversion where data exists that is not quite the needed data
- Piece together data from other sources to create an entire picture
- Obtain estimates from personnel involved based on experience or expectations
- Use industry data from literature to approximate current situation
  (Kellner, Madachy, & Raffo, 1999)

One of the major roadblocks for process improvement within an organization is often the lack of accessible tools for pre-implementation evaluation of proposed solutions. Simulation is one such tool. It is useful for both understanding the problem and trialing competing potential remedies. Its inherent flexibility makes it ideal for analysis of APEG's processes. (Hlupic & Robinson, 1998)

Process mapping and simulation are powerful tools when used in the right situations. APEG's complex, expensive process is nearly ideal. Both of these methods are low cost and can be implemented fairly reliably even if there is no empirical process data. Both methods can reveal problems hidden by the complexity of their process, and both are re-useable with minor changes as the process is altered.

Chapter 4: Complexity Framework Development

Once one begin[examining APEG'[proce[[it become[clear that they [truggle with a variety of complexities, many of which have never been codified. In order to evaluate and understand these complexitie[and their effect[on APEG'[proce[[e[a framework wa[developed. Thi[framework'[primary uses are to aid in communication, facilitate [mulation development and improve APEG'[understanding of their own capacity.

Types of Complexity at APEG

Through discussions with APEG personnel, it became clear quickly that there was no standard method for evaluating project difficulty. In general, a project was described as easy, medium or hard difficulty, but each group defined 'difficulty' differently. Exten[ve di[cu[[on with bench worker[, management and executives revealed that an individual project had 3 specific inherent characteristics –disease complexity, solution complexity and solution platform complexity–that affected its difficulty level and thus impacted step duration and decisions. Each project possessed these characteristics, and each characteristic could be ranked from easy to hard in difficulty. It is important to note that these characteristics may only be fully understood after project completion; however, they affect the entire process path, and can be estimated fairly reliably early on.

The differenced in defining 'difficulty' between group[were a direct re[ult of group[having differing dependencies upon these characteristics. For example, Group A, as a result of its position as earliest step in the APEG process, is heavily dependent upon characteristics of the targeted disease. At this stage, lack of knowledge of the target can have huge impact on process times; for a difficult target, extensive research and experimentation must be conducted before the project has progressed enough to pass to Group B1 or Group B2. Group E, on the other hand, is almost entirely independent of disease difficulty. As the last step in the process, by the time a project reaches them the disease is well understood, and resulting difficulties have been overcome. They are, however, highly impacted by solution and solution platform difficulty. The other Groups fall between these extremes; Groups B1 and B2 are dependent on all three, with disease being more prominent early on, and solution platform difficulty dominating latter steps. Groups C and D are both minimally dependent upon disease difficulty. Group C is equally dependent on solution and solution platform difficulty, while Group D is slightly more dependent on solution difficulty. Group E, as discussed, is virtually independent of disease difficulty.

Purpose of Framework

Within APEG it[elf, the[e nuance[of 'difficulty' were under[tood intuitively between group[but not overtly recognized. As a result, no major misunderstanding had resulted from miscommunication. However, each project is overseen by an external group, Group α. Group α doe[not have thi[intuitive understanding, and it is often difficult to communicate the difficulties of a project to them. Additionally, APEG sometimes has difficulties evaluating its project load. In general, APEG has a number of projects, for example 30, and can e[timate each project'[general 'difficulty' to determine a qualitative project load. However, a[previou[y di[cu[[ed, 'difficulty' can have a plethora of meaning[within APEG, and communicating these nuances is difficult. It became clear that APEG would greatly benefit from a

defined difficulty framework dedicated to clearly communicating the difficulty of different characteristics and providing a way to asses overall difficulty quantitatively.

There are three potential applications for such a framework.

1. Facilitating both internal and external communication. Communicating the difficulties inherent in a complex, technical process to outsiders can be extremely difficult. Having a defined method for evaluating and communicating these difficulties will allow more precise communication between APEG's internal group and the external Group α.
2. Internal Evaluation of APEG's project load. Given its current situation, APEG has a very good idea of its overall project load and capabilities. However, an easily updated, quantifiable metric for evaluating project load would allow APEG to set capacity metrics, either overall or by difficulty type.
3. APEG's delivery timelines are heavily dependent on project difficulty, for two reasons. First, a more difficult project may have biological complexity that results in cell replication, protein generation or testing taking longer than for a similar project. Second, a more difficult project is more likely to fail tests and cycle through the process multiple times before a satisfactory solution is reached. Having a nuanced understanding of project difficulties and their effects on the projects path through APEG is essential to accurately predicting project timelines. As a result, this framework is a necessary prerequisite to simulation.

Framework Development

To address this complexity, the Technology Readiness Levels (TRLs) APEG framework was developed. The framework is three dimensional, possessing three characteristics-based axes. These axes are the aforementioned characteristics of disease, solution and solution platform. These complexity characteristics are quantified by numerical Technology Readiness Levels (TRLs) of Easy (1), Medium (2) and Hard (3). Increasing difficulty corresponds to increasing value to allow for the adoption of higher numbers as new technologies or diseases become accessible. See Figure 9 for more information.

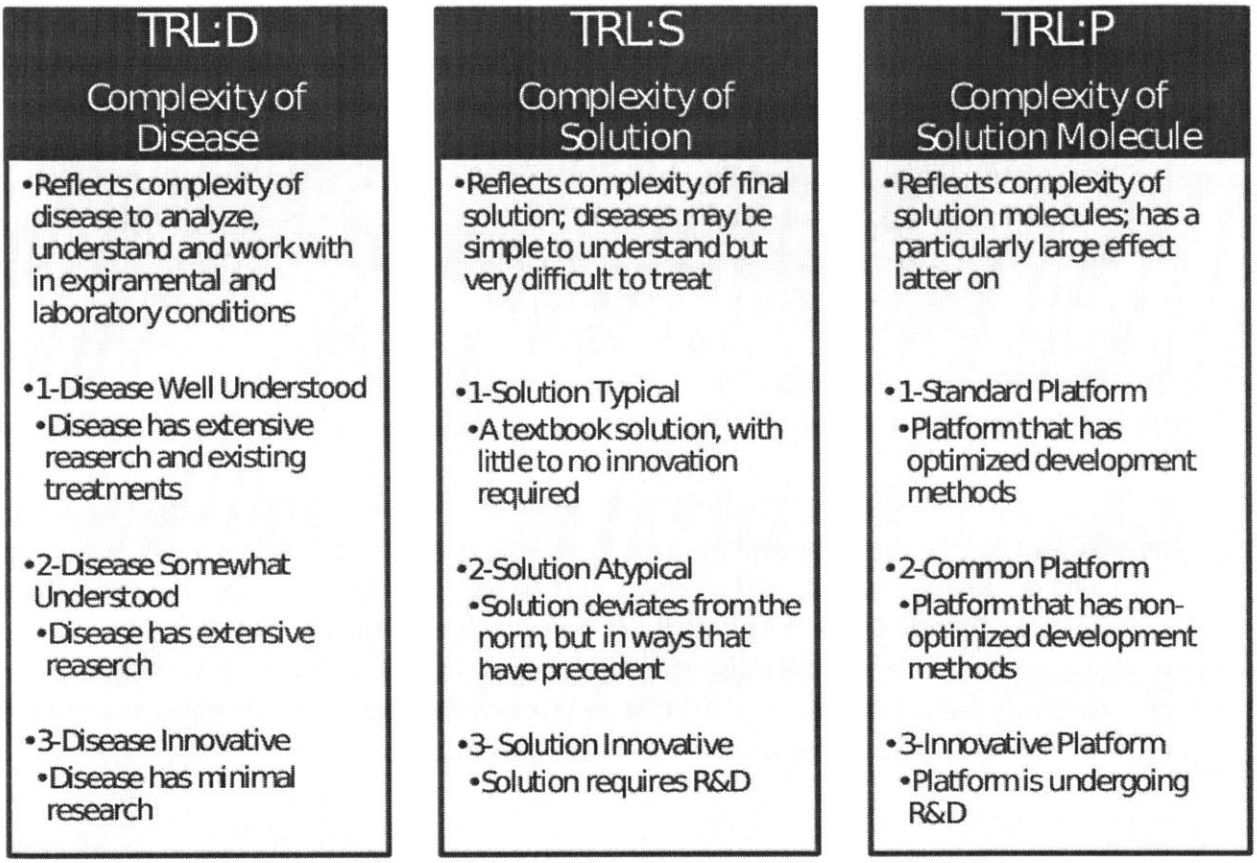


Figure 9: TRL Types and Ranking

These three axes can be summed to obtain the overall project difficulty, a value from 3-9. A hard project would have an overall value of 8-9, or at least two hard axes. Similarly, an easy project would have a value from 3-4, or at least two easy axes values. A medium difficulty project includes the remaining value of 5-7. This allows for both general, overall comparison of projects and more nuanced, axes based evaluation.

The framework is designed to allow APEG to initially evaluate their projects based off of minimal information, so that the potential impact of a project on APEG's portfolio can be estimated before work begins. As the project moves through APEG's process and more becomes known about it, values can then be adjusted to more accurately reflect the projects actual difficulties. The framework is also designed so that APEG can evaluate a portfolio in a similar manner. The portfolio can easily be evaluated by summing the TRLs of its projects; a portfolio with a total TRL of 100 would be very different from a portfolio of 150. Similarly, a portfolio with aggregate Disease:Solution:Platform values of 50:20:20 would have very different implications than a portfolio with values of 20:50:20. In the former, there would be massive delays early on in the projects, as Disease heavily effects early projects; In particular, Group A would be extremely impacted. In the later, some delays would result in the middle of APEG's process, but they would be milder as the projects would be spread over several groups.

The TRL framework provides APEG with a quantities method for communicating, evaluating and assessing project difficulty. It assess the three axes of Disease, Solution and Solution Platform complexity. From these axes, a nuanced understanding of both individual projects and the overall APEG portfolio can be achieved. This has a multitude of potential uses, including improving communications externally and improving internal capacity planning.

Chapter 5: Solution Development and Results

There were two stages to understanding APEG's processes-exploration and evaluation. Exploration consisted of various methods of data gathering, basic analysis and process mapping. Evaluation resulted in a thorough understanding of APEG's process, motivation, group and culture. Evaluation included in-depth data analysis and model development, validation and assumptions. Evaluation resulted in working simulations and recommendations for APEG to improve its processes.

Process Exploration

Data on APEG's current processes was gathered in three ways: (i) Interviews; (ii) data mining; and (iii) process flow mapping.

Interviews

Due to APEG's lack of a workflow tracking data system, interviews were the primary source of information obtained. Interviews were chosen over surveys because of the inherent depth of information available from interviews. (Harrell & Bradley, p. 11) Three levels of management were interviewed; APEG's senior director, the manager of each subgroup and 3-5 members of each subgroup. Each person was interviewed at least twice; most were interviewed three or four times. At the bench level each interview typically lasted 1-1.5 hours. Management interviews were typically around 1.5 hours each. Some interviews took as long as 3 hours. A large number of interviews collected from a large number of people is the best way to ensure data accuracy across a group. (Harrell & Bradley, p. 10)

There are, generally speaking, four potential interview pitfalls: traditional technique based mistakes, the so-called feminist mistake which relates to inherent power imbalances, narrative mistakes which rely on the interviewee to determine the significance of various bits of knowledge and accompanying biases, and clinical mistakes, where people are reduced to simple numbers and extenuating circumstances are not considered. (Hollway & Jefferson, pp. 30-31) Awareness of these potential issues is crucial to determining the best interview approach and interpretation of results.

For APEG's situation, the unstructured, semi-structured and structured interviews were all used. Unstructured interviews have little control over what is discussed, and typically become narrative. Thus, they are highly susceptible to bias and becoming sidetracked. However, they also provide a deep understanding of the situation and build trust between the interviewer and the interviewee. (Harrell & Bradley, p. 26) This trust is very important to obtaining buy-in within a community. Unstructured interviews with a few open ended questions were utilized for the first interview with each individual. This allowed them to put forward what they believed to be most important about their work, their own understanding of that work's processes and built rapport between the interviewer and interviewee. First round interviews within a given APEG group were conducted in close succession, and resulted in an initial draft version of a map of that group's process.

Semi-structured interviews were used for most subsequent interviews. In a semi-structured interview, specific questions are asked but the order is flexible and there is room for adaptation to the conversation. The primary advantage of a semi-structured interview is that it allows for a deep dive into areas of interest, while still allowing for the investigation of unknown areas. Typically, semi-structured interviews allow for the deepest understanding. (Harrell & Bradley, p. 27) These interviews were conducted using the in-development process map as a guide, and resulted in many changes to said map. At the conclusion of these interviews for each group, a finalized process map was developed. Semi-structured interviews were also used for simulation evaluation at the completion of each simulation.

Structured interviews consist of fixed questions asked in a fixed order, and were used for post-process map interviews. These interviews were generally in search of quantitative data such as timelines or step capacity. Structured interviews excel at generating data that can be generalized, particularly when conducted over a large group. (Harrell & Bradley, p. 28)

Data Gathering and Analysis

During the interview process, interviewees were all asked about workflow recordkeeping focused upon time and effort per project within their group. Most groups did not keep formal records for specifically tracking time required for tasks. Some individuals kept informal records, but these often only tracked the past few months' worth of work and were inadequate to capture a process that may extend beyond the interval when effort was tracked. However, two groups - Group A and Group E- both had extensive workflow tracking.

Information on data gathered from each group can be found in Appendix A.

Process Flow Mapping

Process mapping was done at three levels, roughly corresponding to Madison's levels of Macro, Functional-Activity and Task-Procedure, in order to better understand the process and its significant steps. The three levels were named Executive, Management and Bench as indicators of who is most knowledgeable concerning each level. Explanation of these three levels can be found in Figure 9.

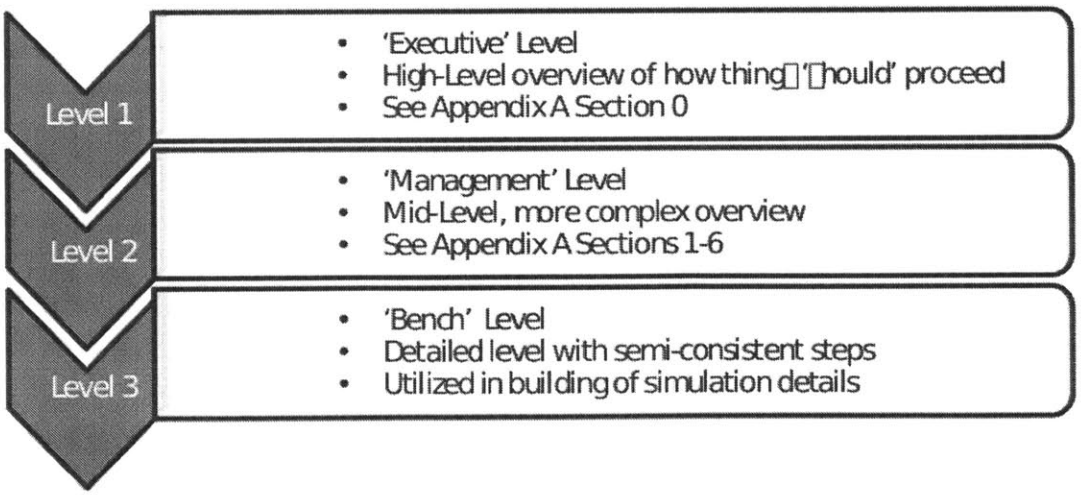


Figure 10: Levels of process maps

These maps were all developed sequentially from 1-3. This allowed for issues concerning APEG's upper management to be explored throughout all lower level and obtained management buy-in early. Each level of process maps had advantages and disadvantages.

The Level 1 process map provides an overall framework for understanding the process as a whole. It is meant to present the view a Graybel Executive would have of APEG's processes. As APEG is organized into functional groups, steps within this process are identified by their group owner. Developing this map was an excellent opportunity to determine upper management's concerns, planned changes and metrics used for evaluating lower levels of the organization. Mapping processes at Level 2 (i.e., Management) revealed many complexities that were hidden at the executive level, while maintaining a level of abstraction that resulted in fairly consistent process steps. This level was intended to reflect the view of the process held by each of APEG's group's top management. It revealed new concerns and planned changes, and gave a very good feel for general management dynamic for each group. Level 3 process mapping revealed complexities glossed over at level 2, many of which were then incorporated into the simulation. This level was meant to reflect the process done by bench scientists which are equivalent to front line workers in other industries. Additionally, it gave a very good feel of the individual culture of each subgroup, which varied widely.

Example Process Map

As an example, Figure 11 shows the process map for Group B1, which is also given in Appendix A 2. The key for process map labeling can be found at the start of Appendix A.

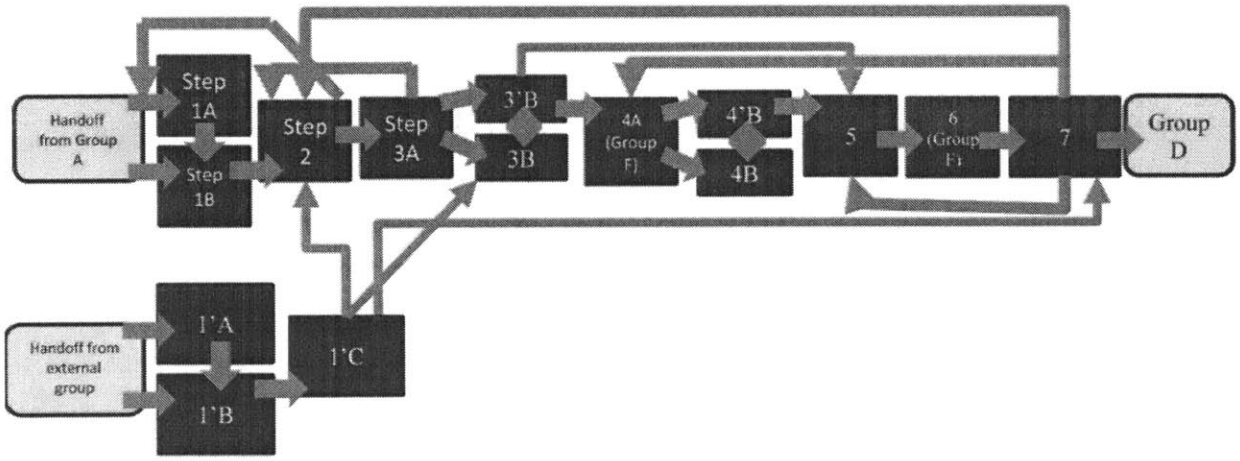


Figure 11: Example B1 Process Map

Group B1 may have projects initiated by two different sources, Group A, an external group or both. The vast majority of the time Group A begins a project and, if used, material from the external group is introduced later. As shown by the arrows, the process is generally linear, but decouples into parallel processes (indicated by ') at steps 1, 3 and 4. Many steps have the potential to backtrack to other steps and there is a chance that Step 4 is skipped entirely. Some steps, such as Step 3, consist of two important contributing steps and is therefore broken into steps A and B. At the end of the process, the project is delivered to Group D.

See Appendix A for more details on each group.

Process Evaluation

Data Analysis

As discussed previously, two types of data were gathered- empirical workflow tracking data and anecdotal.

It became apparent early on during the interviews that many recurring steps were shared across groups. For example, one of the most vital steps in many groups' processes is to run assays; most groups run assays 2-3 times per project, even if there is no backtracking. What these assays are, specifically, differs from project to project. The time to develop these assays differs as well. However, the time needed to run the assays is fairly consistent-generally 1 week, occasionally 2. Many data synergies between groups like this exist, especially between groups that have similar processes such as Groups A and E and Groups B1, B2 and D. Recognizing these similarities allowed for larger samples of anecdotal data, and also allowed some empirical data from Groups A and E to be applied to other groups.

Empirical workflow data from Groups A and E underwent three stages of analysis: (i) curation; (ii) pattern analysis; and (iii) distribution. Curation focused on removing extreme outliers, inaccurate data points and experimental projects outside of the scope of this project. Pattern analysis, both algorithmically and by eye, was used to determine potential process paths that were unlikely. For example, Group E has a total of 8 potential project paths for its lower branch because any step or combination of steps within said group could be skipped. Each project path had a characteristic pattern of missing data entries indicating skipped steps. Algorithms were then used to determine the total number of projects that traveled each path. Analysis of the resulting data determined that only 3 of these paths had a more than 1% chance of occurring. Paths with more than a 1% chance of occurring were considered significant and continued through analysis to simulation. In preparation for use in the simulation, significant data was used to build timeline distributions for all possible steps.

Data gathered was also split along non-source based lines into five groups: path data, timeline data, quantity/capacity data, decision data and personnel data. Path data was often derived from process maps and repeatedly checked with multiple members of each group and management. It is, as a result, fairly reliable. Timeline data was derived from interviews and empirical data and, due to the previously discussed synergies and empirical data, often had cross-group data that increased its reliability. Project quantity and capacity data is, for some groups, very reliable. Groups A, B1, E know very well what their capacities are and typical project quantities, as well as the maximum projects that they are able to work on at a time. Groups D and B2 were able to provide fairly reliable estimates across many members. Group C, on the other hand, is intensely individualistic, and these numbers varied widely from person to person. Decision data[8] could, in some cases, be approximated from the empirical data collected from Groups A and E. In all other cases, it was obtained through iterative interviews with group members,

[8] Decision data, in this case, refers to the outcomes of decisions. For example, if a given decision has 3 possible outcomes, the decision data might be that there is a 20% chance of outcome 1, 30% of outcome 2 and 50% of outcome 3.

followed by a review by management. Through this process, approximate decision values were estimated. These estimations were then simulated to ensure that the results mirrored reality, and adjusted when necessary. Personnel data was obtained by estimating a forty hour work week for each individual in the group or subgroup, and noting the tasks that they were responsible for. General personnel data for each group is noted in Appendix B.

Simulation Development

Simulations were developed to provide APEG the means to preform low-cost exploratory piloting without negatively impacting their existing projects. As such, they were developed with an emphasis on flexibility and adaptability. Potential uses for the simulations include but are not limited to:

1. Projecting the impact of changes in TRL levels of projects. This is particularly useful because APEG's TRL distribution changes over time; one can project expected future TRL levels, observe their impact on processes and then investigate ways to fix potential issues before they develop.
2. Projecting the impact of bench-level processes changes on a given group's delivery times. Higher-level process changes can also be modeled, but require some revision of the simulation.
3. Determining the impact of introduction extra personnel, automation, or other changes that impact capacity or process step duration.
4. Evaluating the implications of alterations of project introductions to process steps, groups or the entirety of APEG. For example, uniform project distribution vs random project introduction, or 20 projects vs 50 projects.
5. Evaluating the impact of having process steps done by external groups.
6. Any combination of any of the above.

Models were built in the Simul8 program. Each group's process was simulated individually, to avoid compounding assumptions. Each simulation has three essential primary components: (i) potential process paths, the simulation version of the process maps; (ii) decision nodes; and (iii) timeline data. Capacity data and personnel data were added where possible and appropriate. For example, Group C's general lack of information made modeling of personnel work-hours unproductive.

Process path modeling closely followed the process maps in Appendix A. Details were added where necessary to ensure model accuracy. For example, Group B1 has a rigorous R&D cycle that is not technically part of their process path; however, it does affect active projects, so the affected steps were modeled in more detail to ensure these effects were included. Each process path begins with the generation of the group's basic unit- i.e., projects, μ's (Group A), ξ's (Group C) or λ's (Group E). These base units flow along the process path, deviating to different branches and backtracking as dictated by decision nodes. When concluded, each project is sorted by project duration.

One of the most beneficial elements of the Simul8 program is the ability to 'tag' each base unit both at generation and as it passes through each step/decision node. These individual project 'tags' can be used in any equation within the simulation, allowing each project to have identifying characteristics. This was heavily utilized in the simulations, particularly in ranking project difficulty with difficulty values from the TRL framework. TRLs are especially important because of their effect on decision node outcomes.

Decision nodes are where decisions within the simulation are made. For example, after a series of tests a decision must be made based upon the outcome of these tests. The decision node following the simulated tests would look at the project characteristics and the potential outcomes and determine what the outcome of these tests would be for each project. Decision nodes are both the most important elements of the simulation, and the most difficult to accurately model. There are three types of decision nodes: Simple, Complex and Compound.

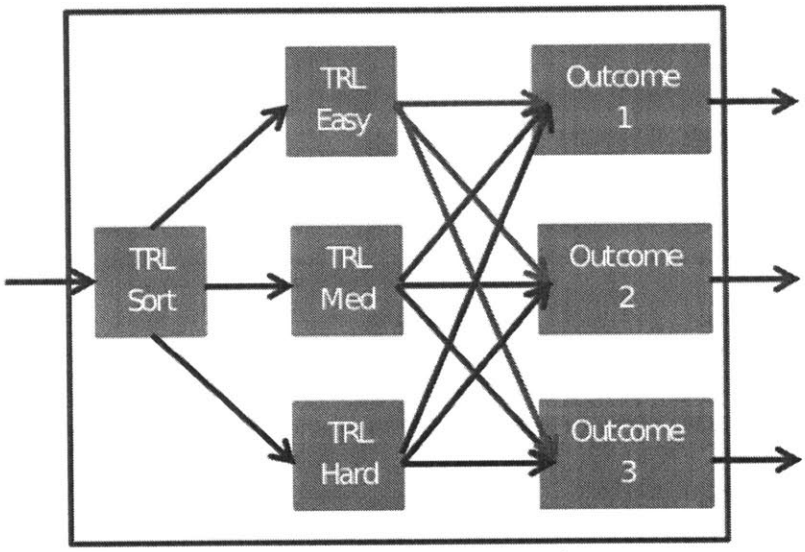


Figure 12: Complex Decision Node

Figure 12 demonstrates the basic layout for a complex decision node. A given decision node may have as many outcomes as it needs. First, a project enters the node. It is then sorted based on its TRL level. Some nodes depend on only one TRL; for these, easy-hard correspond with 1-3 as normal. An example of this would be early testing done by Groups B1 and B2, which is usually focused on testing specific characteristics relating to TRL: S. Some decision nodes depend on two aggregate TRLs, with easy corresponding to 2-3, Med to 4 and Hard to 5-6. For example, mo[]t of Group E'[]proce[][]i[]dependent on only TRL:S and TRL:P. Rarely, a node will depend on all three TRLs, with Easy corresponding to 3-4, Med to 5 -7 and Hard to 8-9. This typically occurs in latter groups, where testing may be dependent upon all three TRLs. Each TRL level may have each potential outcome with some probability. So, for example, TRL: Easy may have a 90% chance for Outcome 1, while TRL: Hard has a 10% chance of the same. Each outcome leads to a different step in the process path. Outcome 1 may proceed along the normal path, Outcome 2 may backtrack a small amount, and Outcome 3 may lead to project cancelation. A simple decision node omits the TRL sortation step; outcomes are semi-random and are only dependent on total percentage of projects to proceed to each potential outcome. These tend to be used for management decisions unrelated to the biology of the disease. Occasionally, simple decision nodes depend upon non-TRL based characteristics tags, such as the number of times that a project has passed through a specific step due to backtracking, which is indicative of total time spent at that step. Compound decision nodes combine complex and simple; they are identical to complex, except that some or all of the outcomes lead to simple decision nodes. Percentages involved in decision nodes were

determined empirically when possible, but the vast majority of the time were determined through a combination of anecdote and trial and error.

Times were calculated in a variety of ways. Where possible, a probability distribution for each 'step' duration was derived from empirical data and included explicitly in the simulation. If this was not possible but empirical data was available, the distribution was approximated through a combination of empirical and anecdotal information. Typically, this was done when empirical data was available for combined steps. For example, if the total time taken for steps 1-3 was known, anecdotal data would be used to fill in the gaps. For steps without empirical data, there were many different ways to approximate a probability distribution. The simplest method was to assume a normal distribution over a range of times. If a step was said to take 2-4 weeks, a normal distribution with $\mu=3$ weeks and $\sigma=0.5$ weeks was assumed. Many steps, particularly assay panels and other tests, had durations that were dependent upon TRL. For example, a TRL: Easy project would take a week, a TRL: Med project two weeks, and a TRL: Hard project three. In these cases, a formula was derived that would give the desired duration. For the above example, if duration was dependent on a single TRL, TRL #*weeks would be used. If it were instead dependent upon two TRLs, two formulas may be used depending upon the situation. If the durations were 'hard' durations—that is, inflexible and consistent with a basic unit of weeks, they would be coded in explicitly. If instead they were 'soft'- in other words, duration correlated to difficulty but not in set units of a week, Total TRL #/2*weeks would be used. Occasionally, these two methods—TRL equation based approximation and normal distribution approximation were combined. This was typically done when something was both heavily dependent upon TRL and had significant variation. For example, if a single TRL dependent step had a TRL: Easy-Med-Hard durations of 2-3-4 weeks on average, ±1 week with a minimum duration of one week, the formula would be 1 week+TRL #*N weeks, where N is a normal distribution of $\mu=1$ weeks and $\sigma=0.5$ weeks. Finally, the occasional step duration was determined experimentally through simulation trials, and then confirmed with APEG members.

Example Simulation

In general, the simulations are too complex to be accurately represented in this document. Figure 13 shows the simulations for Group B1, complete with decision nodes.

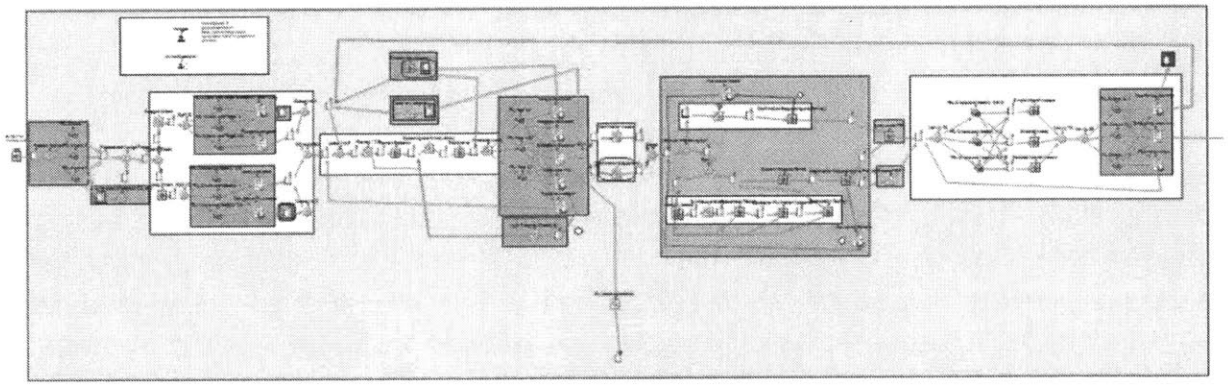


Figure 13: Simulation for Group B1

In order to more clearly discuss simulation results, some of these steps have been grouped together, and backtracking has been omitted in the simulation overviews given in Appendix B. The simulation overview for Group B1 has been reproduced in Figure 14 for comparison to Figure 13.

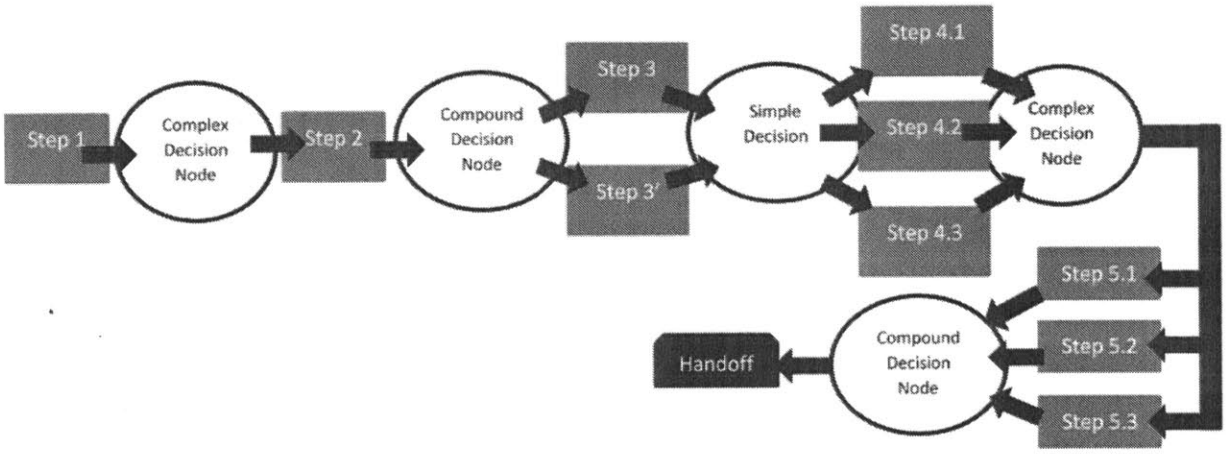


Figure 14: Group B1 Simulation Overview

Model Assumptions

Each simulation began with a few consistent assumptions. The most important of these were the TRL assumptions. Through discussions with management, the current distribution of each TRL was determined to be approximately 65% Hard, 25% Medium and 10% easy. This gives the overall distribution shown in Table 1. While it may seem odd that there is such a plethora of hard projects, this is to the nature of drug development; it is inherently complex. Another assumption was made concerning the typical number of projects per year. These were introduced into the simulation through use of a Poisson distribution of average ρ. For simulations where the base unit was not projects, this assumption held, but then each project wa multiplied by a modifier. For Group A' μ and Group E' λ this modifier was TRL-dependent. Group C' ξ was purely percentage based. Each simulation was allowed to run for 100 years to populate it, and then run for another hundred years to provide 100 yearlong data segments. This was done instead of generating new random numbers because of Simul8 limitations. Personnel were assumed to have an initial 85% availability, with the other 15% dedicated to R&D. This was adjusted as necessary for each group, for a range of availabilities from 65% to 85%, with 65% being management who had process-step responsibilities. While not an assumption, it is important to note that a week in the simulation is 5 days, as only work days are simulated.

Overall TRL Σ Distribution		
3	0.1%	Easy
4	0.8%	
5	3.8%	Medium
6	11.3%	
7	24.9%	
8	31.7%	Hard
9	27.5%	

Table 1: TRL Distributions

Model Validation

Simulation validation had many distinct parts, and was one of the greatest challenges of this project due to the lack of historical data for comparison. Before construction began, each assumption and basic simulation structure (in the form of process maps) was confirmed with members of each

group/subgroup, management for each group and upper management. These confirmation interviews took around 10 hours total for each group, and were heavily focused on evaluating workflow paths, estimates of process step time (including TRL dependencies) and locations and potential outcomes of process nodes.

The simulation was then constructed. Additional assumptions were made where needed, often derived from existing data but experimentally estimated through simulation runs where necessary. For example, it may be known that a project should take 4-5 weeks to progress through a series of steps containing a decision node at the midpoint, and the time for all process steps is known. Experimentation would then be used to estimate the outcomes of the decision node that give results matching known data. Once the full simulation was build, preliminary results for each step[9] and overall process time would be checked for accuracy with expectations. The inevitable inaccuracies would then be assessed, with a goal of determining what area of the simulation they derived from. For example, a simulation may be broken into 3 parts, and the duration of each of those three parts checked for accuracy. Generally one would be inaccurate, narrowing the scope of the potential problem. Gross inaccuracies resulting from calculation inaccuracies, path routing problems, inaccurate decision nodes and simulation bugs were then resolved. Often, preliminary results were very different from reality. Simulation assumptions, decision nodes and basic construction were adjusted iteratively, with check-ins with group members and comparisons to available data to confirm changes and assumptions as needed.

If still inaccurate, the simulation as a whole was then reviewed with group members, management and executives to determine the source of the inaccuracies. For Groups A and E, historical data was available to aid in validation, and thus accuracy was fairly easy to ensure. For other groups, this resulted in a reasonably accurate simulation. For example, Group B1's simulation returned results ~1-2 months longer than their process in reality; for a process that takes 1-2 years, this is somewhere between 8%-4% off. That assumes, of course, that reported development times are not optimistic. However, there is no way to improve the accuracy without more data; as more data is collected, the information within the simulation can be updated to improve accuracy.

Model Experimentation

Once the basic simulation was deemed acceptable, queue analysis was conducted for major steps to determine the location of each process bottleneck. For detailed information on each group's queues, see Appendix B. Group A has a current bottleneck at Step 5, Groups B1 and D[10] have a latent bottleneck at Step 4.1, Group B2 has a serious bottleneck at its own Step 5, Group C lacks queues-likely due to its cyclical nature and the minimal data available for the simulation, and Group E has no current bottleneck.

Once bottlenecks were identified, each simulation was experimented with to determine potential solutions. Some suggestions proposed by APEG personnel were also experimented with to determine

[9] See Appendix B for simulation results for average and maximum queue size for each step and average wait time in each queue. These were the values used for validation of individual steps.

[10] Groups B1 and D have nearly identical processes—this step and those immediately preceding are the same for the two groups.

their potential impact. These solutions include the addition of personnel or automation[11], uniform introduction and potential new process steps done by external groups. Detailed results from this can be viewed in Appendix B. The bottleneck at Group A Step 5 was particularly responsive to additional personnel. Group B1 has proposed process alterations with the aim of decreasing overall lead times; this change has potential but could not conclusively be determined to be beneficial or detrimental. Piloting is recommended, as it will likely not have a significant negative impact. The bottleneck at Step 5 of Group B2 was somewhat responsive to additional personnel. Groups C and E had no changes on the current situation tested, as a bottleneck could not be identified.

TRL sensitivity testing was conducted with 8 variant TRL assumptions, show in Figure 15, for a total of 9 potential TRLs.

TRL Distributions Tested						
Variations on the Current Situation	Current		Slightly Easier		Slightly Harder	
	1	10%	1	15%	1	5%
	2	25%	2	25%	2	25%
	3	65%	3	60%	3	70%
Extremes	Uniform		Extremely Hard		Extremely Easy	
	1	33.33%	1	0	1	100%
	2	33.33%	2	0	2	0%
	3	33.33%	3	100%	3	0%
Projected Futures	Hard Future		Harder Future		Hardest Future	
	1	10%	1	5%	1	0%
	2	10%	2	15%	2	20%
	3	80%	3	80%	3	80%

Figure 15: Experimental TRL Variations

Variations on the current situation were experimented with for two reasons: basic TRL sensitivity testing and to determine if the simulation responded to variations in TRL in a reasonable manner. Often in early simulation development, this revealed nonsensical results or extreme reactions. Part of validating these simulations was building in appropriate responses to minor TRL changes. All simulations respond appropriately to minor TRL variations, with minor changes in overall time that make intuitive sense for their process.

Extreme TRLs were tested for similar reasons. If Extremely Easy returned results that took less time than was possible for the actual process that was a red-flag that there were inaccuracies in the duration assumptions. In addition, Extremely Easy gave an approximate best-case scenario for the group, and Extremely Hard gave a worst-case. Uniform gave an intermediate and i□the 'ideal' □tuation for APEG'□ desire to balance innovation and standard work. These three TRL settings gave a very good idea of overall trends as TRL is changed. If a simulation was too sensitive to TRL, or not sensitive enough or sensitive in a way that did not make sense, extreme testing revealed that. Extreme testing also provided

[11] In the simulation, the two are essentially synonymous as both increase capacity and personnel work hours.

benchmarks to use in evaluating the implications of future testing. It was extreme testing that confirmed that the bottleneck for Step 4.1 of Groups B1 and D was latent; Said bottleneck disproportionately effects easy projects, and as a result the Extremely Easy TRL setting results in massive queues. In reality, these queues would be mitigated by a redistribution of resources, so this is likely a simulation artifact rather than an actual issue. Group C, on the other hand, is very resistant to TRL changes as a result of the lack of data available to build it. Most simulations returned reasonable values for Extreme TRLs.

Projected Futures were not tested for validation; instead, they were meant to test how TRL levels 2-5 years from now would affect each group's process. It was estimated that 80% of projects would have a TRL of 3/Hard for each TRL type, a TRL of 2/Medium for 15% and a TRL of 1/Easy for 5%. This, obviously, is the Harder Future TRL setting. Slight variations-Hard Future and Hardest Future- were also tested to determine sensitivity. The impact of potential changes was also tested for Harder Future, to determine the future impact of those changes. It was this testing that revealed bottlenecks for Group E which are the most sever in the organization; discussion with Group E personnel revealed that these bottlenecks already exist, and are only being mitigated through herculean effort. Adding 1 or 2 extra staff members is recommended as soon as possible. Additionally, through this analysis it became clear that adding an additional person to Group A will become essential in the future. It did not provide any more data on Group B1 and D's proposed process change.

The detailed results and analysis of simulation experimentation for each group, including graphs detailing the effects of changes and initial queues can be found in Appendix B.

Example Model Validation and Experimentation

Once again, Group B1 will be used as the example group. Fully detailed data for Group B1 is in Appendix B.2.

The first step in validating each group was obtaining timelines reasonably similar to those given by data. Empirical data required a close match, while anecdotal required a slightly less precise match. After that, data for step queues was compared to reality. If a large queue was forming in an unlikely place, that step and those leading to it were examined and adjustments made. Often making these adjustments increased the accuracy of the simulation as a whole. The queue validation data for Group B1 is given in Table 2.

	Average Queue Size	Maximum Queue Size	Average Wait
Step 1	0.10 Projects	3 Projects	4.11 Days
Step 2A	1.56 Projects	9 Projects	7.47 Days
Step 2B	1.43 Projects	11 Projects	5.03 Days
Step 2C	0.02 Projects	11 Projects	0.69 Days
Step 2D	1.63 Projects	15 Projects	4.94 Days
Step 3	0.14 Projects	4 Projects	1.87 Days
Step 3'	0.10 Projects	4 Projects	3.87 Days
Step 4.1	4.90 Projects	18 Projects	9.93 Days
Step 4.2	0.25 Projects	4 Projects	4.75 Days
Step 4.3	0.02 Projects	2 Projects	0.35 Days
Step 5.1	0.04 Projects	4 Projects	0.69 Days
Step 5.2		not currently active	
Step 5.3	0.20 Projects	4 Projects	1.67 Days

Table 2: Group B1 Queue Validation Data

Once the simulation was confirmed to be operating accurately, queues were checked for bottlenecking. Figure 16 shows the only bottleneck for Group B1.

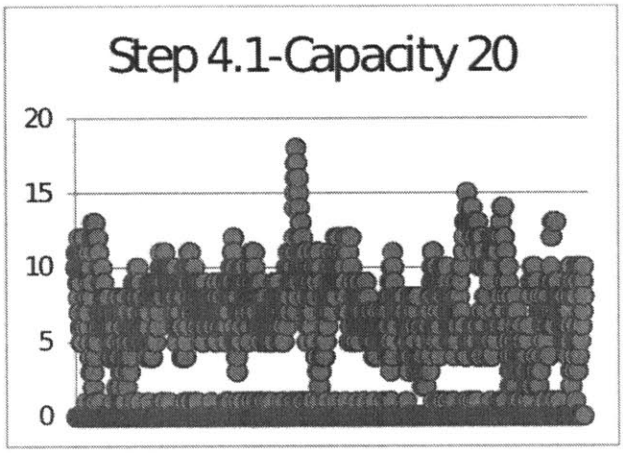


Figure 16: Daily Queue Amounts for Group B1 Bottleneck

This step has a few characteristics that mark it as a bottleneck, the most important of which is the sudden spikes in queue quantity over time. These spikes are not sudden enough to be the result of a sudden influx of projects; there is clear buildup to each peak. However, the capacity of this step is 20 projects, an amount that the queue never reaches. This indicates that while it may be a bottleneck, it is likely not a severe one. In addition, Group B1 was simulated off of anecdotal data; this bottleneck may not exist in reality. It is therefore recommended that this step be monitored but not otherwise addressed at this time.

Group B1 also has a proposed new step, Step 5.2. Analysis was conducted to determine if implementing this step would affect project timelines; this was non-standard, and is included in Appendix B.2.

The next step in validation was TRL variation, as shown in Figure 17.

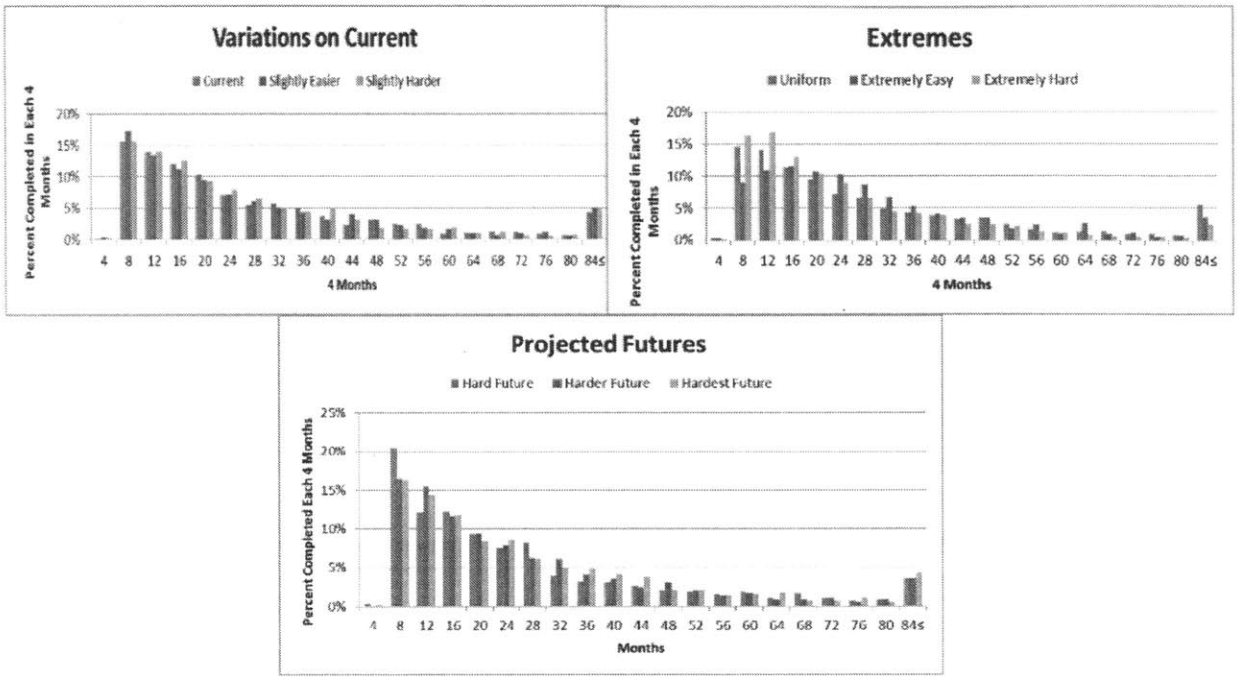


Figure 17: TRL Variation Testing for Group B1

Variations on Current and Extreme TRL testing were performed to test the simulation sensitivity to TRL. The above results show acceptable sensitivity. Looking at Extremes reveals something unusual; Extremely Easy TRLs result in later delivery times. This is due to the bottleneck at Step 4.1, which disproportionately affects easy projects. With all easy projects, the step is overwhelmed. In reality, this would not happen, as Group B1 members can perform all of the Step 4s interchangeably, so as capacity would increase at Step 4.1 as need decreased at the other steps. Projected Futures reveals that as future project difficulty increases so does delivery times, but in a reasonable manner. This is as expected, and indicates that the 4.1 bottleneck is not an immediate issue.

Projects with proposed process changes then had Harder Future TRLs applied to the potential changes, to determine potential future effect. In some cases, this showed that these changes were essential to maintain productivity.

Exploring APEG's current processes in depth lead to a nuanced understanding of their methods, motivations, challenges, structure and strengths. This knowledge was then applied to simulations of APEG's processes and used to evaluate potential issues, both current and future, along with potential solutions.

Chapter 6: Recommendations

Once the simulation experiments were complete, a number of recommendations were developed. Some of these were simulation based, and some were based on information that was collected during the process mapping phase. Recommendations took three forms: new metrics, appropriate times for data tracking and process changes.

Implement Framework

Currently APEG has no formal, defined method for communicating project difficulty. People assigned to said project have a very good understanding of the project's complications and certain project types have characteristic difficulty levels that are well understood within APEG. Within APEG itself the ability to efficiently communicate project difficulties, while beneficial, is not essential. However, APEG does not exist within a vacuum.

APEG's project loads are determined by the various Group α's that it interacts with. Group α's are incentivized to initiate projects based primarily on value to the patient population, and may not be familiar with the potential technological complexities for any given project and resulting impacts to APEG's proce[illegible]e[illegible] APEG Looking at the various Extreme TRL variation results in Appendix B shows clearly why this is problematic; the more difficult the projects, the longer the cycle time. Currently, APEG deals with the issue by educating Group α on the technological risk associated with each project, such that a balance of risk/reward across Group α's portfolio can be achieved. Having a quantifiable scale-such as TRL- to evaluate project difficulty on and communicate relative difficulties would aid in these discussions. It would be very beneficial to conduct preliminary TRL evaluations on the three TRL axes-Solution, Disease and Solution Molecule- to better communicate with Group α. In other words, APEG can use TRLs as a method of approximating project cycle times and then use that information to influence the projects it takes on.

As projects progress through APEG's proce[illegible] and more become[illegible] known about them, the TRL[illegible] would be adjusted as needed. TRLs could then be used as a method of evaluating internal project load; if APEG is responsible for 20 projects, this could mean an accumulative TRL of 60 to 180 as all three TRLs range from 1 to 3. APEG could estimate or determine empirically the maximum TRL that they can accommodate, for example 150, and use this value to evaluate when additional projects can be taken on, or when projects should be put on hold. Groups within APEG could do the same. Implementing the use of TRL metrics is low cost and would be useful both internally and externally. APEG has expressed interest in the application of TRL, and members of APEG have already begun using the terminology.

Data-Tracking Recommendations

It is vitally important that APEG gain a better under[illegible]tanding of Group C's proce[illegible]. This became clear during interview[illegible] and while trying to map Group C's proce[illegible] and i[illegible]al[illegible]p [illegible]hown through Group C's [illegible]mulation's inability to cope with TRL change[illegible]. Without this understanding, improvements cannot be made. Within APEG, Group C i[illegible]viewed a[illegible]a [illegible]rt of 'black box'-people know what goes in and what goes out and the general approach taken but not much more. Group C itself has both a very individualistic culture and the general belief that every project is highly unique. As a result, Group C views themselves as improvisers with a set of tools that they adapt to each project. This makes it difficult for them to think

of what they do as having a set process. Changing this culture, while difficult, would make gaining and maintaining understanding of Group C much easier. Unfortunately, changing a group's culture is extremely difficult and takes a great deal of time, and Group C's fiercely independent mindset makes it unlikely that this change will happen anytime soon.

APEG's other groups understand quite well what their basic processes flow is. Groups A and E, in particular, have both a detailed understanding of their process and the empirical data necessary to identify, evaluate and fix potential problems. The other groups, however, would benefit greatly from similar data tracking. As part of simulation development, decision nodes and their potential outcomes were determined; by definition, these decisions have a large impact on project timelines. It is recommended that these groups track the outcomes and respective dates of these decision nodes. Most nodes would only need one or two possible outcomes tracked. At 2-5 nodes per group, this would not be especially burdensome. It would be especially effective if this were implemented with APEG's potential workflow tracking program. APEG upper management has expressed interest in doing this once funding is available.

Recommended Future Changes

A number of issues and potential fixes were identified across groups. These are summarized in Table 3. More details on analyzing these issues and potential fixes can be found in Appendix B.

Group	Step	Type	Severity	Recommendation
Group A	Step 5	Bottleneck	High	+1 person at Step 5
Group B1	Step 4.1	Bottleneck	Minimal	Monitor
Group B1	Step 5.2	Proposed Change	Moderate	Pilot change
Group B2	Step 5	Bottleneck	Moderate	Cross train additional staff
Group D	Step 4.1	Bottleneck	Minimal	Monitor
Group E	Steps 2.1, 2.2	Future Bottleneck	Very High	+1-2 additional staff for lower branch

Table 3: Summary of Recommendations

It is recommended that an additional person be hired or automation with a similar impact developed for Group E's action upon approvable. While the predicted bottleneck is not currently an issue, this is due to unsustainable effort being performed by the responsible subgroup. This bottleneck has the potential to cause huge delays if it is not addressed. Group A's bottleneck is less severe, but has the potential to impact every other subgroup, as they may be called upon at any time by any group. As a result, hiring an additional person or implementing automation to assist with Step 5 would have a disproportionately large beneficial effect on overall delivery times. Group B1 and D's Step 4.1 bottleneck is, in fact, the same bottleneck for the same step in two very similar processes. In both cases, while there is a bottleneck at this location, it is not severe. It is recommended that this step be closely monitored, but no action needs to be taken at this time. Group B1 is also thinking of adding external Step 5.2 to its process. Initial analysis suggests that this may not be useful, as it causes only minor changes in project deliveries. In fact, it may be slightly detrimental. It would, however, reduce Group B1's utilization and may be beneficial depending on which projects pass through it; it is therefore recommended that this change be piloted. Group B2 has a semi-significant bottleneck at Step 5. Additional staff for this step

does reduce the resulting production times, but not hugely. Additionally, some members of Group C assist when this step builds up a large queue. It is therefore recommended that more personnel be cross-trained to assist with this step and that they work to prevent the creation of the queue, rather than assisting after the queue has already built.

Unfortunately, adding additional people to APEG is difficult at this time. It is possible that Group E will receive additional staff, but unlikely that Group A will as it does not have an immediate issue. Fortunately, the other suggestions are relatively low-cost and thus have a higher chance of being implemented.

Conclusions

APEG consists of extremely skilled, very intelligent individuals who have been dealing with a complex, changeable process remarkably well. They have, however, reached the point where process improvement will be very difficult without better data. This is particularly true of Group C, but applies to Groups B1, B2, and D as well. In order to further understanding of their processes, simulations were built based primarily on anecdotal data. These simulations have revealed a number of potential bottleneck issues, both current and future, that need to be addressed. Additionally, these simulations can be used in the future to evaluate the potential impact of process changes. APEG would also benefit from introducing a TRL-based ranking system for evaluating and comparing project difficulty and potential cycle times, both with other groups and with internally.

Appendix A: Process Maps and Data Details by Group

Process Map Key:

Parallel proce[]e[]are indicated by '. i.e. 1 and 1' are parallel

Sub-processes are indicated alphabetically. i.e. 1b follow 1a.

Exclusive process steps are indicated numerically. i.e. 2.1 and 2.2 would be mutually exclusive process steps following step 1.

Section 0: Overall Process Map

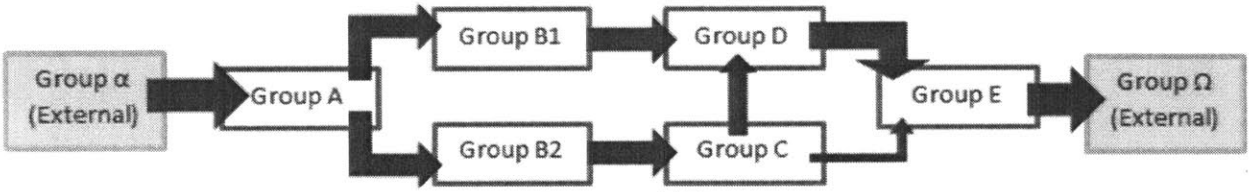


Figure A.0 1: Overview of GBT process.
Arrow width roughly corresponds to number of projects passing through each potential handoff

At the executive level, APEG has very good data on its processes, though it was sub-optimally organized for this kind of project. Figure A.0 1 shows an executive overview of APEG'[]workflow through the respective teams. An external Group α reque[]t[]a project, which is assigned a project lead. Group A then initializes the project and begins preliminary work. The project is then handed off to either Group B1 or Group B2, depending on the project requirements. Projects that pass through Group B2 must then pass through Group C. Almost all projects then pass through Group D. Finally, all projects pass through Group E before being handed off to the external Group Ω.

It is worth noting that this is a representation of the most likely possible project paths; there are a plethora of other, less likely options. For example, a single project may pass through Groups B1 and B2 simultaneously, though this is rare. Additionally, backtracking from any stage to almost any other stage is possible. If a project is experiencing problems in Group C, it may then backtrack to Groups A, B1, or B2. In situations like this, it is much likely that a project will return to its previous project path (i.e., if it passed through B2, it will return there instead of B1), but this is not certain.

Often, a given project will have many different subprojects in different groups; thus, Groups B1 and E may be working on the same project simultaneously. This is the case for virtually every project. For example, a given project may contain 100 different molecules. If 50 of those molecules successfully pass all tests within a group and 50 do not, there is no reason to hold the successful 50 molecules back. They will proceed to the next group, while the 50 failing molecules remain. Typically, many of these subprojects are on hold and are canceled once a []ubproject further along reache[]Group Ω or is canceled.

The maps within this section are Level 2 (Managerial). Level 3 (detailed) maps for each group exist, but are far too complex to be accurately represented in this report.

Section A.1: Group A

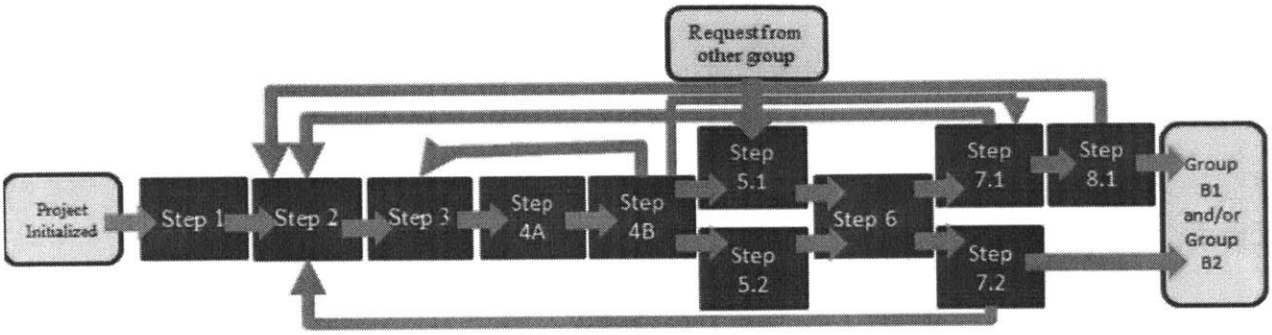


Figure A.1 1: Overview of Group A Processes

Group A is one of the groups with the most advanced understanding of their process. This is unsurprising, as they are also one of the groups under the most time pressure. In addition to initializing each project, Group A is also often called upon by the other groups for additional work. This work typically involves executing only part of Group A's process, but is time consuming nonetheless. The basic 'unit' of work for Group A shall be referred to as μ and is correlate to TRL. Harder projects have more μ's. Each project may have many μ's, and new μ's may be developed throughout the early project development stages. Generally, by the time Group D is working on a project μ development is complete; it must be complete by the time a project has passed to Group E. Some μ may be developed by external groups, though this is rare.

Group A is organized into specialization-based subgroups. These subgroups each have precise, well understood processes that do not change much from μ to μ. Additionally, Group A has very good tracking data for the majority of its process steps. This data consists primarily of excel files tracking the dates that each μ enters each step. Group A has been actively working to improve its process steps for many years, and as a result knows fairly well what to track and where issues may arise.

Within the organization, Group A is highly respected. Their manager has worked for APEG for longer than any other manager, and their interaction with many different groups gives them high visibility. They are viewed as reliable and highly competent.

Group A's output is a collection of μ's which is handed off to Group B1 or B2 or the requesting group.

Section A.2: Group B1

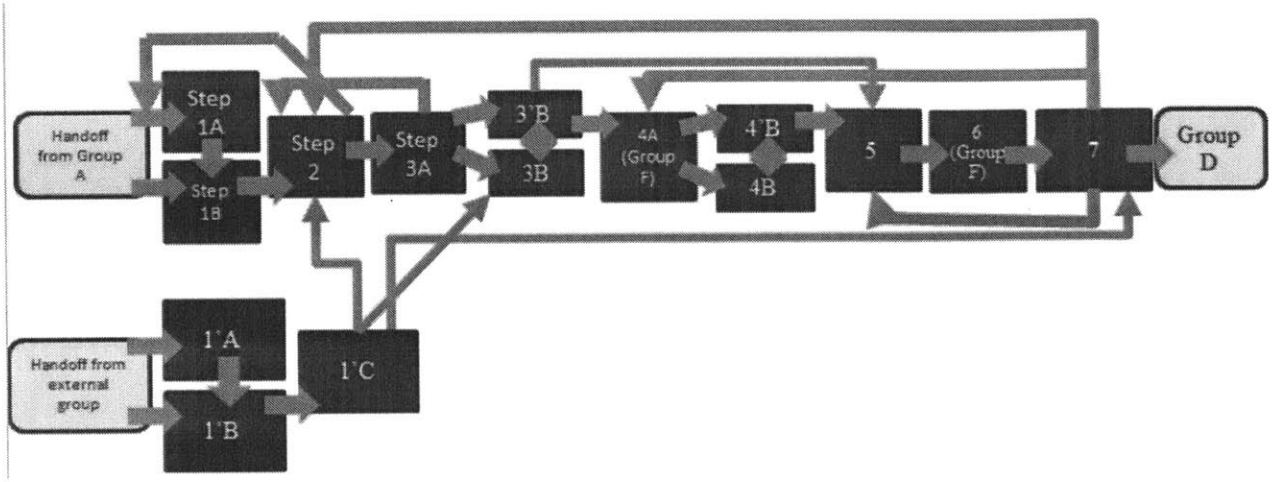


Figure A.3 1 Overview of Group B1 Process

Of all groups, Group B1 understands the intricacies of its process the best. They have recently and repeatedly analyzed their processes in an effort to make improvements, and it shows. In fact, a recent initiative by Group B1- the creation of Subgroup G- has reduced development times for all groups by 2-4 weeks each time Subgroup G is utilized.

Group B1's proce[illegible] i[illegible] complex but fairly linear, except after te[illegible]ing where backtracking to previou[illegible]tep[illegible] may occur. The basic unit for Group B1 is projects; they cannot begin working until sufficient µ'[illegible] have been delivered by Group A and, potentially, other external group[illegible]. µ'[illegible] may continue to be delivered throughout their processes.

Group B1, unusually, does not have process data tracking to support their excellent understanding of their processes. However, their understanding of their processes as a whole and individually gives them excellent tribal understanding of the timelines involved, so this is not a huge obstacle. Generally, a project is assigned to a given group member, who is responsible for all stages of that project with a group. A given group member may have ~5 projects, but at most two are active at a time. The other projects may be on hold, waiting for results from another group or otherwise inactive.

Group B1 is well respected within the organization. Their comparative lack of direct interaction with other groups means that many other groups do not know exactly what they do, but they are viewed as reliable and innovative.

Group B1 outputs projects, all of which pass to Group D.

Section A.3: Group B2

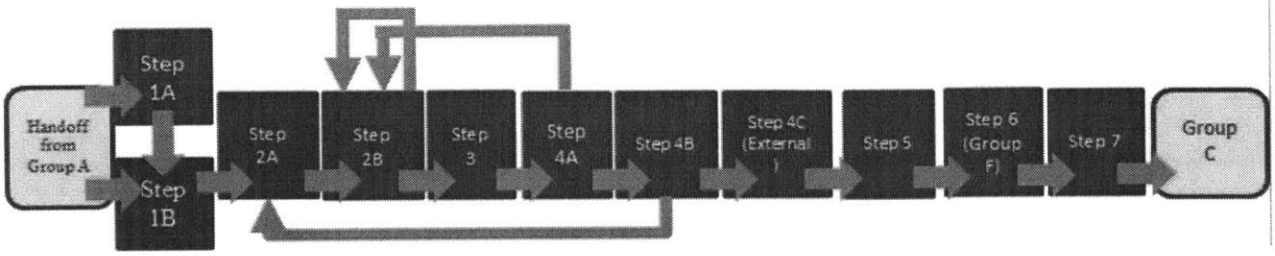


Figure A.3 1: Overview of Group B2 Process

Group B2 is a recent creation. Previously, they were a subgroup of Group C. Establishing B2 as an independent group has required a modification to their processes. As a result, their processes are not firmly established, though they parallel Group B1 fairly closely. Figure A.3 1 reflects the group's understanding of their processes, through further discussion with both Group B2 and other groups indicates that the process is, in fact, fairly close to Group B1's process, but with the specifics of each step altered, and different potential reasons for backtracking.

More than any other group, B2 is constrained by basic biological restrictions affecting what can and cannot be done. This, combined with the recent formation of the group, makes determining potential process improvements difficult.

Group B2 has a very good general understanding of their process and its steps, but both detail and workflow tracking are lacking. Projects are, like in Group B1, assigned to a group member for much of their process, though this is much more flexible than in Group B1. Similarly, a given individual may have many assigned projects on hold- waiting for results from another group or otherwise inactive. Group B2's process is fairly work-light at the start, so more active projects may be carried at one time. Step 5 is always performed by a specific subgroup, who are only responsible for this step.

Group B2 is viewed fairly neutrally within the organization. While its work is respected, it is a new group, with a new manager from outside of Graybel. Their primary unit of work and output, like B1, is projects; similarly, their input is μ's.

Section A.4: Group C

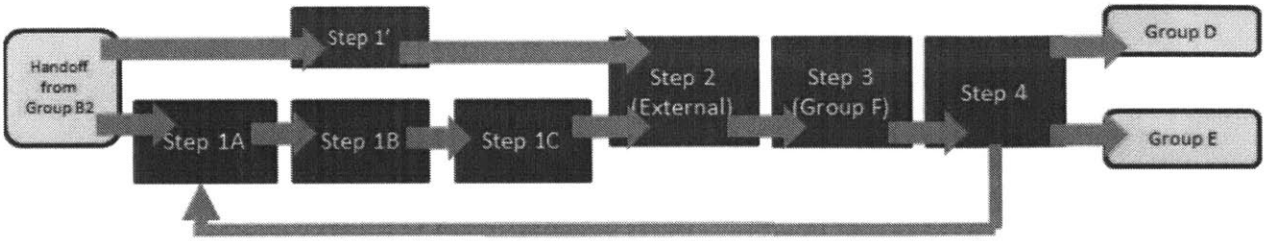


Figure A.4 1: Overview of Group C Process

Group C occupies an interesting niche within the organization. All projects that pass through Group B2 must pass through Group C. In addition, the majority of project leads come from within this group. As previously noted, Group C tended to also be responsible for Group B2's processes.

Group C's process is markedly different from all other processes within APEG; in general, APEG's processes are linear with potential backtracking. Group C, on the other hand, is very cyclical. It has a very linear, short process with a very high chance of backtracking. Group C possesses the most experimental process within APEG.

Most members of Group C do not recognize their process as a process. They think of it as a series of experimental steps that are highly customized to each project, and thus not consistent enough to be a 'process'. From discussions with upper management and certain group members it is clear that, while this is somewhat the case, it is possible to abstract these experimental steps into a coherent, consistent whole. However, due to the general culture of the group, it is impossible for a detailed understanding of the process to be achieved at this time. Nevertheless, Figure A.4 1 shows the abstracted process in as much detail as possible. Group C has no project tracking data.

The basic unit of Group C, like Group A, would in an ideal case be similar to μ; i.e., multiple subprojects per project dependent upon TRL values. However, the general lack of workflow data makes this impossible; for the duration of this report, Group C's base unit is ξ, and is purely percentage based. In other words, a given project has multiple ξ's, but these are independent of TRL.

Members of this group view themselves as having a broad, diverse technical skill set. These skills are adequate to perform tasks typically done by some, but not all, other Groups. If a group is in need of additional manpower, Group C members can often assist. They are respected within the organization. Interestingly, while the individual members of the group are viewed as highly reliable, the group itself as a whole is viewed as somewhat unpredictable due to a combination of variable cycle times, variable member skillsets and an external lack of understanding of Group C's process.

The majority of Group C's outputs are handed off to Group D. In certain cases, however, their projects are instead passed off to Group E directly; this is because Group C process is, essentially, a specialized version of Group D's.

Section A.5: Group D

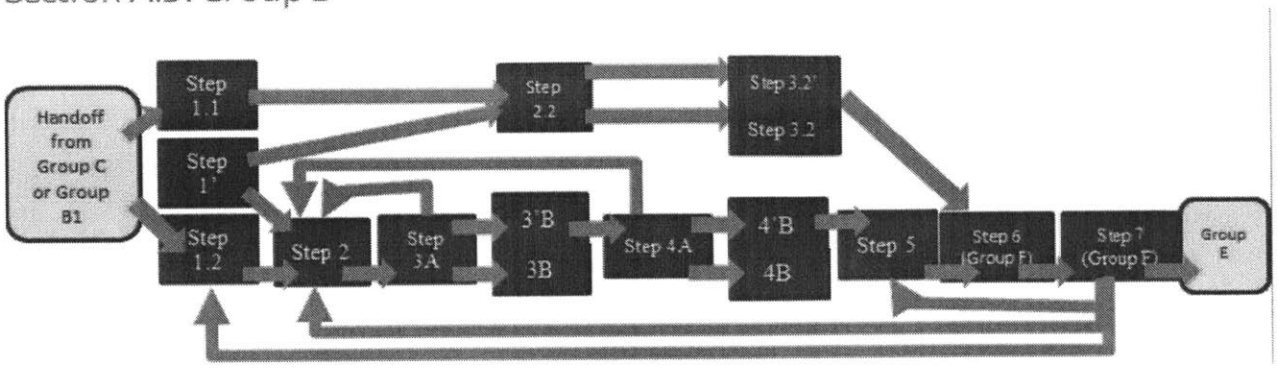


Figure A.5 1 Overview of Group D Process

Group D is the only group not located in the U.S. Instead, they are located in Europe. Their process is very similar to Group B1's process, with some additional early steps and an additional alternate path that is still in development. As a result, they occasionally takeover Group B1's role when Group B1 is at capacity and new projects need to be started.

Group D's process is fairly linear, with a lower chance of backtracking than either B group. Certain projects within Group D are suited to an alternate, highly linear process that is much faster; this is the upper path in Figure A.5 1. This process is very new, and there is not enough data at this time to analyze it.

Group D's process is well understood by its members, though they lack the process improvement focus of Group B1. Instead, they focus on technological and biological innovation to improve their timelines. This dichotomy between the two groups' improvement methods is very useful; innovations within one group are shared with the other, improving both groups' processes and methods. They are also shared with other groups that may benefit, though this is less common due to process differences. Group D does not track workflow or process times in any detail. Like B2, the basic unit of Group D is projects. All of their outputs are handed off to Group E.

Group D is regarded very well by other groups. The distance involved means that there are fewer connections between individual group members, but the group as a whole is viewed as reliable and very knowledgeable.

Section A.6: Group E

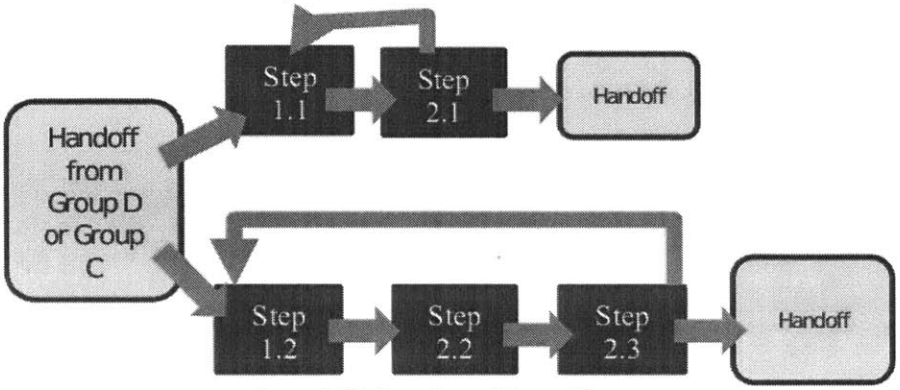


Figure A.6 1 Overview of Group E Process

Group E's process is fairly similar to the end of Group A's (Steps 5+). Like Group A, the basic unit of Group E is not projects; for the duration of this report, it will be referred to as λ. Each project has multiple λ's. Like Group A, Group E is under extreme time pressure and as a result is thoroughly aware of how their process works and the potential issues that may arise.

As shown in Figure A.6 1 there are two process paths for Group E. The upper path is primarily focused on internal deliverables; their handoffs mostly go to other groups within APEG. The upper path also, in some instances, is responsible for Subgroup G's work in later stages of the project. This is very dependent on the project needs and biology of the relevant molecules. Prior to Subgroup G's formation, the upper path was used for the majority of Subgroup G's work, though some was done internally within other groups. The lower path is primarily focused on external deliverables, and is located off-site with Group Ω. The primary difficulties faced by Group E are biological and technical instead of process-based; by the time a project reaches them, it is nearly complete. Both groups are responsible for converting APEG's method into Group Ω's process to facilitate handoff. Each path has an assigned subteam responsible for all steps within that path. Group E has workflow tracking data available, primarily the entry date for the various steps. This group is unique in that any process step or steps may be skipped, depending on the project and its requirements.

Group E is generally well regarded by other group members, though they encounter some pressure related to their roles as final project steps.

Appendix B: Results by Group

Section B.1: Group A

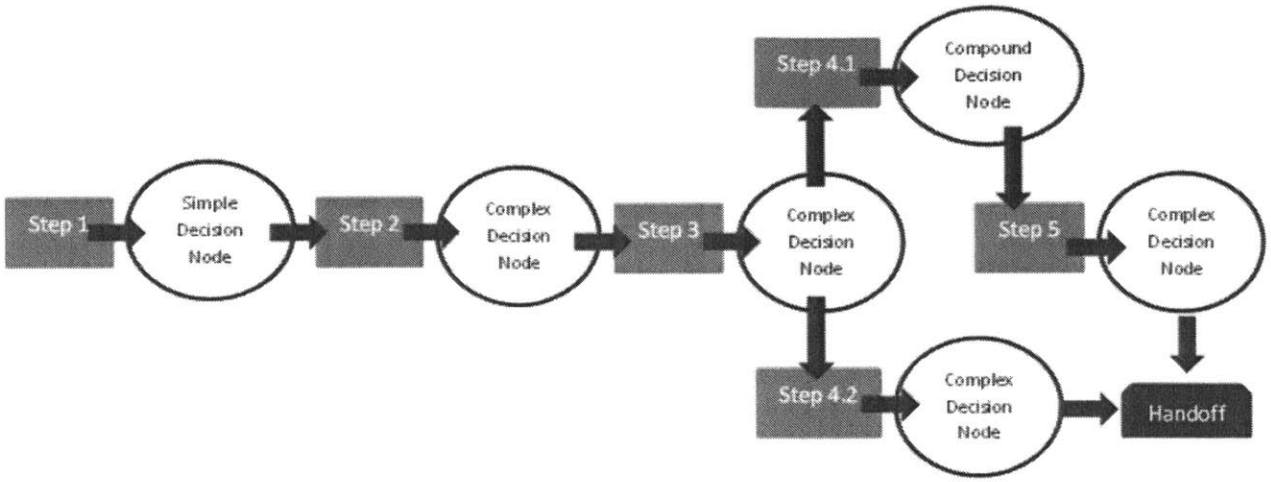


Figure B1.1: Simplified Overview of Simulation

Omits minor backtracking for clarity; See process map in Appendix A for non-simplified version

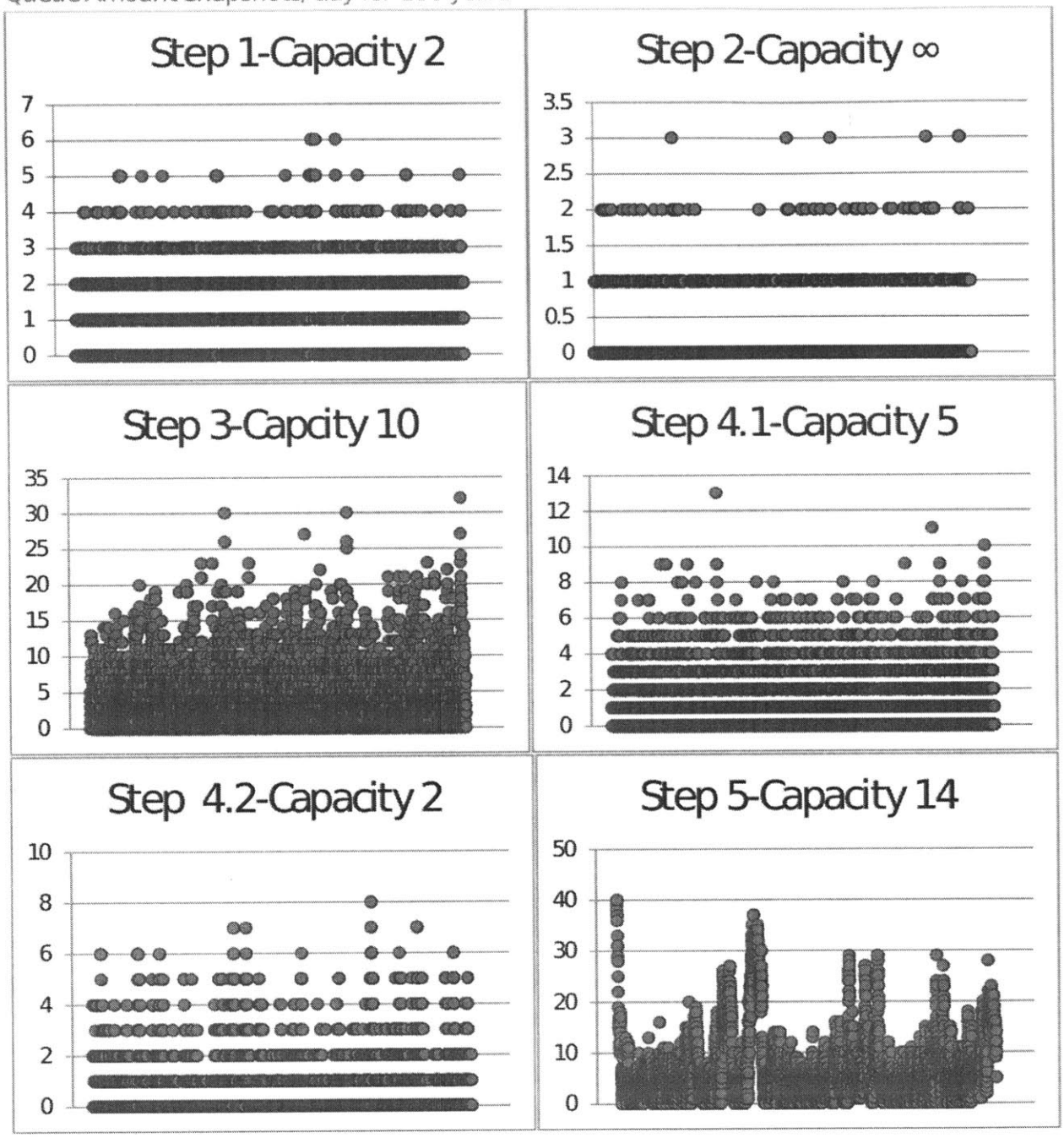
Steps 1 and 2 are each performed by an individual and external group working together. Steps 3 and 4 are performed by a single subgroup, each on a weekly basis. Steps 3 and 4.2 each also have their own dedicated subgroups. Projects are converted into μ between Steps 2 and 3. Step 2 is external and thus has infinite capacity.

Preliminary Results

	Average Queue Size	Maximum Queue Size	Average Wait
Step 1	1.11 Projects	6 Projects	13.97 Days
Step 2	0.17 Projects	3 Projects	2.19 Days
Step 3	3.85 μ	36 μ	5 Days
Step 4.1	1.25 μ	13 μ	4.28 Days
Step 4.2	0.75 μ	8 μ	13.53 Days
Step 5	6.49 μ	43 μ	8.40 Days

Group A is unique in that two of its steps-Steps 3 and 4.1- adhere to consistent weekly schedules. Each Step is started on a Monday and concluded on the next Monday for all μ. As a result, the wait times for these steps are higher than one would expect from their queues. Step 5, on the other hand, is artificially lowered due to simulation design. Each μ passes through Step 5 and its respective queue 2-3 times; In other words, the actual accumulated wait time for each project is approximately 21 days. These numbers are similar to those provided by empirical data, and match expectations for those supported by anecdotal data.

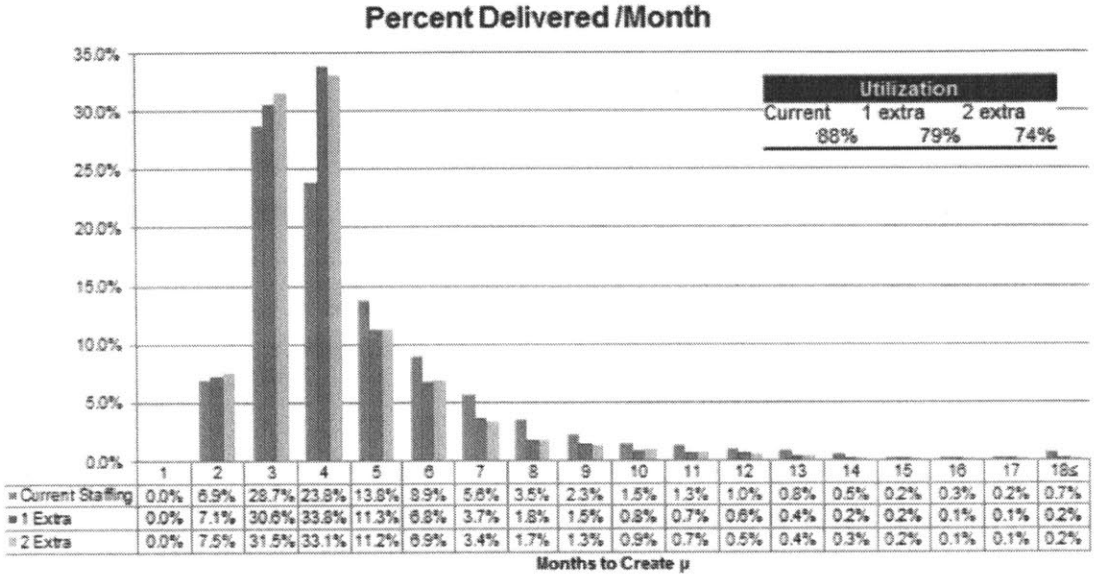
Queue Amount Snapshots/ day for 100 years



Note that Step 5 is clearly the bottleneck, with queues nearly 4 times the capacity and prone to the resulting characteristic huge, abrupt swings in queue quantity once capacity is reached. The next most significant bottleneck is Step 4.2, with queues hovering around 3-4 times capacity in extreme situations. Unsurprisingly, these are also the steps that take the most time to perform. Step 2'□capacity i□infinite because it is done by an external company with a very large capacity.

Proposed Bottleneck at Step 5 Fixes

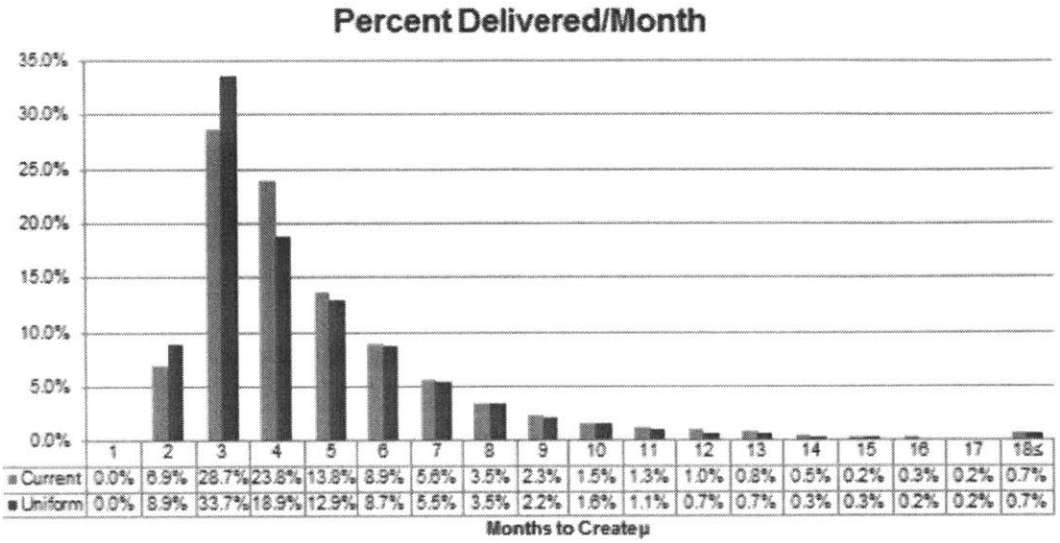
Two potential methods of fixing the Step 5 Bottleneck were proposed- additional staffing and uniform introduction of projects. The results of these potential fixes on overall project delivery times are below.



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18≤
Current Staffing	0.0%	6.9%	28.7%	23.8%	13.8%	8.9%	5.6%	3.5%	2.3%	1.5%	1.3%	1.0%	0.8%	0.5%	0.2%	0.3%	0.2%	0.7%
1 Extra	0.0%	7.1%	30.6%	33.8%	11.3%	6.8%	3.7%	1.8%	1.5%	0.8%	0.7%	0.6%	0.4%	0.2%	0.2%	0.1%	0.1%	0.2%
2 Extra	0.0%	7.5%	31.5%	33.1%	11.2%	6.9%	3.4%	1.7%	1.3%	0.9%	0.7%	0.5%	0.4%	0.3%	0.2%	0.1%	0.1%	0.2%

Figure B1 2: Effects of Additional Staff at Step 5 on Total Production Time

Both uniform introduction and additional staff prove at least somewhat helpful. A single additional staff member proves hugely beneficial in early months. This is particularly noticeable in month four, increasing the number of projects delivered by 10%. A second staff member is also beneficial, but the comparative gain over a single staff member is relatively small. Increased staffing provides a continuing benefit for all projects, increasing the number of projects delivered early on while decreasing the number delivered later.

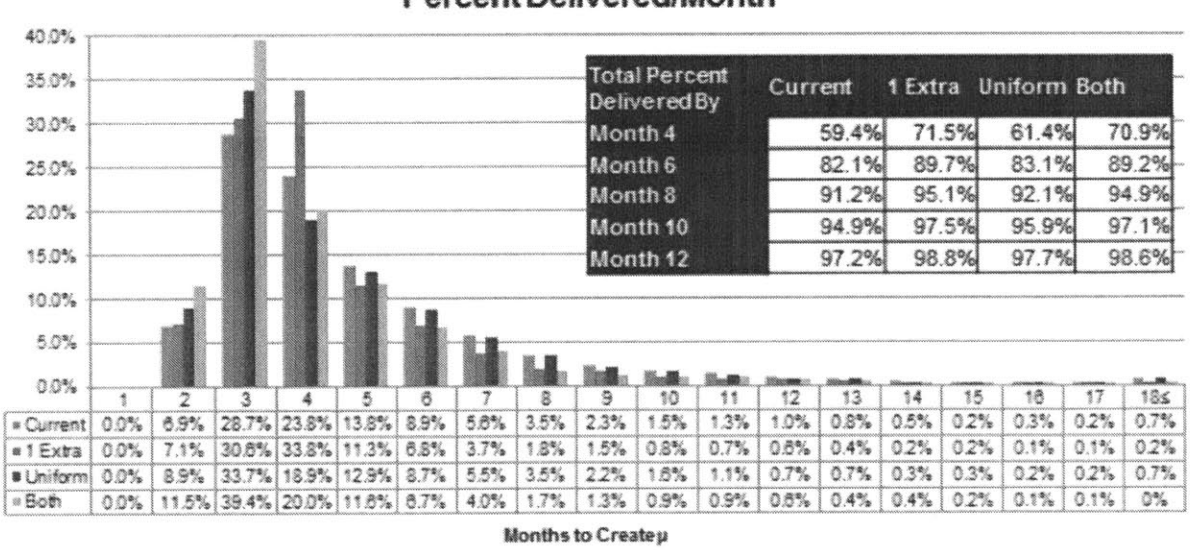


	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18≤
Current	0.0%	6.9%	28.7%	23.8%	13.8%	8.9%	5.6%	3.5%	2.3%	1.5%	1.3%	1.0%	0.8%	0.5%	0.2%	0.3%	0.2%	0.7%
Uniform	0.0%	8.9%	33.7%	18.9%	12.9%	8.7%	5.5%	3.5%	2.2%	1.6%	1.1%	0.7%	0.7%	0.3%	0.3%	0.2%	0.2%	0.7%

Figure B1 3: Effects of Uniform μ Introduction to Group A

Uniform introduction increases the number of projects delivered in months 2 and 3 by 7%, but decreases the number delivered in months 4 and 5 by 6%; after the first 5 months, the number of projects delivered each month is nearly identical. In other words, it only affects projects whose delivery takes 5 months or less, and accelerates their development by 1-2 months. This is likely due to the weekly scheduling of steps 3 and 4.1, which create a pseudo-uniform distribution whenever they have a queue.

Given that both methods created at least some improvement, the effects of both methods applied concurrently was then modeled.



Total Percent Delivered By	Current	1 Extra	Uniform	Both
Month 4	59.4%	71.5%	61.4%	70.9%
Month 6	82.1%	89.7%	83.1%	89.2%
Month 8	91.2%	95.1%	92.1%	94.9%
Month 10	94.9%	97.5%	95.9%	97.1%
Month 12	97.2%	98.8%	97.7%	98.6%

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18≤
Current	0.0%	6.9%	28.7%	23.8%	13.8%	8.9%	5.6%	3.5%	2.3%	1.5%	1.3%	1.0%	0.8%	0.5%	0.2%	0.3%	0.2%	0.7%
1 Extra	0.0%	7.1%	30.6%	33.8%	11.3%	6.8%	3.7%	1.8%	1.5%	0.8%	0.7%	0.6%	0.4%	0.2%	0.2%	0.1%	0.1%	0.2%
Uniform	0.0%	8.9%	33.7%	18.9%	12.9%	8.7%	5.5%	3.5%	2.2%	1.6%	1.1%	0.7%	0.7%	0.3%	0.3%	0.2%	0.2%	0.7%
Both	0.0%	11.5%	39.4%	20.0%	11.6%	6.7%	4.0%	1.7%	1.3%	0.9%	0.9%	0.6%	0.4%	0.4%	0.2%	0.1%	0.1%	0%

Figure B1 4 Effects of Uniform Introduction, 1 Extra Staff Member and Both Compared

As one could predict from the individual models, months 2 and 3 show improvement with both uniform introduction and 1 extra staff member over either individually. Month four is where things become interesting, with a massive increase from one additional staff member that is absent from all other variants. Looking at the total percent of projects delivered by month four makes things much clearer. After 4 months, the number of projects delivered is roughly equivalent for the current situation and uniform introduction. Projects delivered for 1 extra staff member and both improvements are also roughly equivalent. These equivalencies exist for all projects delivered after month 4. From this, it is clear that an additional staff member at Step 5 would greatly improve delivery times. Adding uniform introduction to this would have some effect early on, but may be more trouble than it is worth.

Effects of TRL Variation

Nine TRL variations were tested, as shown in Figure 15.

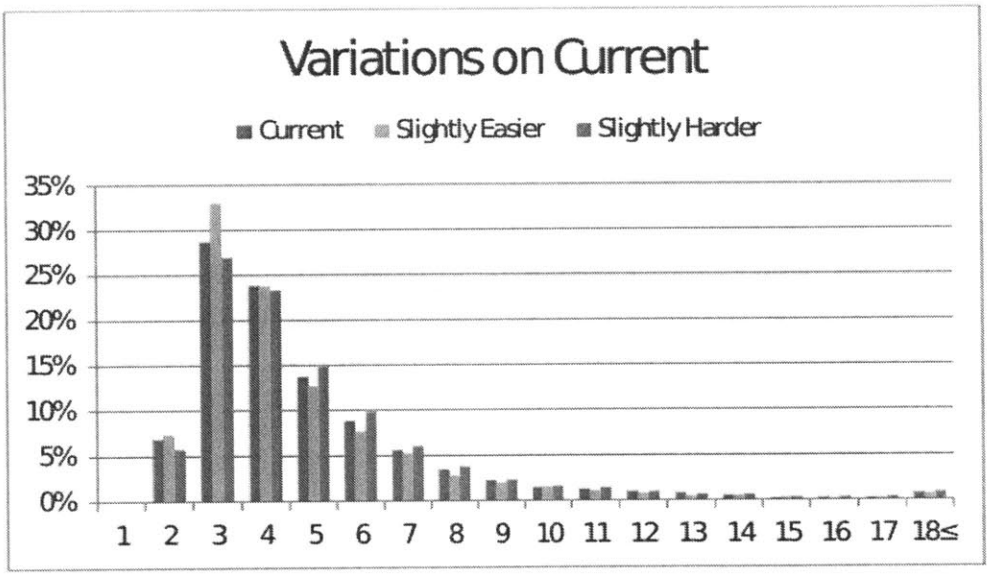


Figure B1 5: Variations on Current TRL

Slight variations in TRL Distribution result in slight variations in percent completed each month. As expected, slightly easier TRLs take less time to produce, and slightly harder take more. Thus, the simulation is responding as expected and is not overly sensitive to TRL. This also indicates that the decision node outcomes are reasonable, as they are heavily TRL dependent.

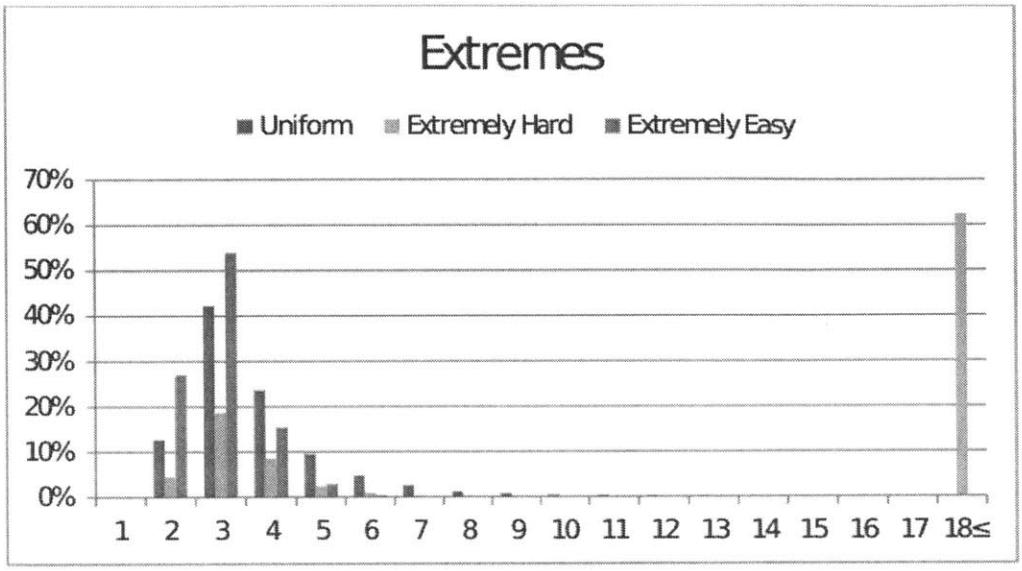


Figure B1 6: Extreme TRLs

Extremes indicate that a project cannot be concluded in less than a month, which matches expectations. Similarly, with all hard projects almost all projects take over 18 months to create; this is due primarily to the bottleneck at Step 5. The number of times a project passes through Step 5 is TRL dependent, so extremely hard TRL settings results in many more repeat passes through said step. This matches expectations of what would actually occur in this situation.

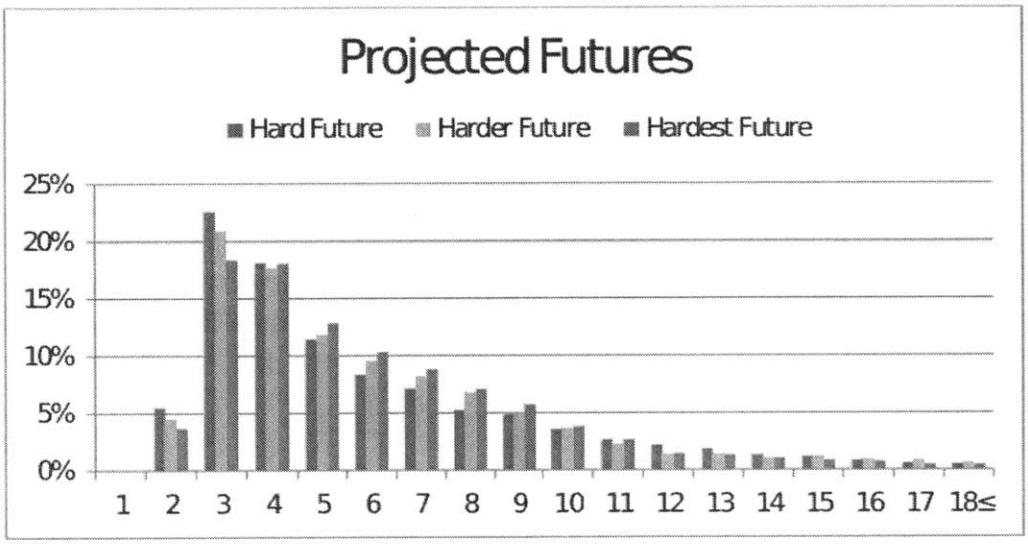


Figure B1 7: Projected Future TRLs

Projected Future TRL variations also react as expected, with delivery times taking longer for more difficult futures.

Analysis of Future and Step 5 impacts

It is worth it to also test the projected effect of an additional staff member on projected future TRLs.

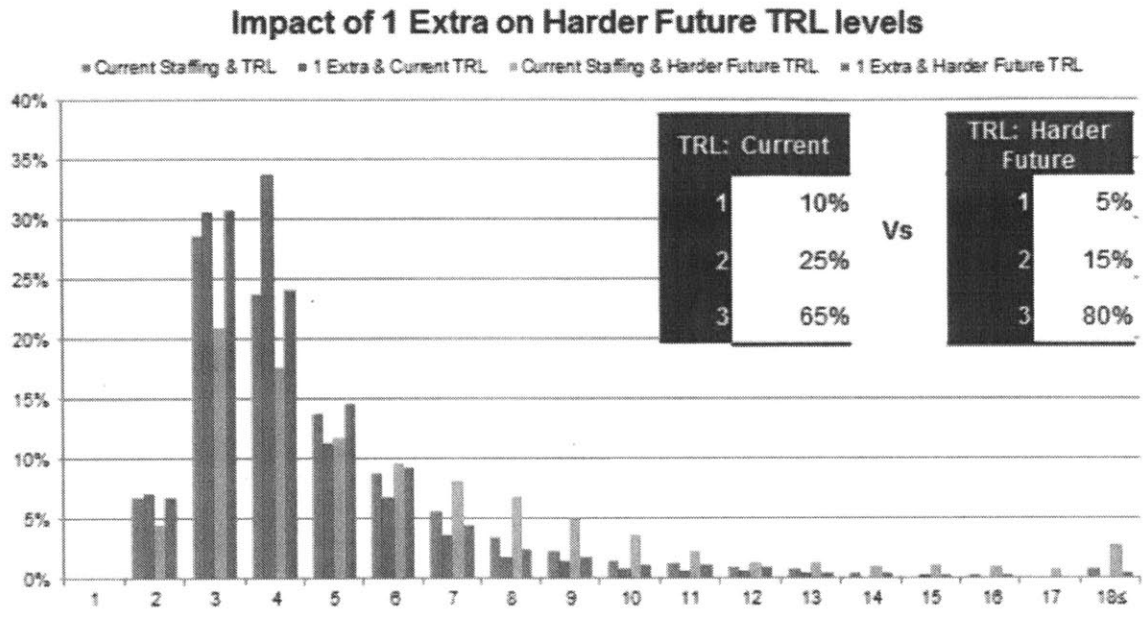


Figure B1 8: Effects of Most Likely Future and Step 5 Staffing Variations

It is interesting to note that adding one additional staff member to Step 5 causes projected future project deliveries to be roughly equivalent to current deliveries, in addition to improving current delivery times. From this, it becomes clear that it is would be very beneficial to hire an additional staff member.

Section B.2: Group B1

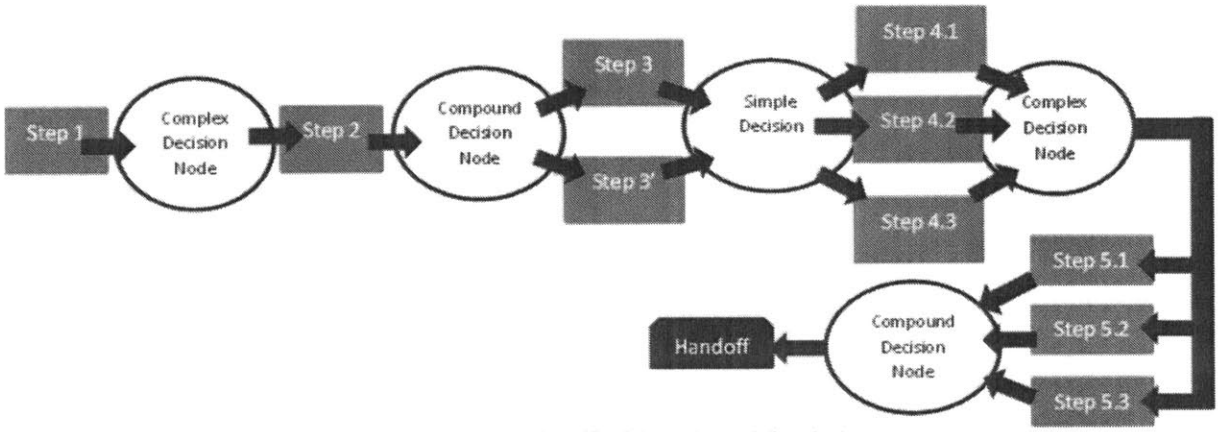


Figure B2 1: Simplified Overview of Simulation
Backtracking omitted for clarity; See process map in Appendix A for non-simplified version

Group B1 assigns members to projects at Step 1, and that member performs all non-external project steps. Steps 2C and 3' are external.

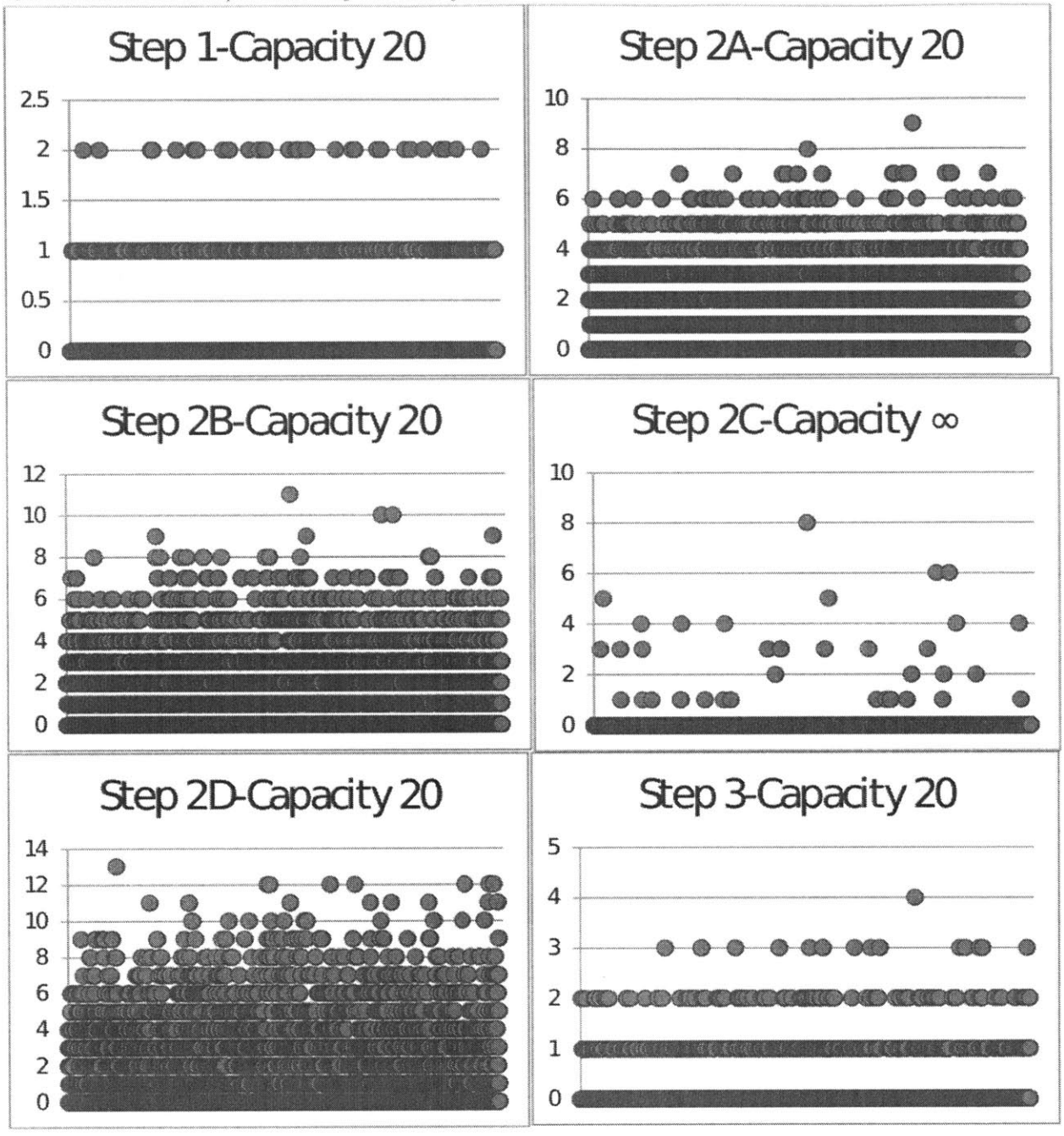
Preliminary Results

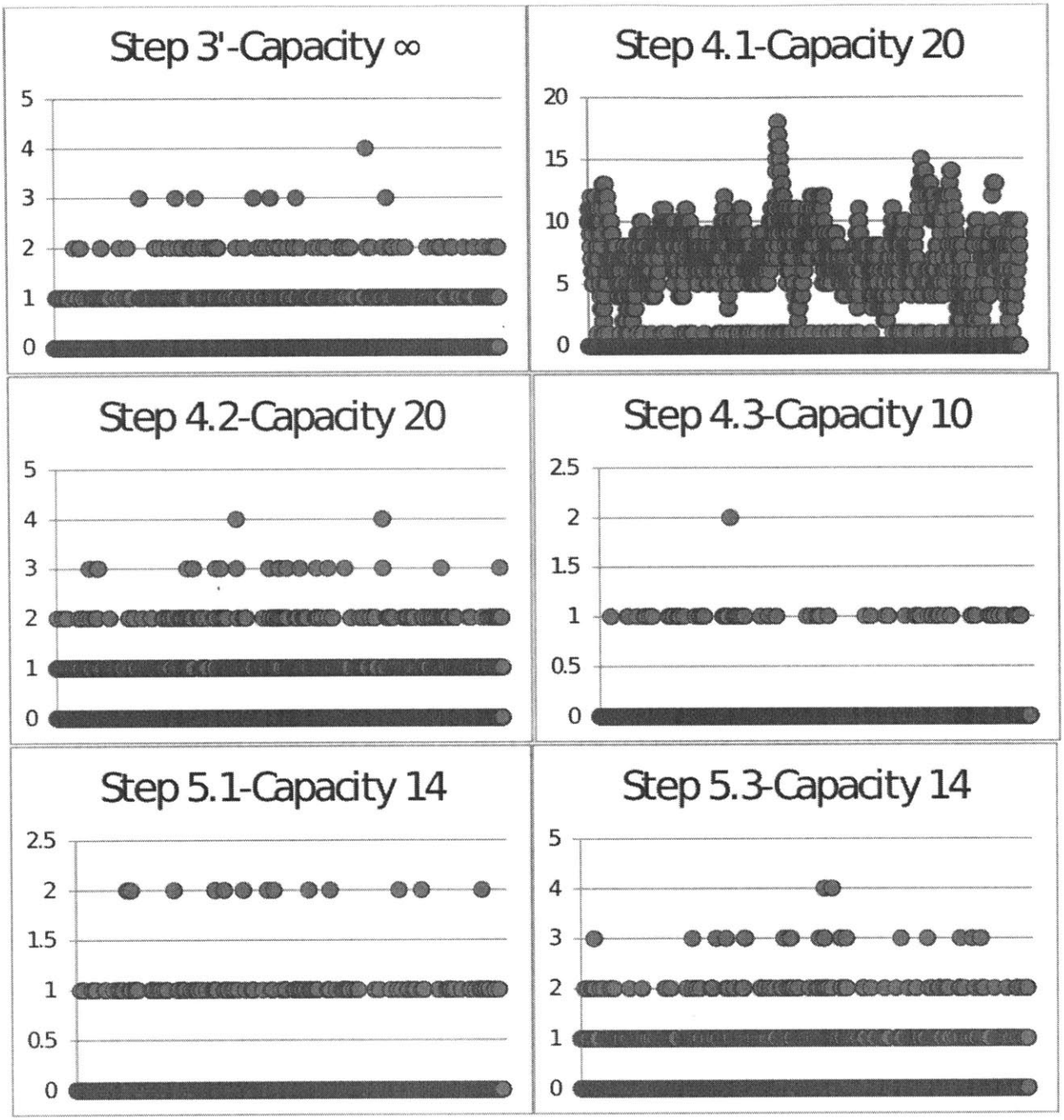
	Average Queue Size	Maximum Queue Size	Average Wait
Step 1	0.10 Projects	3 Projects	4.11 Days
Step 2A	1.56 Projects	9 Projects	7.47 Days
Step 2B	1.43 Projects	11 Projects	5.03 Days
Step 2C	0.02 Projects	11 Projects	0.69 Days
Step 2D	1.63 Projects	15 Projects	4.94 Days
Step 3	0.14 Projects	4 Projects	1.87 Days
Step 3'	0.10 Projects	4 Projects	3.87 Days
Step 4.1	4.90 Projects	18 Projects	9.93 Days
Step 4.2	0.25 Projects	4 Projects	4.75 Days
Step 4.3	0.02 Projects	2 Projects	0.35 Days
Step 5.1	0.04 Projects	4 Projects	0.69 Days
Step 5.2		not currently active	
Step 5.3	0.20 Projects	4 Projects	1.67 Days

These values generally match expectations. As previously mentioned Group B1 has a very thorough understanding of their process and has been working to reduce timelines. The apparent bottleneck, Step

4.1, is heavily TRL depended. The various Step 4'□are the re□ult of different TRL value□-TRL: Easy and TRL: Medium go to 4.1, while TRL: Hard is split between steps 4.2 and 4.3 based upon other qualities. However, this is may not actually be a true bottleneck, as the 4.2 and 4.3 processes take much longer than the 4.1 process. Even with the higher wait time, projects pass through the 4.1 process faster than the 4.2 or 4.3 processes. Therefore, more information is needed. Step 5.2 is not currently active, but it is something that APEG is considering adding to the process. The implications of this are addressed later in this section.

Queue Amount Snapshots/ day for 100 years





Looking at these queues, none exceeds their respective step capacities. Therefore, while Step 4.1 does exhibit bottleneck characteristics-the abrupt increase in queue amount, in particular- the size that said queue reaches(<1*capacity) is small enough that this bottleneck is not a huge issue. Given that this simulation was created without empirical data, this bottleneck is small enough that it could even be non-existent in reality. This step should be monitored to determine if this bottleneck actually exists and to determine how significant it is.

Effects of Using Step 5.2

Progressing to the three options for Step 5 is dependent on TRL, as it is the output of a complex decision node. Projects are routed to each potential Step 5 based up their TRL values. The TRL ratio variations tested are shown in the table below.

		5.1	5.2	5.3
Current Variation	TRL:Easy	70%	0%	30%
	TRL: Med	50%	0%	50%
	TRL:Hard	30%	0%	70%
Variation 1- Share 5.3's Work	TRL:Easy	70%	15%	15%
	TRL: Med	50%	25%	25%
	TRL:Hard	30%	35%	35%
Variation 2- Share 5.1's Work	TRL:Easy	35%	35%	30%
	TRL: Med	25%	25%	50%
	TRL:Hard	15%	15%	70%
Variation 3- Uniform work	TRL:Easy	33%	33%	33%
	TRL: Med	33%	33%	33%
	TRL:Hard	33%	33%	33%

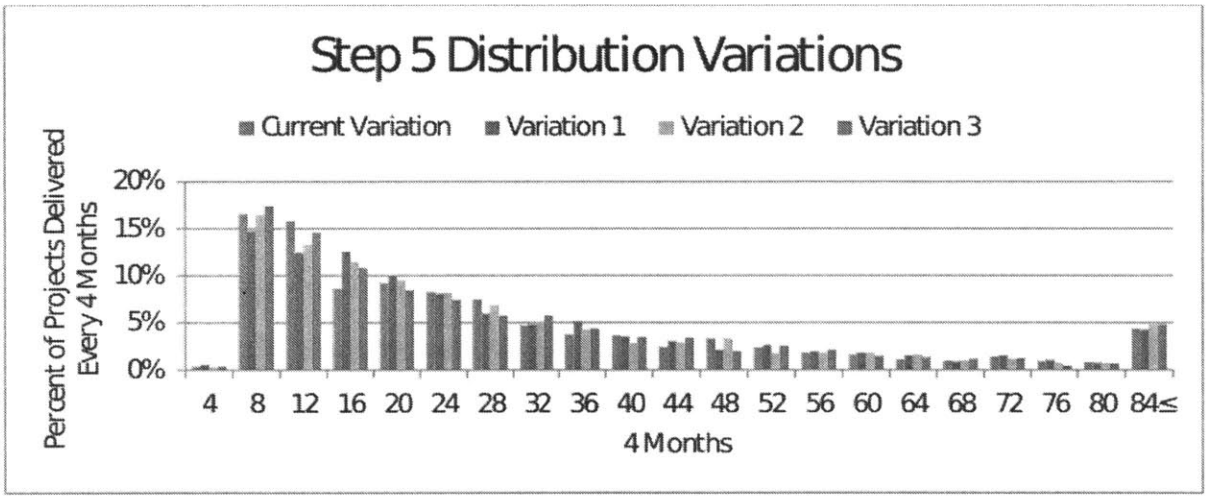


Figure B2 2: Comparison of Step 5 Distributions

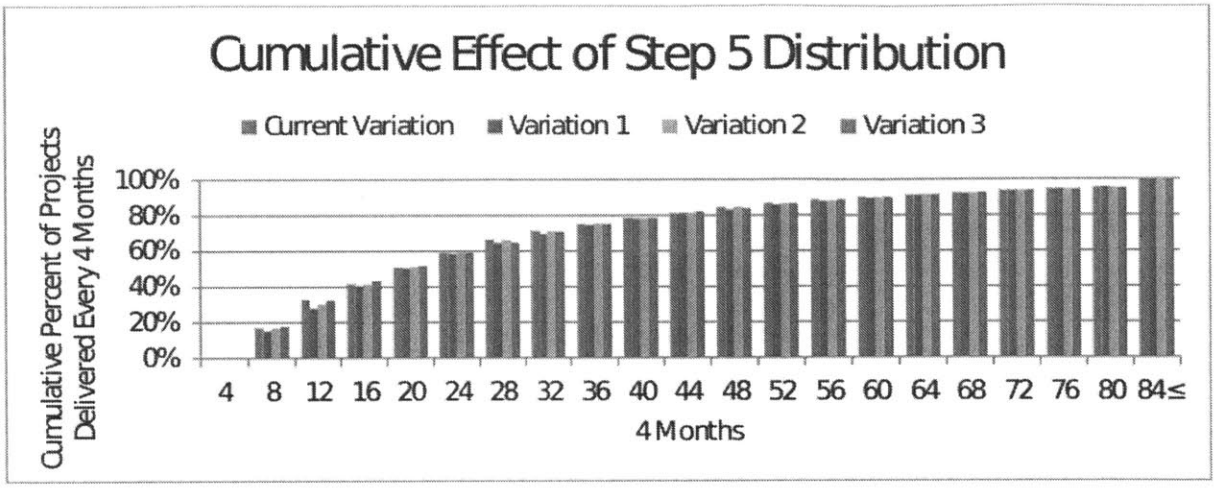


Figure B2 3: Cumulative Comparison of Step 5 Distributions

From this analysis it becomes clear that, timing wise, utilization of Step 5.2 is only beneficial with an even distribution of projects going to each step. However, Step 5.2 is external, unlike 5.1 and 5.3, and Group B1 experience very high utilization (~90%), which can be slightly reduced by sending some of Step 5's work to another group. It will require further investigation, potentially through piloting, to determine if implementing Step 5.2 is beneficial. The simulation does show that the effects of implementing Step 5.2 are only slightly detrimental at worst, so piloting to determine the true effect would be beneficial.

Effects of TRL Variation

Nine TRL variations were tested, as shown in Figure 15.

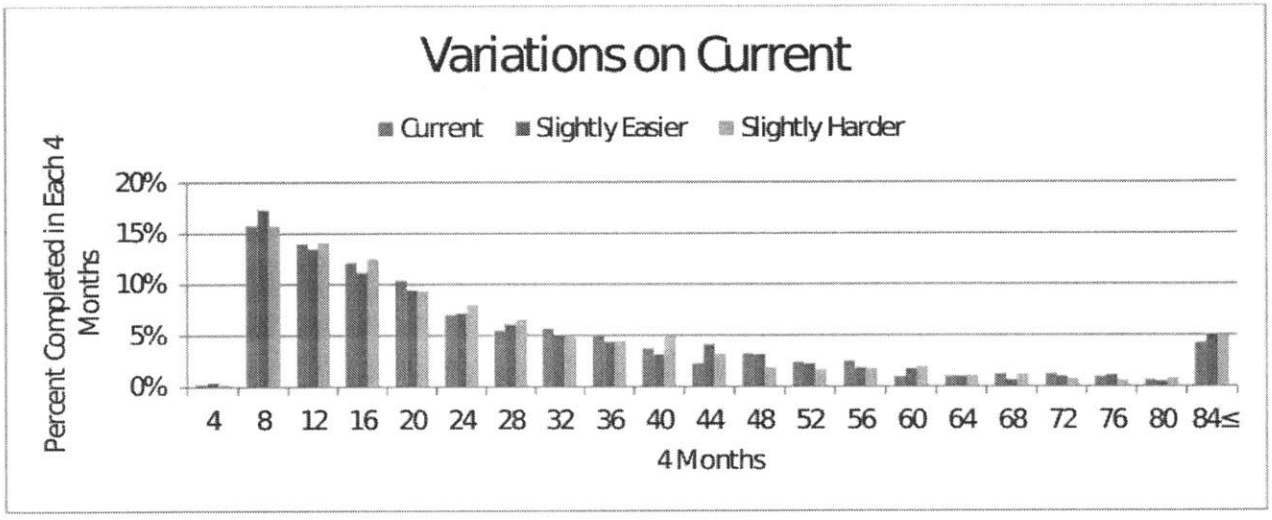


Figure B2 4: Variations from Current TRL

Variation of current TRLs showed expected reactions; slight variation results in slight changes in percent completed each month. It is interesting to note, however, that the case for Group B1 is not nearly as

clear cut as for Group A. For projects that are completed quickly, easier projects take less time and harder projects are roughly equivalent to current. However, the curves are not smooth for Group A. This is particularly evident around months 40 and 44, where both easier and harder clearly deviate from the trend. Looking at the extremes, the reasons for these deviations become apparent.

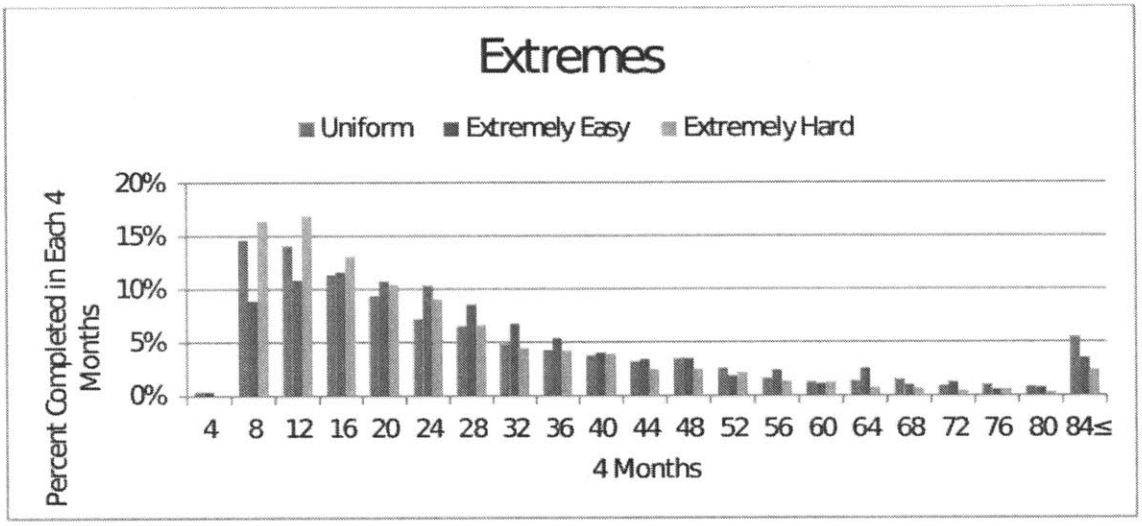


Figure B2 5: Extreme TRL Variations

Contrary to basic expectations, Extremely Hard TRLs take less time than Extremely Easy. This is where the potential bottleneck at Step 4.1 becomes relevant. Extremely Hard TRLs bypass the bottleneck entirely, while Extremely Easy TRLs have all projects passing through it. Clearly, there is the potential for a bottleneck at this step, though may not yet have an effect on overall production times. In reality, if a situation like this occurred, it would be trivial to increase capacity for Step 4.1 while decreasing capacity for Steps 4.2 and 4.3 at the same time, as the only, as they are constrained by personnel (all of whom know how to do Step 4.1) and not equipment. Nevertheless, Step 4.1 should be carefully watched for potential issues,

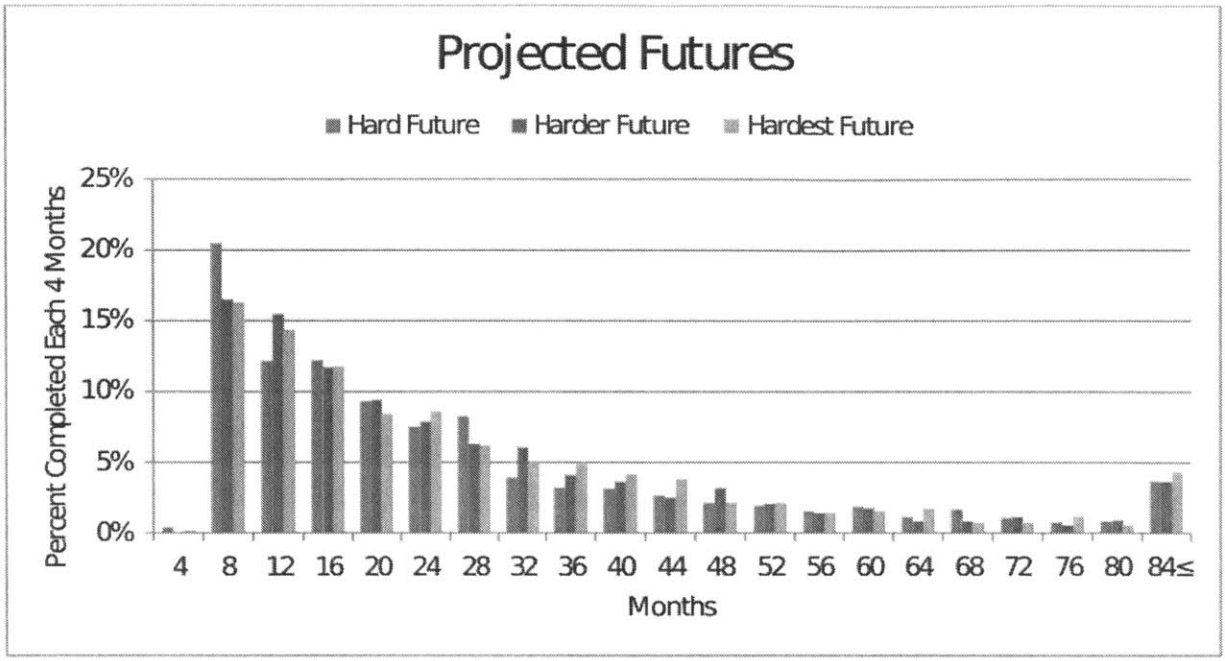


Figure B2 6: Projected Future TRL Variations

Projected Futures tells one important thing about Group B1. Essentially, the prospective bottleneck at Step 4.1 is not yet an issue; as TRL increases in difficulty, time to produce also increases. If the bottleneck, which disproportionately effects easy projects, were truly a problem right now, production times would decrease while difficulty increased. This does happen a bit when comparing more difficult futures to the current situation (see Error! Reference source not found.), so there is some effect from he prospective bottleneck, but it is not yet an extreme issue.

Analysis of Future and Step 5 Distribution

Given the uncertainty around the potential benefit of implementing Step 5.2, it is worthwhile to see if its implementation may have more positive benefits in the future.

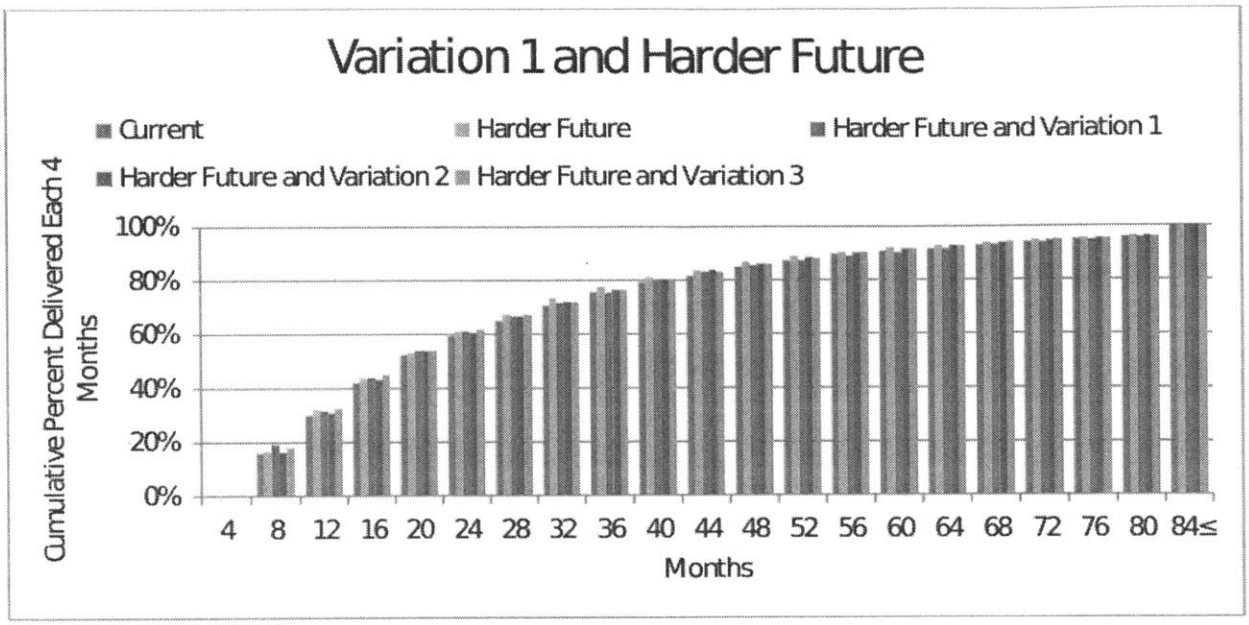


Figure B2 7: Cumulative Effects of Step 5 Variations and Harder Futures

The results of this analysis are very interesting. Variation 1 provides an initial benefit for projects that take less than 28 months and then lags behind the other potential futures for the remaining. Variation 2 generally lags behind all other futures. Variation 3, which was previously found to be potentially beneficial, continues to be so. Early on, it matches or exceeds the percentage of projects delivered by having no step 5.2. Implementing Step 5.2 continues to be something worth further investigation.

Section B.3: Group B2

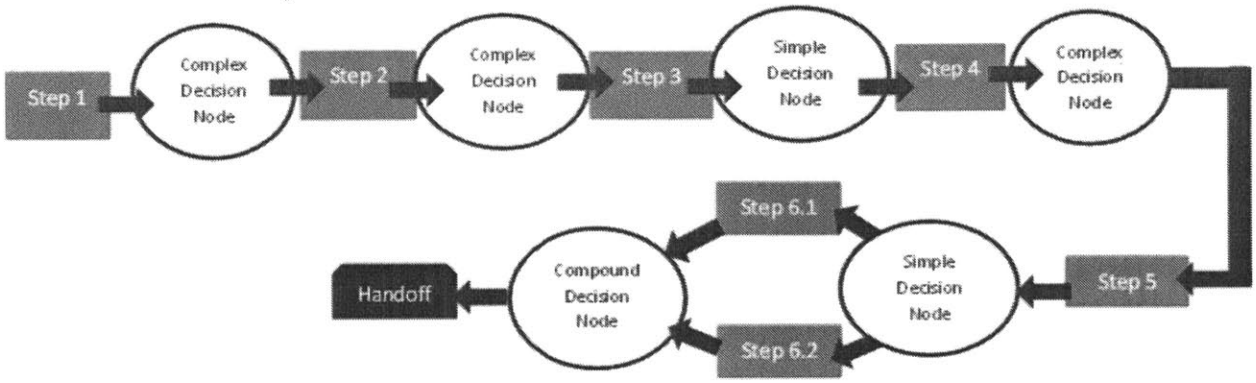


Figure B3 1: Simplified Overview of Simulation

Backtracking omitted for clarity; See process map in Appendix A for non-simplified version

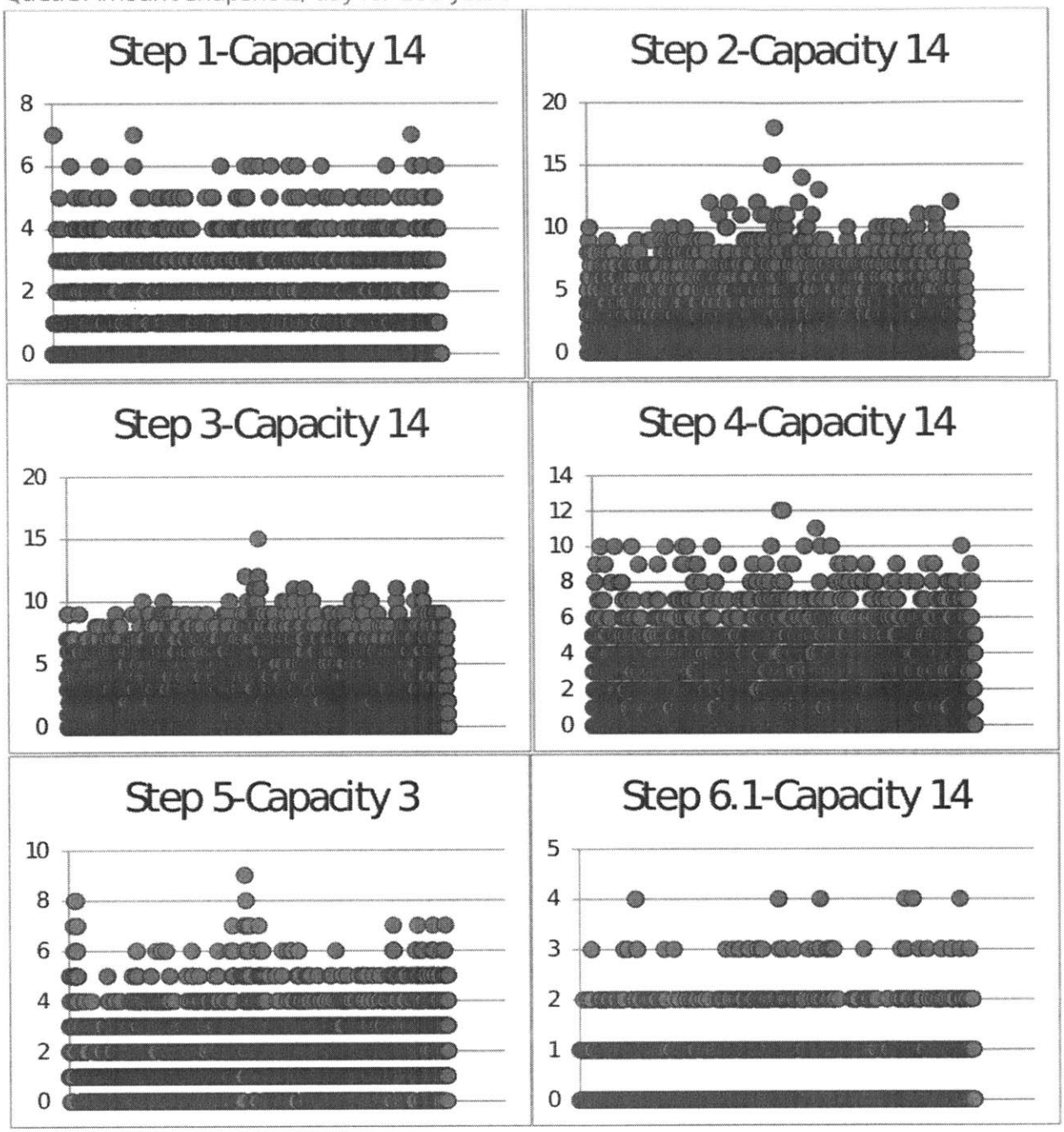
Personnel are assigned projects in Step 1 and follow them for the duration, except for Step 5. Step 5 is performed by a very small group of dedicated experts.

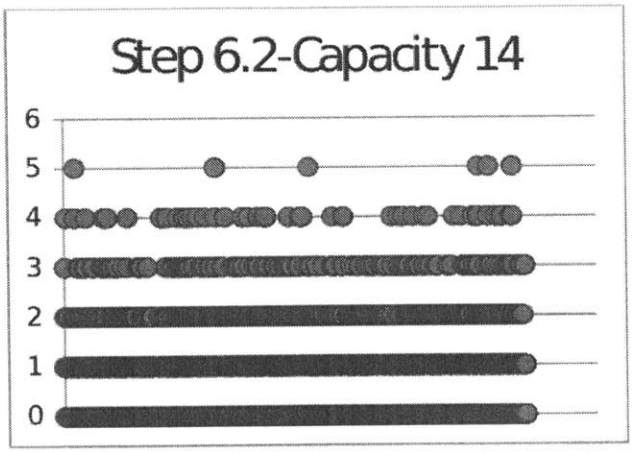
Preliminary Results

	Average Queue Size	Maximum Queue Size	Average Wait
Step 1	0.79 Projects	8 Projects	4.53 Days
Step 2	2.13 Projects	19 Projects	8.04 Days
Step 3	2.59 Projects	15 Projects	5.54 Days
Step 4	2.12 Projects	12 Projects	6.54 Days
Step 5	1.55 Projects	9 Projects	9.56 Days
Step 6.1	0.32 Projects	5 Projects	4.88 Days
Step 6.2	0.74 Projects	6 Projects	6.16 Days

These results match expectations fairly closely. Most steps have around 1 week of lag time, which is expected. Steps 2 and 5 have almost 2 week wait time[], and []hould be looked at further. Step 2'[]lag i[] largely biology related; often, determining what works for this step is trial and error, resulting in relatively high backtracking and churning. Step 5, however, has an over-utilized (100%) subgroup.

Queue Amount Snapshots/ day for 100 years





Looking at the Queues for Steps 2 and 5 tells us quite a bit. First, the sharp spikes characteristic of a bottleneck are absent from Step 2. In addition, the number of projects in Step 2's queue is less than the capacity virtually all the time. This supports the assertion that the longer wait times for Step 2 are not, in fact, indicative of a bottleneck. The situation is markedly different for Step 5. First, Step 5 consistently has a queue of roughly 2-3 times its capacity. Sharp spikes are evident, and the average queue size (about 2 projects) is very close to the step capacity of three projects. Utilization of the subgroup responsible for step 5 is 100%. It is clear that Step 5 is a serious bottleneck.

Proposed Bottleneck at Step 5 Fixes

Figure B3 2: Effects on Delivery Times of Additional staff at Step 5

The effects of adding additional staff at Step 5 are not quite as clear cut as for Group A. While there is a massive improvement in utilization with the addition of just one staff member, and there is an obvious improvement with the addition of 2, there is an unusual dip at 12 months for 1 additional staff member.

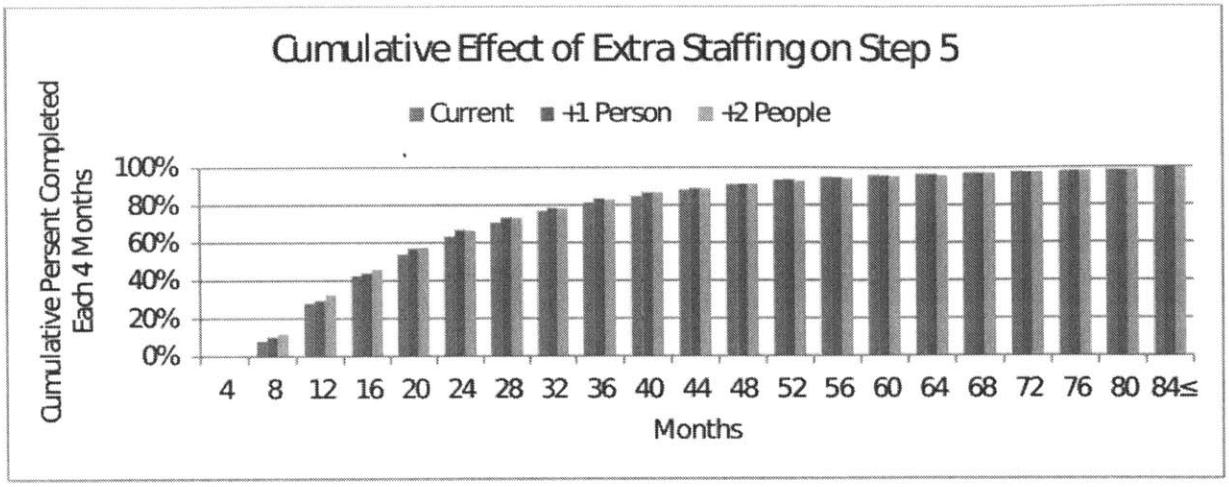


Figure B3 3: Cumulative Effects of Additional Staff at Step 5

From looking at the cumulative percent complete over time, things become much clearer. Having an additional staff is indeed consistently beneficial, though a second staff member initially produces even better results. By month 24, the benefit of a second staff member is roughly equivalent to that of a first. By month 44, any additional staff has no effect on percentage delivered. Therefore, an additional staff member is a good idea, but a second would have reduced effect and is likely unnecessary.

Effects of TRL Variation

Nine TRL variations were tested, as shown in Figure 15.

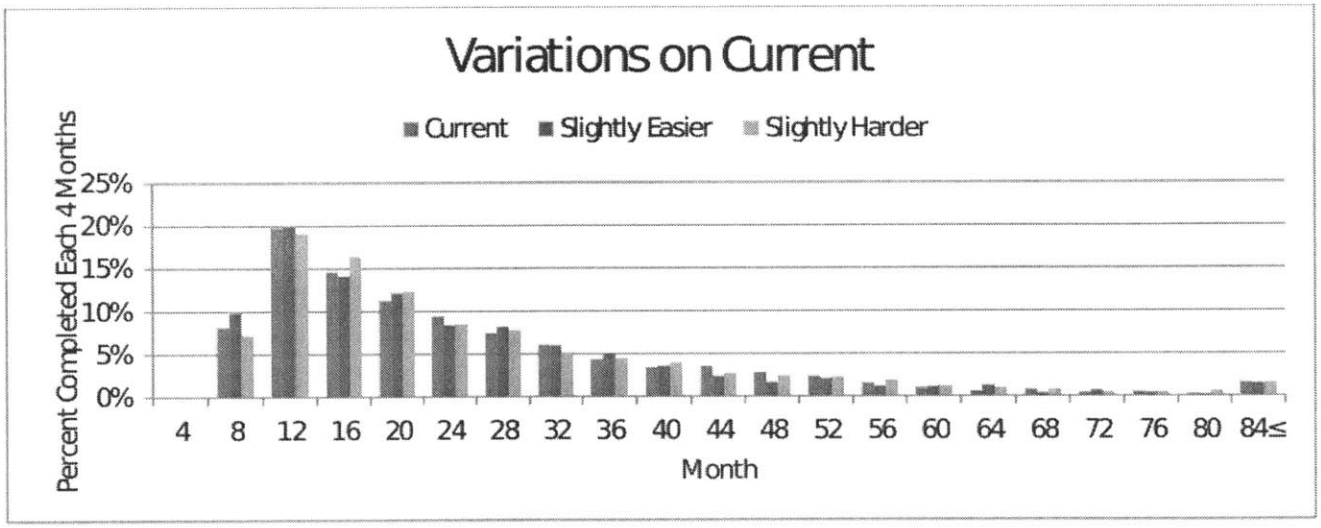


Figure B3 4: Variations on Current TRL

Group B2 reacts as expected to slight variation in current TRLs. Easier TRLs result in faster project completion, while harder TRLs take longer. This is also apparent for extreme TRLs.

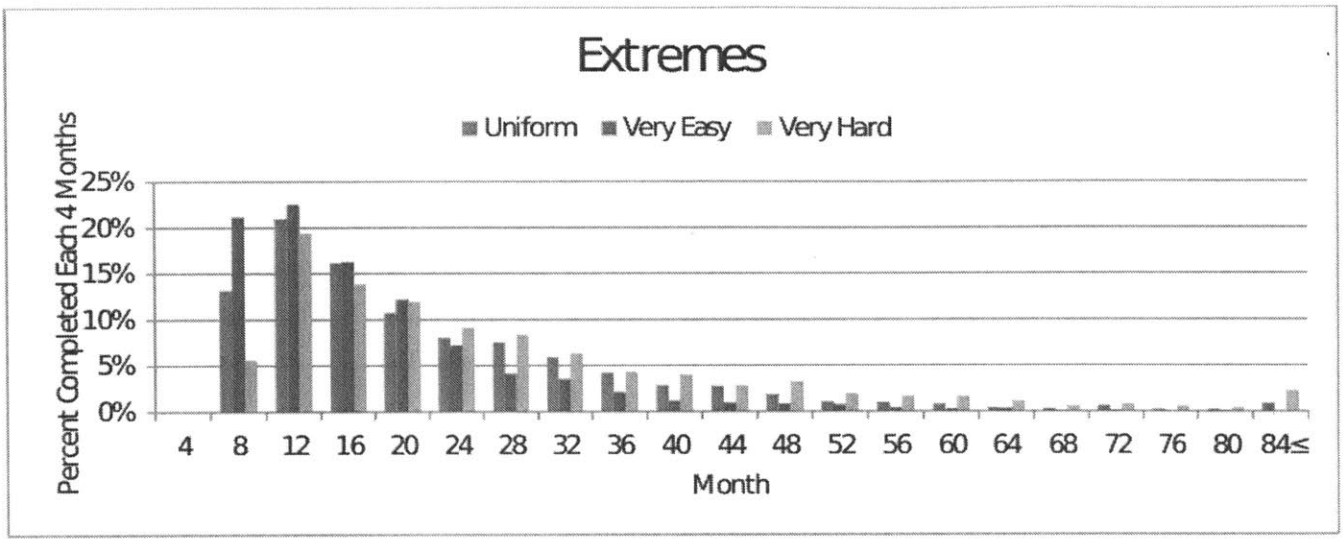


Figure B3 5: Extreme TRL Variations

Group B2's process is far less sensitive to extreme TRL than other groups. This is because, as previously mentioned, most of Group B2's time constraints are biology-based. Therefore, TRL variation only effects the outcomes of decision nodes.

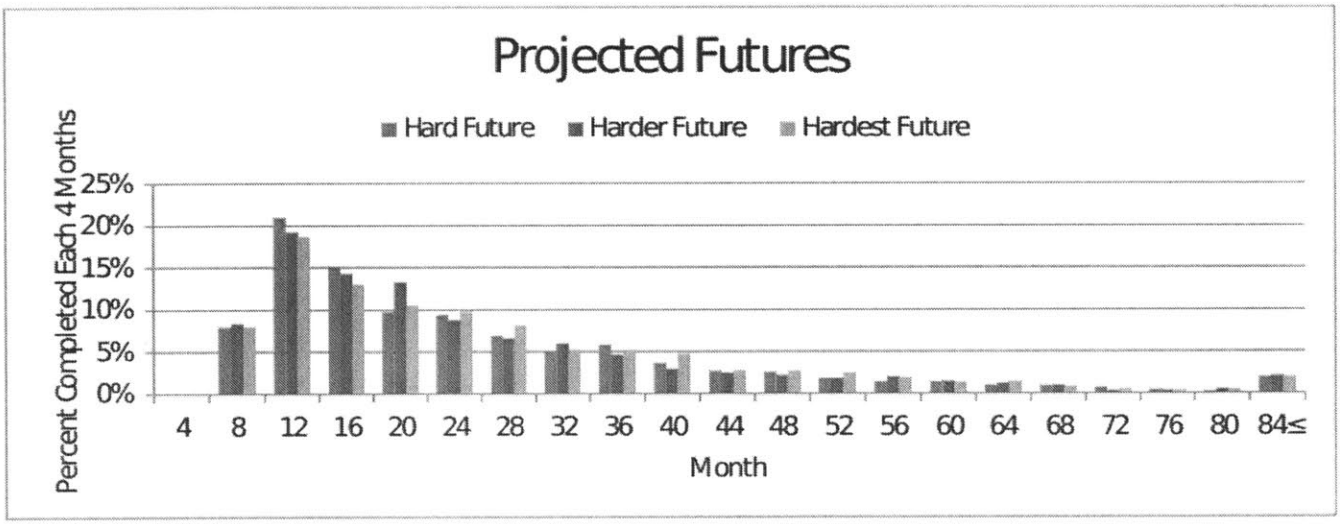
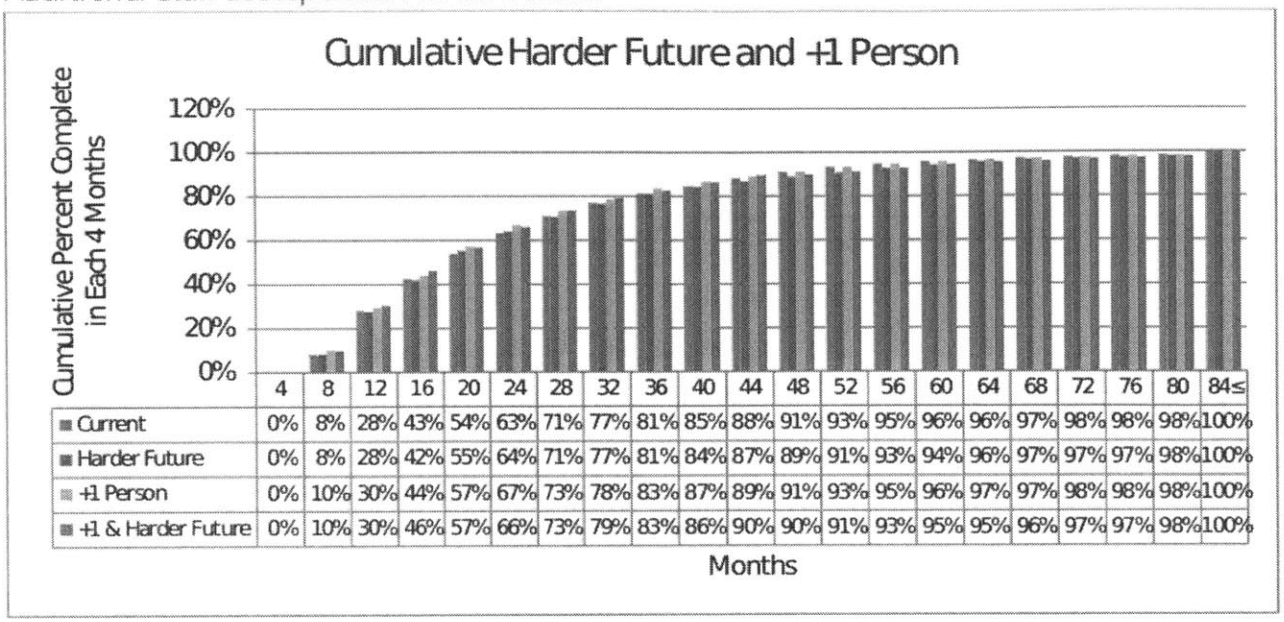


Figure B3 6: Projected Future TRL Variations

As expected, as project difficulty increases, so do delivery times. By month 48, the number of projects has again equalized.

Additional Staff at step 5 and Harder Future



	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84≤
Current	0%	8%	28%	43%	54%	63%	71%	77%	81%	85%	88%	91%	93%	95%	96%	96%	97%	98%	98%	98%	100%
Harder Future	0%	8%	28%	42%	55%	64%	71%	77%	81%	84%	87%	89%	91%	93%	94%	96%	97%	97%	97%	98%	100%
+1 Person	0%	10%	30%	44%	57%	67%	73%	78%	83%	87%	89%	91%	93%	95%	96%	97%	97%	98%	98%	98%	100%
+1 & Harder Future	0%	10%	30%	46%	57%	66%	73%	79%	83%	86%	90%	90%	91%	93%	95%	95%	96%	97%	97%	98%	100%

Figure B3 7: Cumulative Effects of Harder Future and Additional Staff at Step 5

It is clear that having an additional staff member at Step 5 for Group B2 would be beneficial in the future. With an additional staff member, project delivery times in the future would still be improved compared to the current situation. The improvement between Harder Future and Harder future with an additional staff member hovers around 2%, so while there is a clear improvement, it is not huge. The best solution would be to cross-train additional staff to assist with this process. This occurs occasionally with members of Group C assisting when there is a large queue. Having this assistance occur as a preventative measure, rather than after a queue arises, would be far more beneficial.

Section B.4: Group C

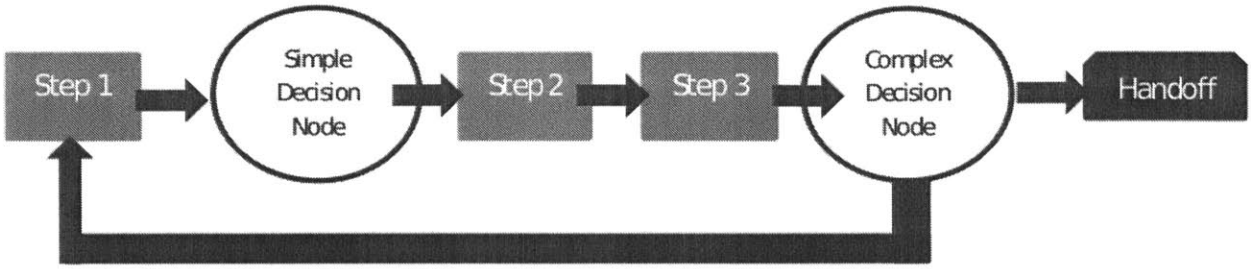


Figure B4 1: Simplified Overview of Simulation

Minor backtracking omitted for clarity; See process map in Appendix A for non-simplified version

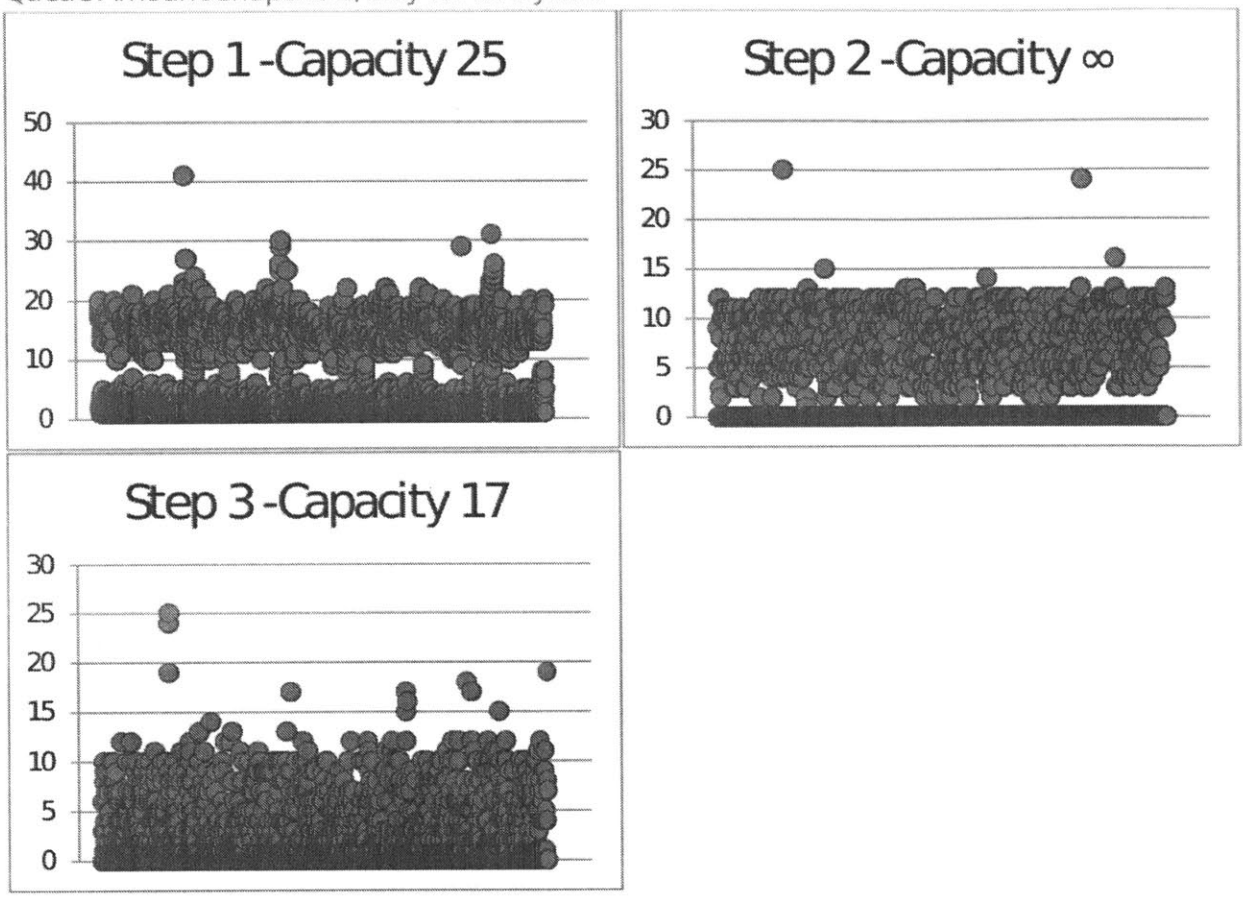
As previously stated, Group C's process is cyclical rather than linear. Most projects are assigned to individual team members; some team members work in pairs on twice the number of projects. Step 2 is performed externally.

Preliminary Results

	Average Queue Size	Maximum Queue Size	Average Wait
Step 1	6.35 ξ	46 ξ	12.11 Days
Step 2	2.04 ξ	25 ξ	7.39 Days
Step 3	1.21 ξ	25 ξ	4.49 Days

These results roughly match what is expected. It is definitely true that the longest wait times are for Step 1. In some ways this is an advantage, rather than an issue, as it allows projects that have fragmented into subprojects at multiple stages time to catch up. The accuracy of the Step 2 and Step 3 wait times is more suspect, but given the lack of available data it is acceptable. In order to determine possible bottlenecks it is necessary to look at each step's queuing.

Queue Amount Snapshots/ Day for 100 years



No obviou bottleneck are evident when looking at Group C' queue Step 1 consistently has queues that are 80% of its capacity, and shows slight spiking, but nothing truly significant. In fact almost all high queue counts in Group C are single points, some of which are significantly reduced immediately and some of which reduce over a day or two. This indicates that they are the results of large amounts of ξ entering simultaneously, rather than the gradual buildup of a queue whose following step cannot keep up with the influx of new work. If there is a bottleneck, it is at Step 1, but as previously noted this may not be a problem.

Effects of TRL Variation

Nine TRL variations were tested, as shown in Figure 15.

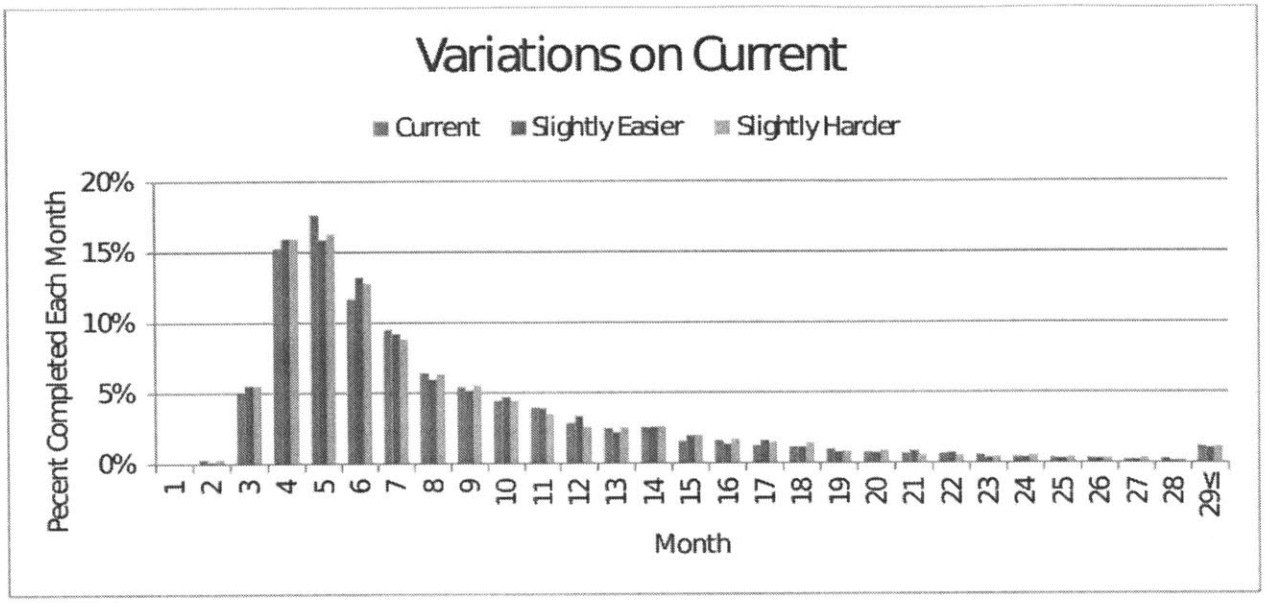


Figure B4 2: Variations of Current TRL

Variations on the current TRL produces very small variations in percent delivered each month. This simulation is far less dependent on TRL than the other simulations, so this makes sense. The changes themselves are somewhat unexpected; both slightly easier and slightly harder TRLs have nearly the same effect on delivery times, and current TRL assumptions do not have results that fall between the two. This simulation is built with minimal data to work with the current assumptions; it makes sense that varying these assumptions, even if only slightly, would have unexpected results.

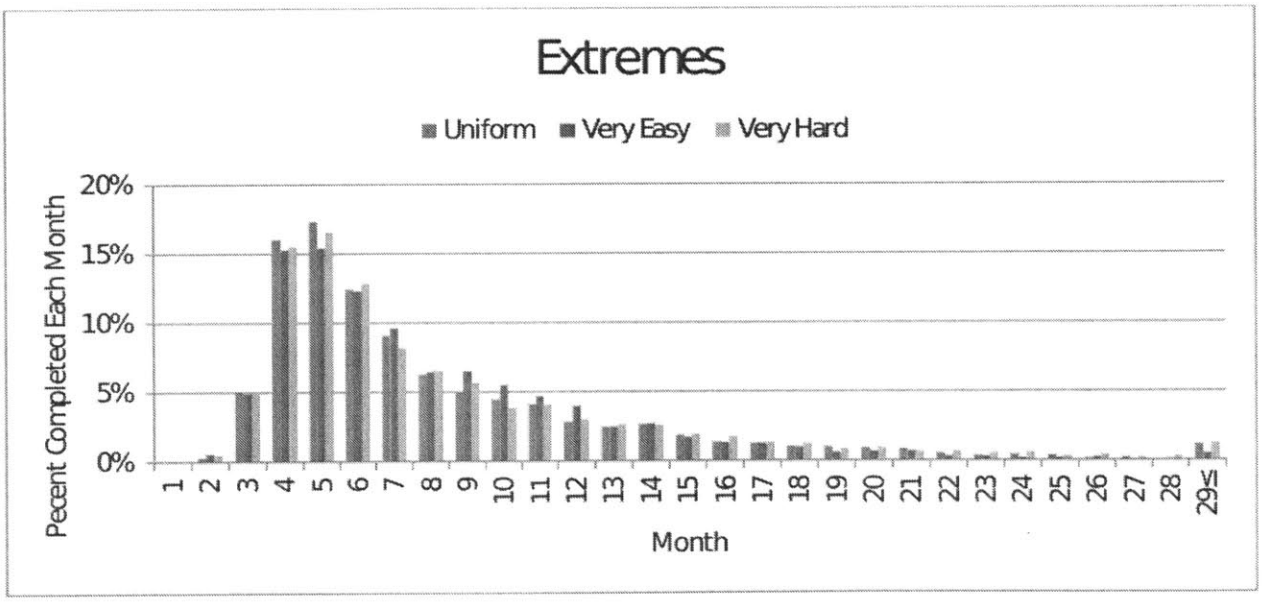


Figure B4 3: Extreme TRL Variations

Extreme TRL variations are very illuminating for Group C, as they magnify the differences hidden in by smaller variations. The primary effect of TRL is how often a ξ cycles through Group C. It makes sense,

therefore, that an easy distribution would take less time than a hard distribution. According to the simulation, however, this is not the case. This may be the result of the assumption that the number of ξ per project i independent of TRL and the general lack of TRL dependencie in the mulation. This causes the simulation to be accurate in only a narrow band of TRLs. Clearly, more data is needed to properly under and Group C' Proce

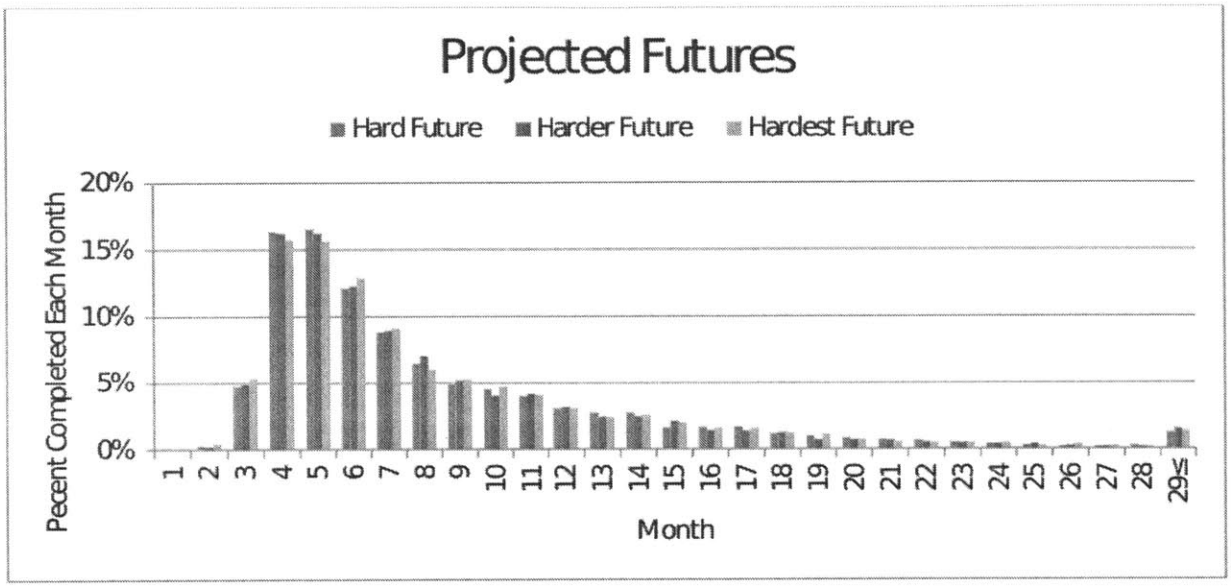


Figure B4 4: Projected Future TRL Variations

Projected future variations are slightly better behaved than the other variations; it is possible that the simulation is biased to be more accurate at harder TRLs. Projected future assumptions also have little effect on project delivery times. Hardest Future delivers more projects in month 3, but the other two variations catch up in month 4. Similar things occur between months 5 and 6. In general, while the simulation is fairly accurate for current TRL levels, it cannot accommodate TRL variations without more data.

Section B.5: Group D

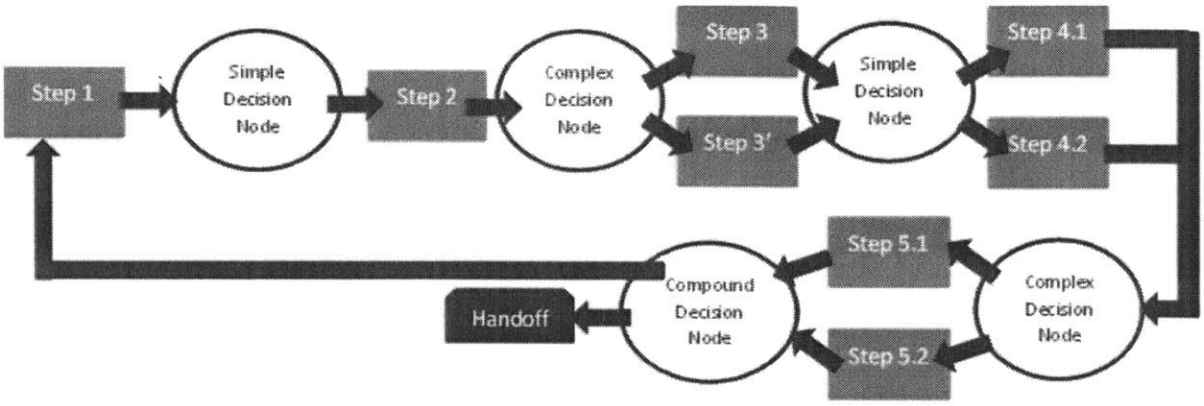


Figure B5 1: Simplified Overview of Simulation

Minor backtracking omitted for clarity; See process map in Appendix A for non-simplified version

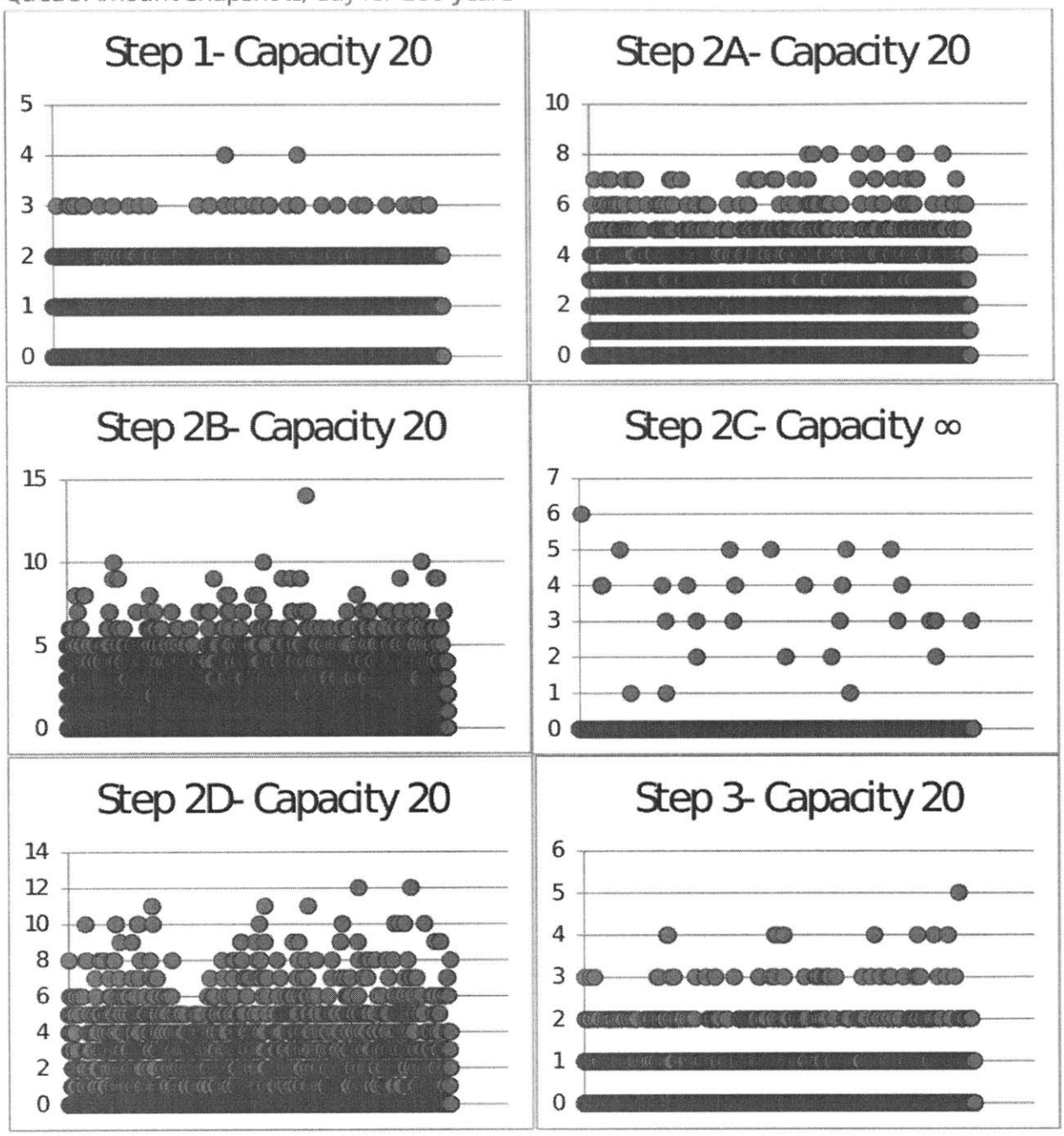
Group D's process is almost identical to Group B1's with an additional initial step and some latter simplification. Additionally, there is a relatively large chance that a project will pass through the entire process 2-3 times.

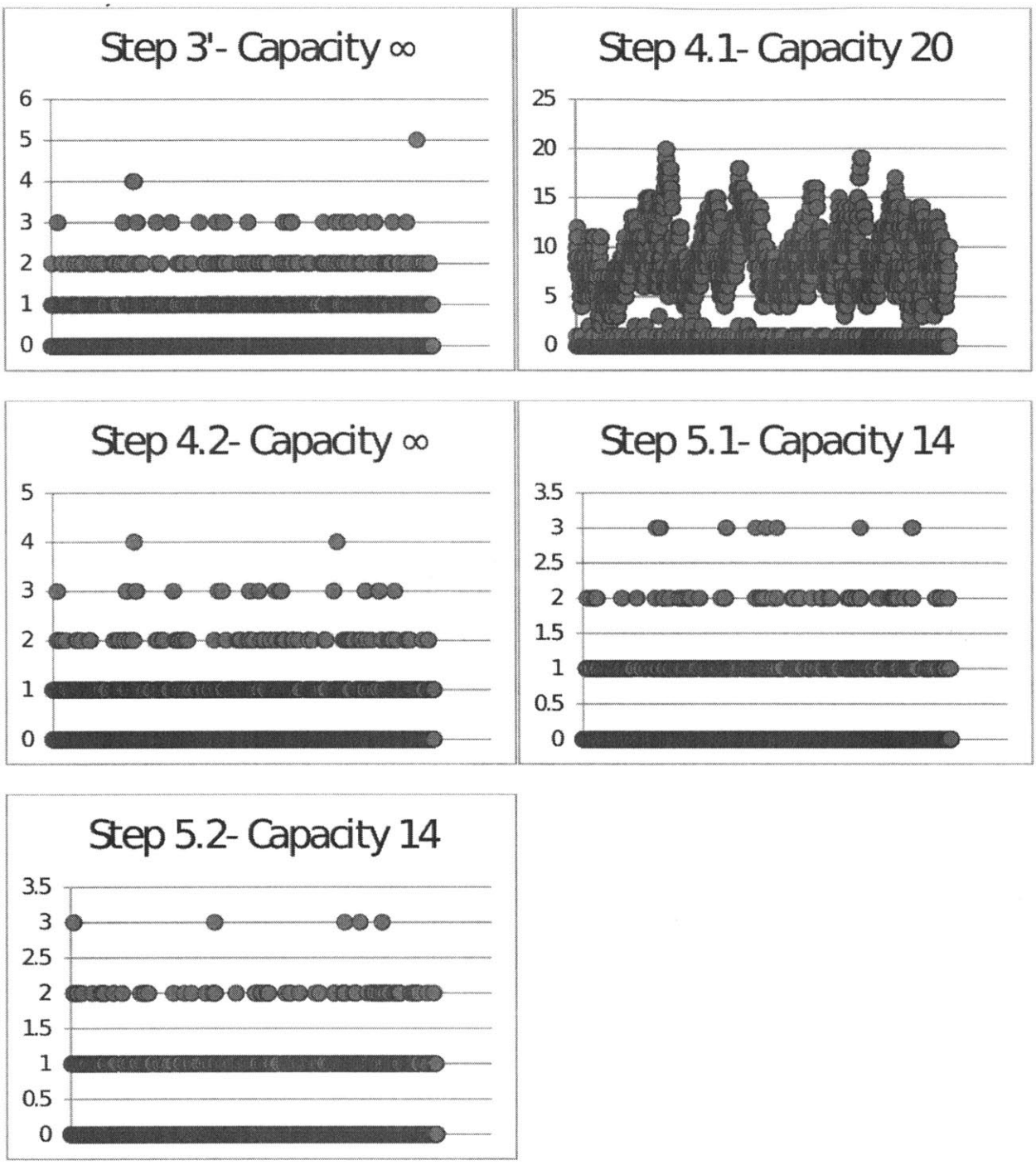
Preliminary Results

	Average Queue Size	Maximum Queue Size	Average Wait
Step 1	0.78 Projects	4 Projects	12.91 Days
Step 2A	1.49 Projects	10 Projects	7.38 Days
Step 2B	1.48 Projects	14 Projects	5.13 Days
Step 2C	.02 Projects	14 Projects	1.13 Days
Step 2D	1.08 Projects	14 Projects	3.80 Days
Step 3	0.23 Projects	5 Projects	2.46 Days
Step 3'	0.13 Projects	5 Projects	3.86 Days
Step 4.1	5.87 Projects	20 Projects	9.86 Days
Step 4.2	0.15 Projects	4 Projects	2.49 Days
Step 5.1	0.13 Projects	4 Projects	3.42 Days
Step 5.2	0.13 Projects	3 Projects	3.47 Days

These results match expectations. As with Group B1, there is a potential bottleneck at Step 4.1. There is an additional large wait time for Step 1, which is a result of the duration of Step 1 (approximately 20 days) rather than the buildup of a queue. The wait time for step 2A is similarly misleading, as that step takes from 3-4 weeks to complete.

Queue Amount Snapshots/ day for 100 years





The similarities between Group B1 and Group D are readily apparent in their queues. Like for Group B1, all queues except Step 4.1 show no sign of bottlenecking. Step 4.1 shows bottlenecking tendencies (spiking), but the queue never exceeds the step capacity. It therefor bears watching, but is not an immediate issue

Effects of TRL Variation

Nine TRL variations were tested, as shown in Figure 15.

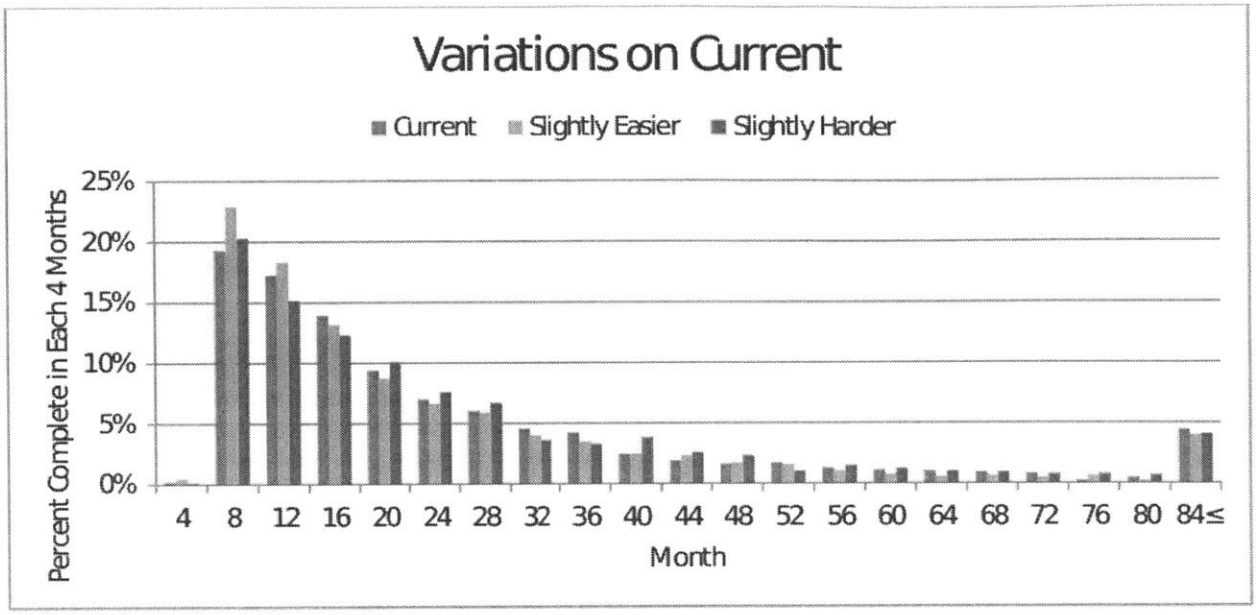


Figure B5 2: Variations on Current TRL

The testing of variations on current TRL levels generally match expectations. Easier TRLs result in faster delivery times, while harder TRLs result in slower. The effect is magnified compared to Group B1 because the probability that a project will cycle through Group D multiple times is dependent on TRL.

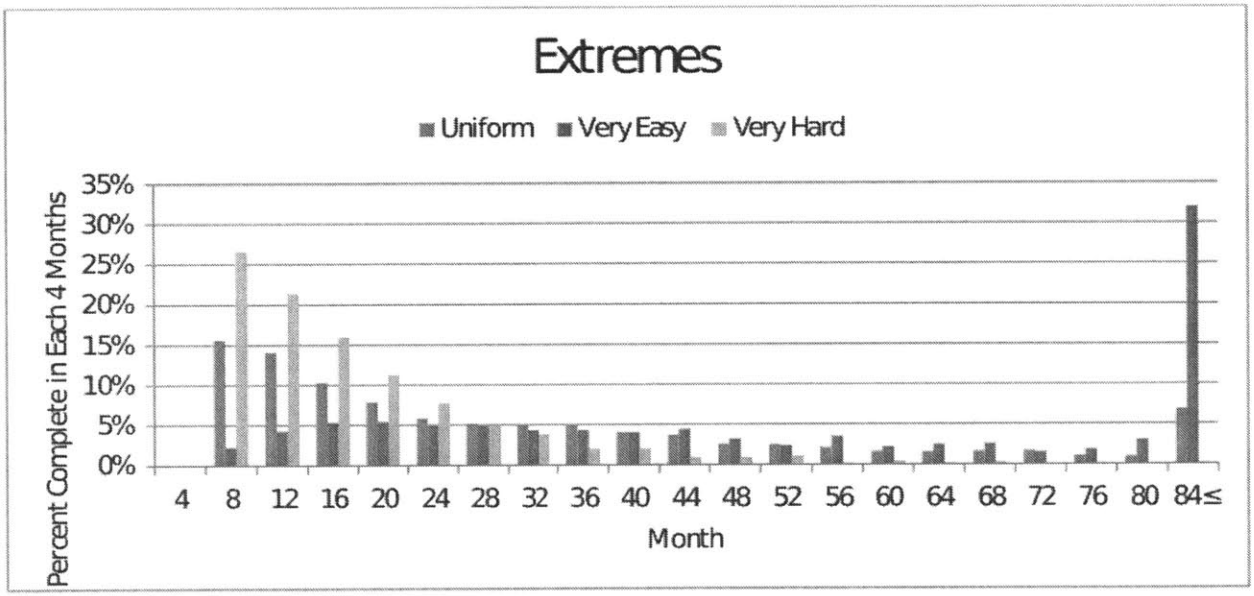


Figure B5 3: Extreme TRL Variations

Like Group B1, Group D has a bottleneck at Step 4.1 for easy projects. This results in the extremely easy TRL distribution having extremely long delivery times. Uniform distribution, having more easy projects, is also affected by this bottleneck, making extremely hard distributions the easiest to deliver. However, like for Group B1, in reality this can be easily compensated for by moving capacity (people) from Step 4.2 to Step 4.1.

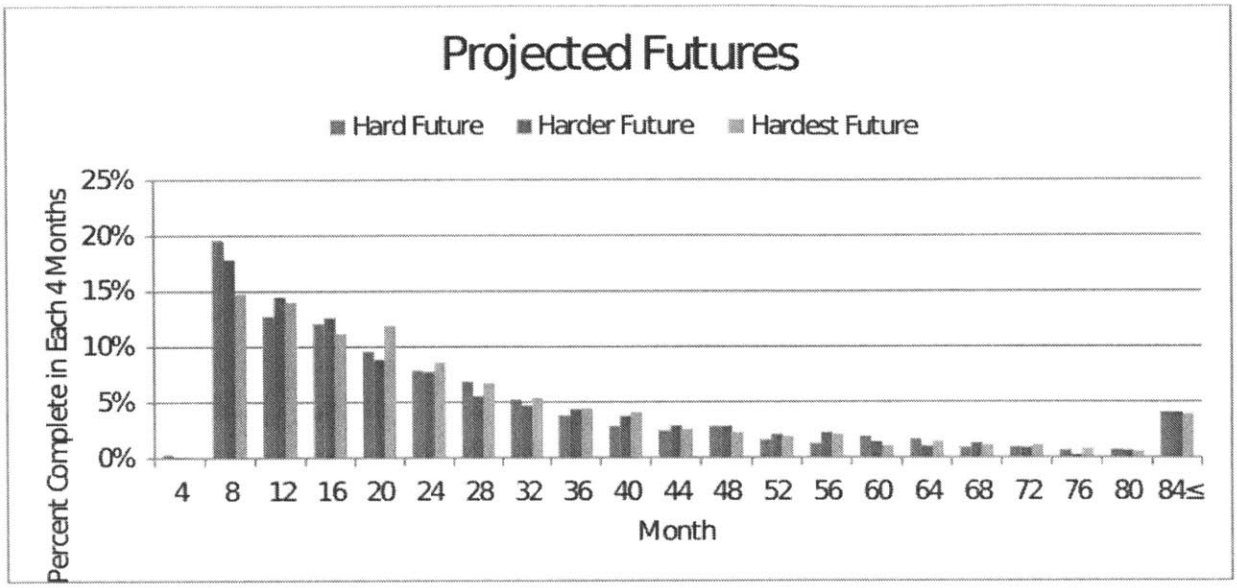


Figure B5 4: Projected Future Variations

Similar to Group B1, early on overall more difficult futures result in longer delivery times. Around months 12 to 24 more difficult futures overtake easier futures, due to the aforementioned easy bottleneck at Step 4.1. Like for Group B1 Step 4.1 needs to be closely monitored to determine if the bottleneck is actually an issue.

Section B.6: Group E

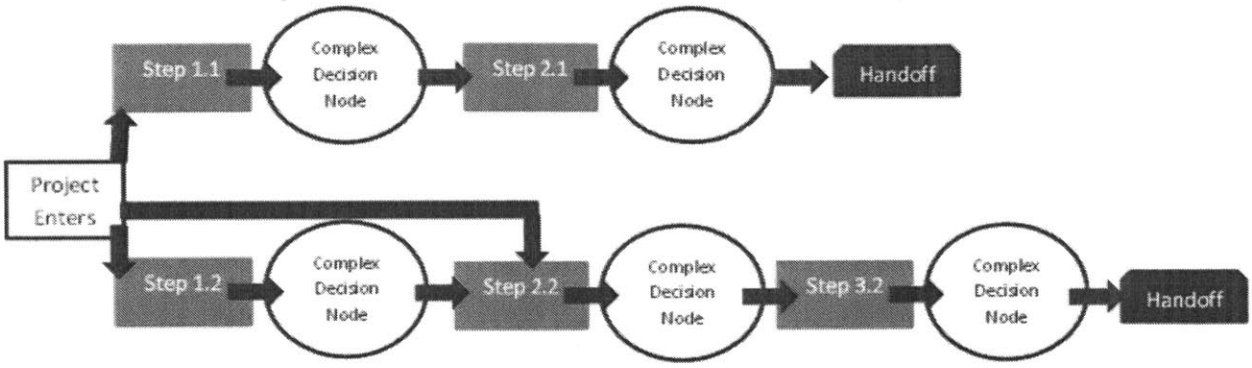


Figure B6 1: Simplified Overview of Simulation
Omits backtracking for clarity; See Process map in Appendix A for non-simplified version

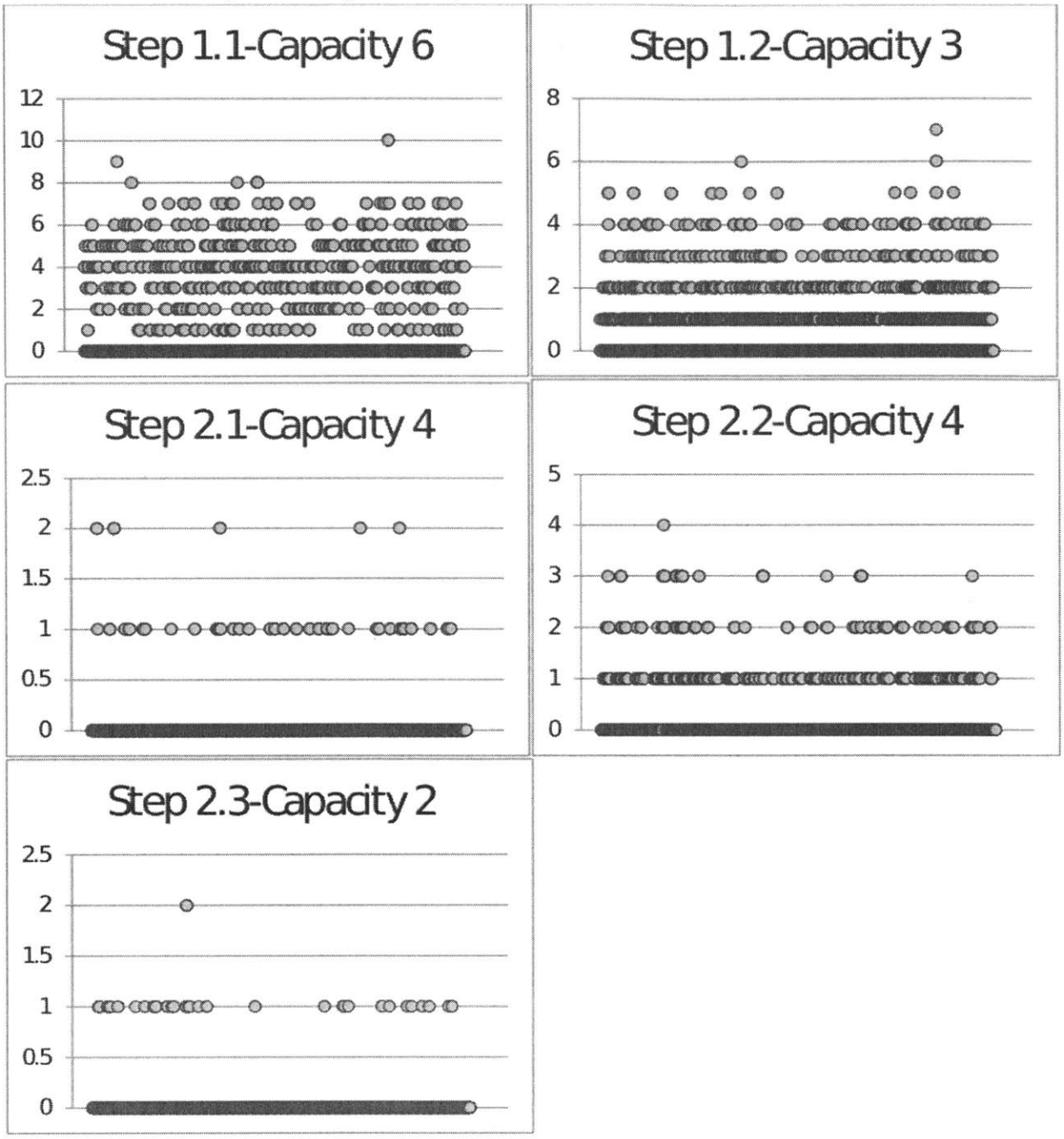
Group E is composed of two distinct subgroups, each of whom controls their own process. The only exception to this is Step 3.2, which while part of the lower process is performed by the group responsible for the upper process branch. These two groups, while part of the same simulation, will be analyzed separately as they are nearly independent processes.

Preliminary Results

	Average Queue Size	Maximum Queue Size	Average Wait
Upper Branch			
Step 1.1	0.75 λ	10 λ	11.14 Days
Step 2.1	0.46 λ	7 λ	6.69 Days
Lower Branch			
Step 1.2	0.02 λ	4 λ	6.17 Days
Step 2.2	0.22 λ	4 λ	9.69 Days
Step 3.2	0.01 λ	2 λ	1.8 Days

While empirical data on wait times does not exist for Group E, these values are reasonable matches for anecdotal data. Steps 1.1 and 2.2 have the longest wait times, which is likely because they are the steps with the longest duration. Additionally, the upper branch has much larger queues, reflecting the larger quantity of projects it deals with.

Queue Amount Snapshots/ day for 100 years



From this data, there is currently no clear bottleneck. However, TRL analysis reveals that this will not always be the case.

Effects of TRL Variation

Nine TRL variations were tested, as shown in Figure 15.

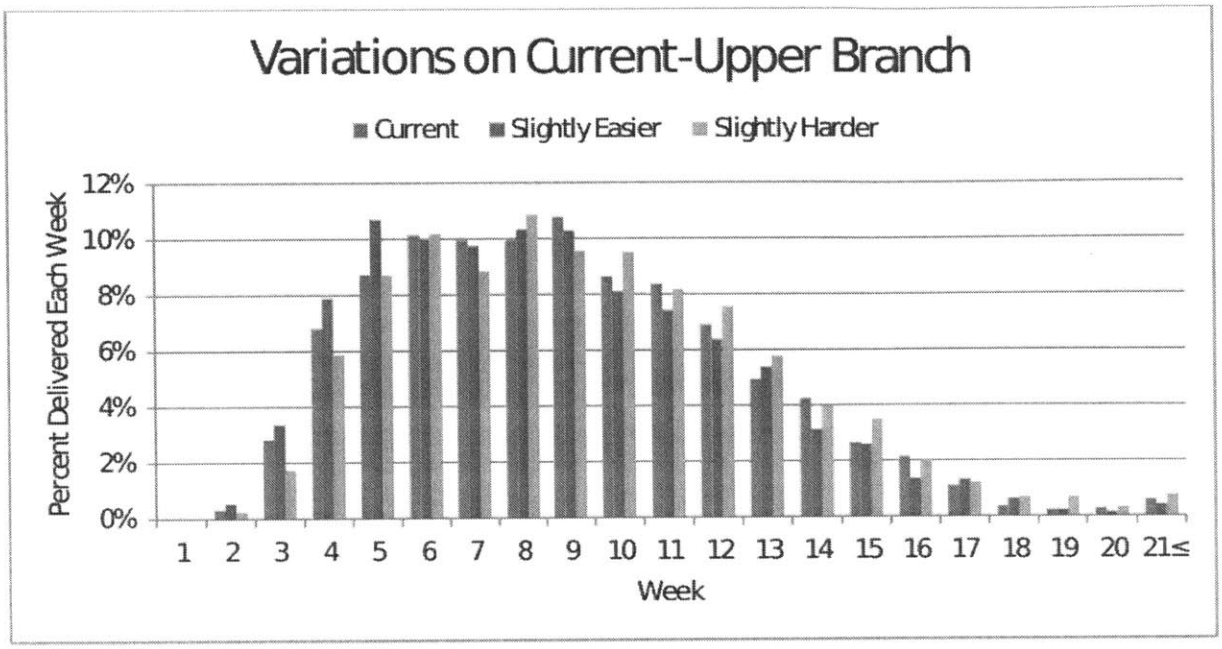


Figure B6 2: Variations on Current TRL-Upper Branch

As expected, easier projects take less time to complete while hard projects take more. The simulation is fairly sensitive to TRL values, which reflects reality. This can also be seen in the extremes comparison.

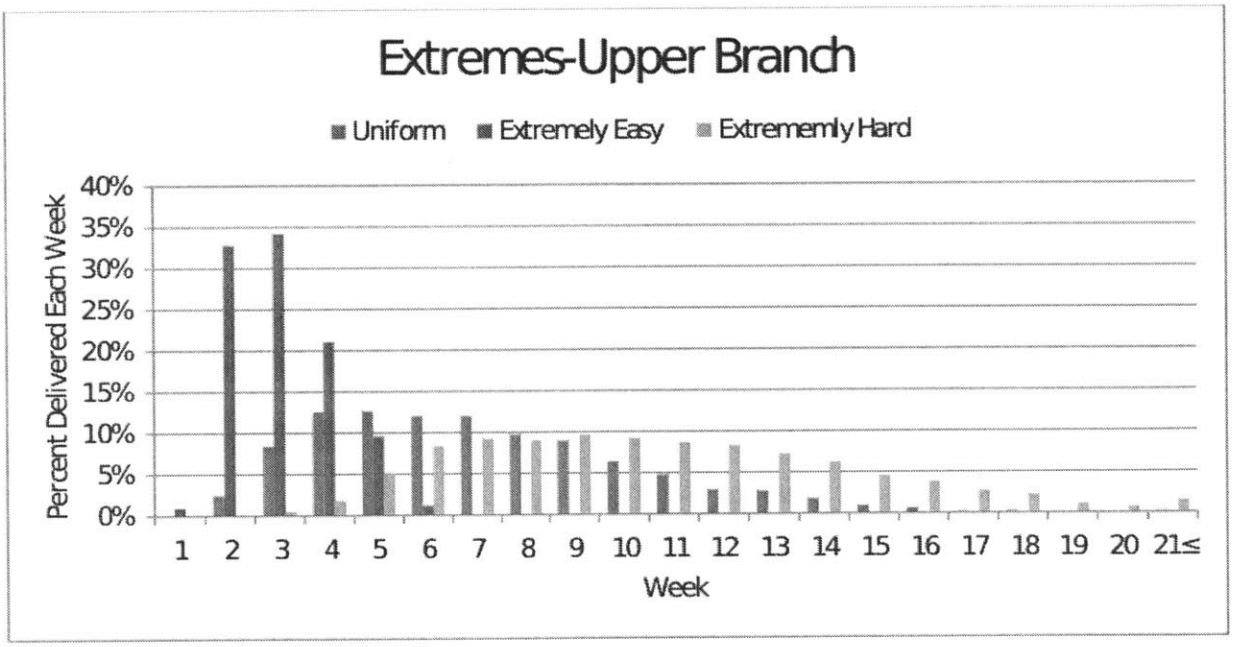


Figure B6 3: Extreme TRL Variations-Upper Branch

Analysis of the extremes provides the expected results- projects for very easy TRL distributions are delivered quickly, they are delivered much more slowly for hard projects, and a uniform distribution falls somewhere between the two.

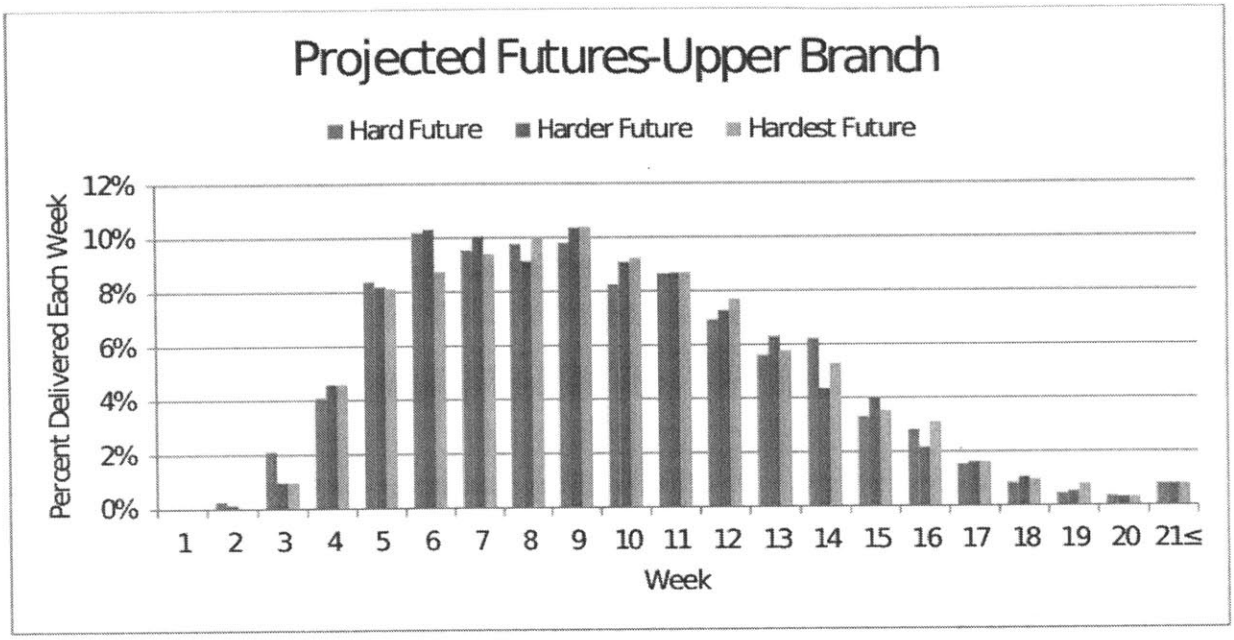


Figure B6 4: Projected Future TRL Variations-Upper Branch

As projected futures increase in difficulty for the upper branch, so do delivery times. This is as expected, as both step duration and decision points are heavily influenced by TRL levels for Group E.

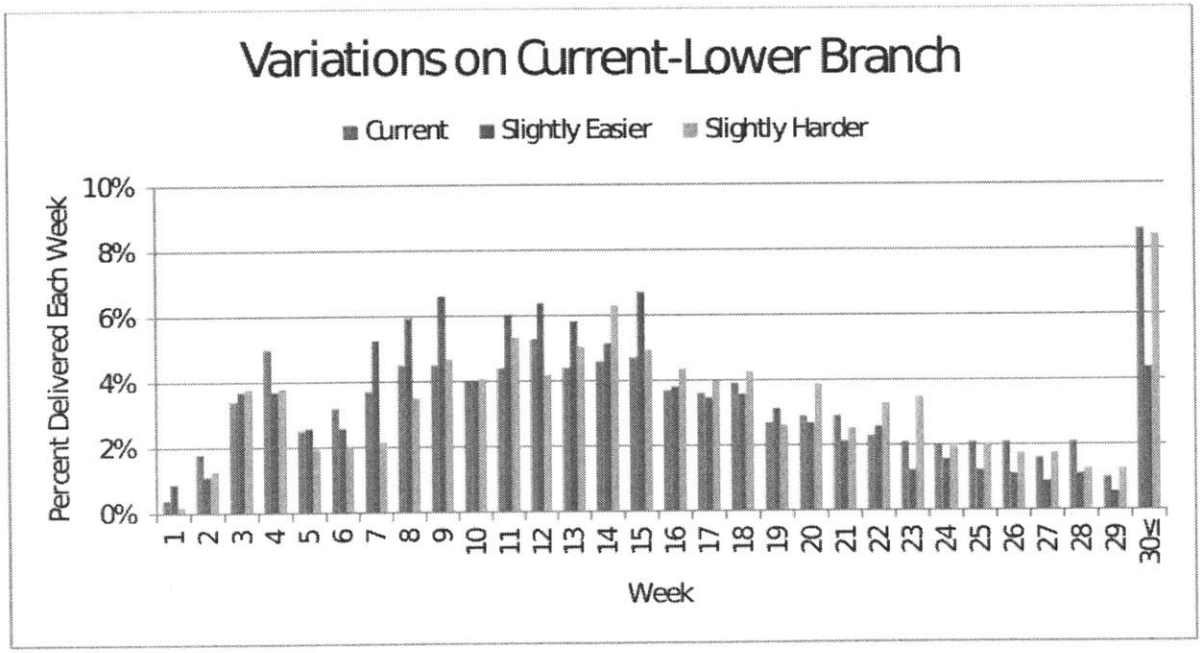


Figure B6 5: Variations on Current TRL-Lower Branch

For this graph, it is important to note that the y-axis scale is much smaller than for most other charts. As a result, the apparently large changes from slight TRL variation are actually at a reasonable scale. Lower

branch delivery times do not have the smooth curve characteristic of most of the other groups; this is due to the potential bypass of step 1.2. The hard distribution is clearly the least efficient. The current distribution results in earlier deliveries for the first 6 weeks, after which the easy distribution quickly overtakes the current distribution. This is, once again, due to the 2.1 bypass.

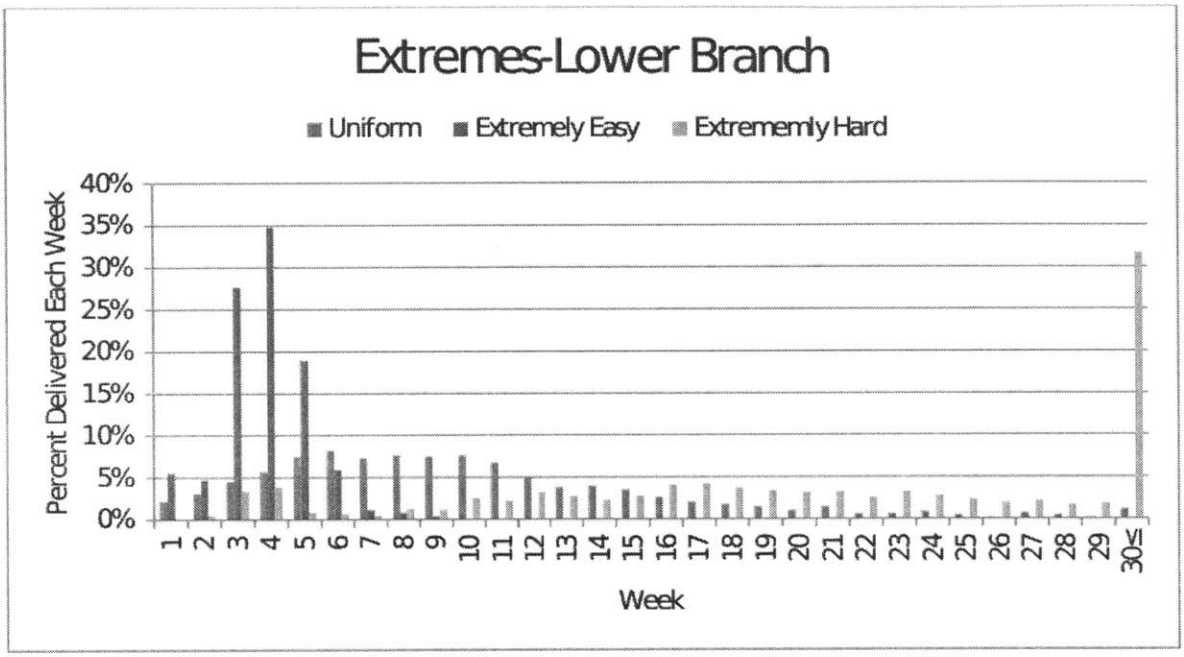


Figure B6 6: Extreme TRL Variations-Lower Branch

Looking at the extremes confirms this distribution is characteristic of the lower branch. Extremely easy TRL settings result in much early project completion, but early on this effect is greatly reduced. Uniform distribution, on the other hand, is essentially a double-peaked bell curve. The hardest TRL distribution results in much slower delivery times with early initial deliveries due to the bypass.

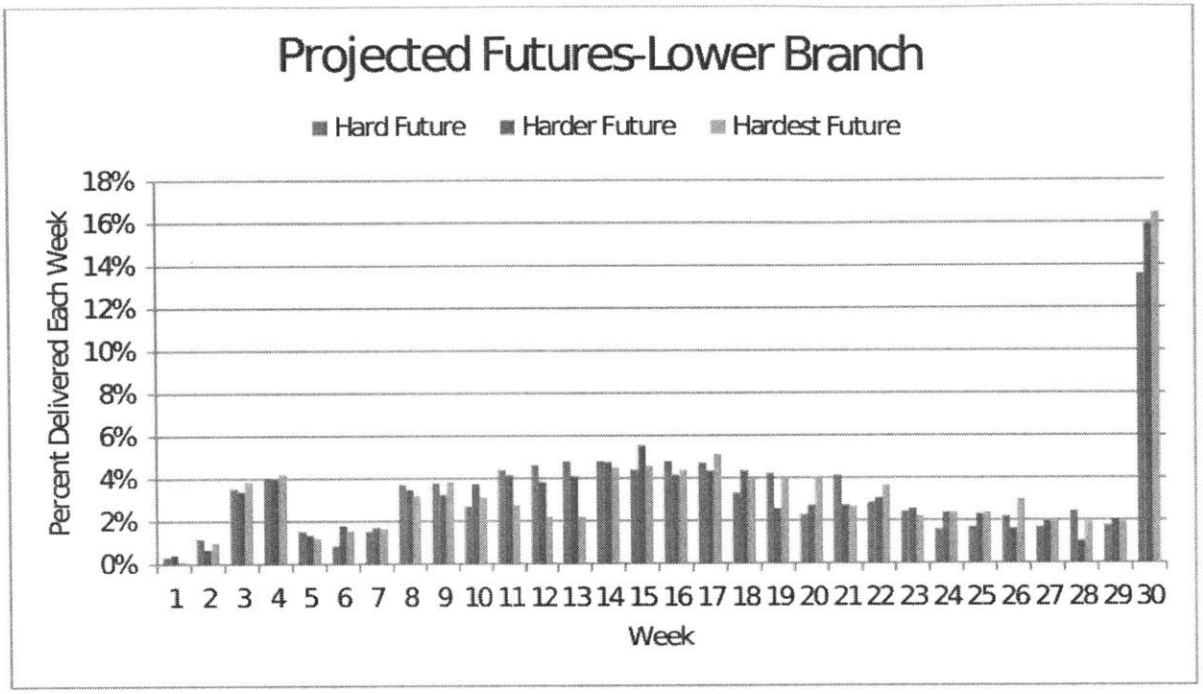


Figure B6 7: Projected Future TRL Variations-Lower Branch

Looking at the projected futures for the lower branch reveals a problem. Even the easiest projected future results in nearly 10% more projects delivered after 30 weeks than current TRL assumptions. Discussion with Group E's lower branch subgroup reveal that this is an expected result. The only reason that current TRL levels are not causing similar delays is through herculean efforts and extensive overtime work. In order to ameliorate these future problems, the potential effect of adding additional staff was analyzed.

Analysis of Extra Staff for Lower Branch

Due to the unique characteristic of TRL variation on Group E's process, cumulative effects are far more informative.

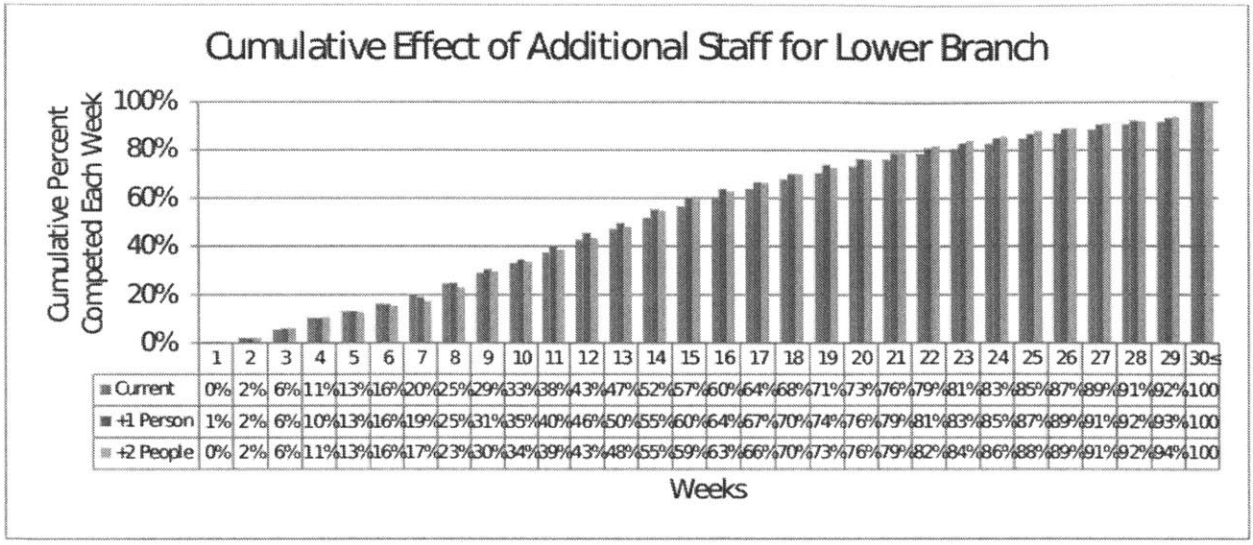


Figure B6 8: Cumulative Effect of Additional Staff for Lower Branch

As expected, additional staff at current TRL levels decreases delivery times, but not by a huge amount. This is because there is not currently a bottleneck. Looking at the effects of additional staff on the projected future TRL tells a different story.

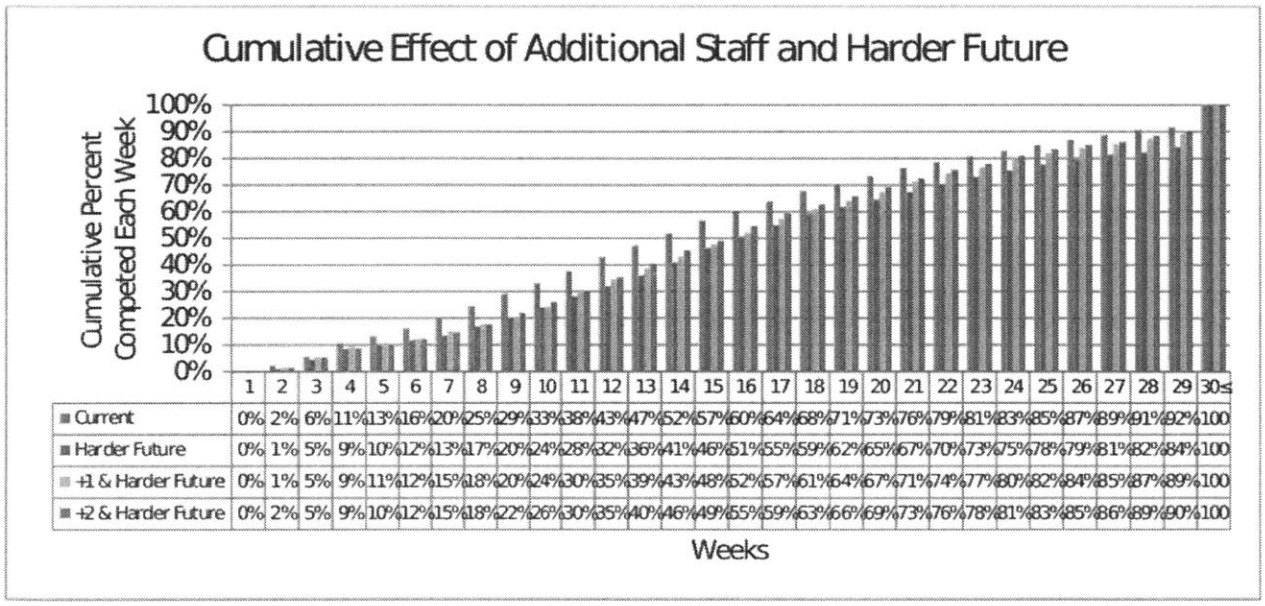


Figure B6 9: Cumulative Effect of Additional Staff and Harder Future

When looking at the effect of additional staffing on projected future project completion, it first becomes apparent that additional staff has very little effect on projects that are delivered early on. However, by week twelve, there is an obvious benefit for each additional staff member. By week twenty-nine, a single additional staff member provides a 5% increase in number of projects delivered. Two provides a 6% increase. In other words, overall delivery times are reduced, and this is more apparent for projects

that would take longer to develop. It is highly recommended that APEG hire at least one additional staff member for the lower branch.

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