Monte Carlo Simulation of Pathogen Reduced Platelet Production

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Abstract: All blood products in Canada undergo testing for transmissible diseases and bacterial contamination. As a result, the risk of a transfusion related infection is estimated at less than 1 in 47,000. Nevertheless, there are infectious agents that are not screened for, as well as the potential for infection from emerging pathogens that are either unknown, or for which screening tests have not been developed. Thus, Canadian Blood Services is introducing pathogen reduction (PR) technologies to further increase the safety of the blood supply. The focus of this study is to identify key input parameters for the PR process and to estimate output dose parameters for the units produced. The unit volume and platelet yield from combining buffy coat platelets into a pool are estimated via Monte Carlo simulation. The value of sorting input buffy coat units according to estimated platelet yield, prior to illumination, is determined. Finally, the model estimates the effects of two different sorting algorithms on output quality control metrics.
The results of the study found that no process changes were required to ensure input units meet input PR process guidelines. However, sorting input units according to platelet yield could significantly improve the proportion of units meeting quality control metrics.

1 INTRODUCTION

Before a blood product can be transfused, numerous safety checks must be completed. All blood products in Canada undergo testing for transmissible diseases and bacterial contamination before being made available to patients. As a result, the risk of a transfusion related infection is estimated at less than 1 in 47,000 transfusions, with most risk being due to bacterial infection, rather than viral agents. Nevertheless, there are infectious agents that are not screened for, as well as the potential for infection from emerging pathogens that are either unknown, or for which screening tests have not been developed (MacDonald & Delage, 2012). Canadian Blood Services (CBS) is introducing pathogen reduction technologies (PR) in Canada (Walsh, 2019). PR works by introducing a compound into a blood product, in this case platelets, and exposing the resulting mixture to ultraviolet light. The compound targets protein strands in DNA and RNA; illumination with UV light causes mis-links to form in the genetic materials of pathogens. The pathogen then becomes unable to replicate.

The product considered in this study is a pool of buffy coat platelets. Buffy coat is the name given to a method of separating whole blood into components of red cells, plasma, and an intermediate layer of material ("a buffy coat") that contains platelets and white blood cells. (Levin, et al., 2008).

During the PR process, some number of buffy coat units (7 in this study) are combined into an illumination container, amotosalen is added, and the resulting unit is exposed to UV light. Upon completion of the exposure cycle, the platelets are split into two separate bags, each representing an adult dose.

What constitutes an adult "dose" of platelets for transfusion is well defined, but there is latitude in the input units that can be used to form a double dose for the PR process.

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2 PROBLEM STATEMENT

The focus of this study is to estimate the key input product parameters (volume and platelet yield) to support the implementation of the PR process, to estimate product output metrics, and to evaluate changes to the manufacturing process to achieve a consistent product.

A Monte-Carlo simulation method is employed to estimate the unit volume and platelet yield resulting from combining buffy coat platelets into a platelet pool that subsequently undergoes pathogen reduction. Additionally, the value of sorting input buffy coat units according to estimated platelet yield prior to illumination is determined.

3 LITERATURE

First introduced in Europe in the 2000's, PR is employed in at least 31 countries (AABB, 2015). Despite its clinical advantages, cost has limited a more widespread application. (Gorria, et al., 2019).

The expense of PR treatment can be offset by a reduction in wastage when platelet shelf life is extended. Thus, platelet inventory management has been a focus of the literature in this area (Gorria, et al., 2019). Blake and Reid (2017) use simulation to estimate wastage rates when platelet shelf life is extended in Canada after the introduction of enhanced pathogen detection systems. Gorria et al. (2019) employ a similar methodology to evaluate reductions in waste due to implementation of PR technology in the Basque Region. Blake, McTaggart, and Couture (2021) in a later paper on PR technology, note that a reduction in shelf life from 7 days to 5 accompanied the original implementation of PR in Canada. They employ simulation to estimate the interaction between PR reduced platelets with a shelf life of five days and apheresis platelets with a shelf life of seven days.

When implemented in North America, PR platelets are often introduced into the formulary of a blood supply chain along side conventional platelets, which may have a different shelf life than treated units (Rebulla & Prati, 2022). The issues of maintaining a dual inventory have inspired a literature on PR implementation. For instance, Allen et al. (2019) discuss the benefits of phased implementation to maintain product availability while scaling up PR platelet production. Nguyen et al. (Nguyen, Rioveros, Ziman, McGonigle, & Ward, 2021) also describe the implementation of PR technology in a dual inventory environment, focusing on issues of technology acquisition and commissioning. An economic evaluation of PR technologies is provided in (Prioli, Katz Karp, Lyons, Herman, & Pizzi, 2018), including an estimate of change in wastage due to an increase in shelf-life of from five to seven days.

Outside of inventory management, there is a wealth of studies on the composition and behaviour of PR treated platelets. See (Prioli, Katz Karp, Lyons, Herman, & Pizzi, 2018) for a detailed review. There are, however, few studies in the literature that focus on analysis and optimization of the processes that create the platelets, be they PR treated or not. Our study is the first that we are aware of to use Monte Carlo methods to evaluate platelet production processes and to estimate unit metrics during and post-production.

Nevertheless, Monte Carlo simulation techniques (problems where the passage of can be ignored) are common in health care settings. For example, there is an entire genre of literature employing Monte Carlo methods to optimize the treatment path for individuals hospitalized for ischemic strokes. See Zhou & Kansagra (2021) for an example.

4 METHOD

The PR process begins when seven buffy coat units, with volume of ~47.5 ml [Normal (47.5, 1.002)] and platelet yield of ~98.2x10^7 platelets [Johnson distributed, with mean 98.2 x$10^7$and standard deviation of 22.1 x10^7], are grouped. The group has a resulting volume of ~332.5 ml [Normal (332.5, 2.66)] and a combined platelet yield of ~687x10^7 platelets. The platelets are extracted from each of the buffy coat units using a press and collected into double input platelet bag. The extraction process causes a reduction in both the volume of product available and the total number of platelets in the combined unit bag. Volume losses are counterbalanced by the inclusion of 280 ml of platelet additive solution (PAS) in the platelet pool; the volume of the resulting platelet pool is 99% [Normal (0.991, 0.034)] the original input group volume after PAS is added. However, platelet yield is approximately 86% of the input group yield [Normal (0.8642, 0.41)]. See Figure 1.

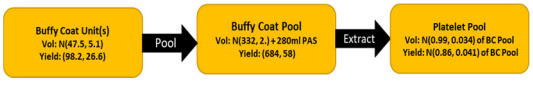

Figure 1: Schematic of unit flow. Each block describes the process step, the expected volume (Vol) and the number of platelets expected to be retained (Yield). Note that BC Pool refers to a Buffy Coat Pool.

Because PRT has been certified in Canada for a specific range of input volume (300 – 375 ml) and platelet yield (250 – 700 x10^7), our analysis focuses on estimating, via simulation, these parameters for input pools. In addition, because platelet yield with buffy coats varies between donors, the study includes an evaluation of sorting algorithms to ensure consistent product input when combined into a buffy coat pool and thus a more consistent output product.

4.1 Sorting Algorithm

The expected platelet yield for a pool of seven buffy coats, after extraction, has a non-standard distribution ($\bar{x}$ = 573.33, σ = 75.6) that is somewhat close to the lower bound for the Canadian Standards Association (CSA) efficacy requirement for pooled platelets, which states that there must be 240x10^7 platelets in 75% of units sampled in a single unit, or 521x10^7 platelets in a double unit after losses for splitting the unit are accounted for. Thus, it is expected that some portion of the units produced by the PR process with randomly selected buffy coat units would fail to meet this standard. If, however, the variability of the input unit could be reduced, fewer pools would fall outside of the standards. The standard deviation of a pool of seven randomly selected buffy coats can be estimated from pilot studies as 57.8 x10^7. However, a sorting algorithm could be used to reduce variance of the group of buffy coats used to form the platelet pool. This would result in an input unit that would still meet production bounds for the PR process and would be less likely to result in completed units that would fail to meet the minimum CSA standard.

A sorting algorithm is a process where some number of buffy coat units are gathered, prior to platelet pooling, based on actual or estimated platelet yield, to achieve more consistent input pools for the PR process. Theory indicates that the larger the number of buffy coats to select from when building a pool, the more consistent the resulting pooled platelet yield should be. However, there are practical limits to how much work in process (WIP) inventory can be held immediately prior to the buffy coat pooling process. Thus, the amount of WIP stored for a sorting algorithm must balance needs for smooth product flow against the value of better information for assembling a pool; only a finite amount of inventory can be held, and pooling decisions must be made in real time, rather than at the end of a production run. In this study, three different sorting algorithms are tested under varying levels of work in process inventory. The sorting algorithms are:

Random Sort: A random sort corresponds to a null sort. A group of seven buffy coats is assembled by selecting each unit in sequence as it becomes available at the end of the production line. A random sort is fast and easy to implement in the operational environment but has no impact on the variability of the platelet pools created. A random sort, however, serves as a benchmark for comparison of other sorting algorithms.

Bin Sort: A bin sort is a simple heuristic algorithm to reduce platelet pool variability in a set of buffy coat pools. Some number (N) of bins is created into which inventory could be placed as it arrives at the pooling station at the end of the production line. The bins would be designated with ranges for platelet yield (i.e., a bin might be designated for units with a platelet yield of between 77x10^7 and 88x10^7 platelets). Periodically, a pool is assembled by selecting units from within the bins. Each unit from a particular bin would have an integer "score" (c_n) ranging from $-\lfloor N/2 \rfloor$ to $+\lfloor N/2 \rfloor$. If we assume x_n to be the number of buffy coats selected from bin n, then the bin sort can be defined as:

$$Min: z = d^- + d^+$$

$$Subject\ to:$$

$$\sum_{n=1}^{N} c_n x_n + d^- - d^+ = 0$$

$$x_n \leq i_n$$

$$x_n \in \{0, 1, \dots\}$$

$$d^+, d^- \geq 0$$

Model 1: Bin Sort.

Where:

- c_n is the score assigned to buffy coats drawn from bin n
- x_n is the number of buffy coat units drawn from bin n
- d^- is a slack variable representing pools below the target score of 0
- d^+ is a surplus variable represent pools above the target score of 0
- i_n is the number of buffy coat units in bin n

The bin sort is defined above as a mixed integer programming (MIP) problem that can be solved with an IP solver (see for example, https://opensolver.org/) or approximated manually by assembling a batch with a penalty score ($\sum_{n=1}^{N} c_n x_n$) as close to 0 as possible.

Optimal Sort: It is also possible to formulate the pool sort as a mixed integer programming problem with an objective of achieving a specified target yield. Instead of selecting from a set of bins, all units would be considered individually for inclusion into a pool. The problem can be formulated as:

$$Min: z = d^- + d^+$$

$$Subject\ to:$$

$$\sum_{i=1}^{I} y_i x_i + d^- - d^+ = Y$$

$$\sum_{i=1}^{I} x_i = B$$

$$x_i \in (0,1)$$

$$d^+, d^- \geq 0$$

Model 2: Optimal Sort.

Where:

- y_i is the estimated platelet yield in buffy coat i
- x_i is a (0,1) variable equalling 1 if buffy coat i is included in the pool
- d- is a slack variable representing pools below the target yield
- d+ is a surplus variable represent pools above the target yield
- Y is the target yield for the pool
- I is total number of buffy coats available in for pooling (i.e., WIP)
- B is the number of buffy coats required in a pool

The sort algorithm above, defined as a mixed integer programming (IP) problem, cannot be (easily) approximated with manual methods. Due to the requirement for an optimization engine and individual identification of units, an optimal sort would be more complex to implement in a production environment, however.

4.2 Simulation

A Monte Carlo methodology was adopted to simulate buffy coat pooling prior to irradiation in the PR process and to evaluate the impact of a pooling algorithm on the ability to meet input process guidelines while creating output that meets CSA standards.

A custom simulation model was constructed in Visual Basic for Applications (VBA) using MS-Excel as the user interface. The simulation employs an object-oriented framework to represent buffy coat units, the pooling process, sorting bins, and the sorting algorithms themselves. A summary of the class objects in the simulation is given below:

clsUnit is a class object that represents a buffy coat unit. Buffy coat units have attributes of volume, platelet yield, and ID number.

clsBin is a class object that represents a bin used in a bin sort algorithm. It has properties of bin ID number, capacity, and score. Methods include a mechanism to store individual buffy coat units, a routine to identify a specific buffy coat within the bin and a routine to remove a unit from the bin.

clsBinSet represents a collection of bins used in a bin sort algorithm. It has properties of capacity (i.e., the maximum amount of end of process inventory or WIP that can be in all bins), bin (a reference to a bin within the bin set), items (the number of units in all bins), unit (a reference to a specific buffy coat within a specific bin in the bin set) and target yield. Methods include routines to add a unit to a bin or to remove a unit from a bin within the bin set.

clsSolver is an object that encapsulates an interface to the OpenSolver add-in for Excel. The object has methods that build both the bin sort and optimal sort models, methods for solving the models, once defined, and methods for returning a solution to the calling program.

4.3 Simulation Flow

The buffy coat pooling simulation generates buffy coat units. Each unit is given a simulated platelet yield and volume. The buffy coat is then added to a bin, based on the unit's platelet yield. When the total number of buffy coats in inventory (WIP) equals the bin set capacity, a platelet pool is formed. In experiments run with the model, WIP limits were set at some integer number of buffy coat pools; this restriction is in place to reduce the number of "orphaned" units that cannot be made into a pool at the end of the simulation run. The simulation then calls the IP solver to build and execute a model to create a platelet pool from a set of input buffy coats.

The list of input buffy coat units is returned to the simulation object. The simulation removes the units from the bins. The pool volume is calculated using a random distribution of changes to the input volume. In this study, buffy coat pool volume is N(0.991, 0.037) times the sum of the input buffy coat volumes. In a similar way, the buffy coat pool yield is estimated from the sum of the input buffy coat yields; the

distribution of buffy coat yields is 86.4% of the sum of the input buffy coat yields [Normal (0.864, 0.041)].

The process of creating buffy coats and assembling them into pools continues for some number of trials. Each time a pool is created, its volume and yield are compared against an acceptable input target range for the PR process: 300-375 ml for volume; 250-700x10^7 for platelet yield. If a pool falls outside of this range, a violation is noted by the simulation. Further, if a group of units results in a platelet pool yield below 521x10^7, a potential violation of CSA standards is noted. At the end of the simulation run, the proportion of pools failing to meet input or CSA targets is returned, as is the overall average pool volume and platelet yield.

5 DATA USED IN THE STUDY

Data for this study was obtained from a sample (n=84) of test buffy coat pools assembled at Canadian Blood Service's research collection and production facility (netCAD) between 05 Sep 2019 and 17 Oct 2019 as part of a pilot project.

Summary statistics and a box plot for buffy coat platelet yield appear below.

Table 1: Summary statistics for platelet yield based on N = 84 buffy coat units. Note that yield statistics are reported as platelet count x 10^7.

N	Mean	St Dev	Median	Min	Max
84	96.95	21.85	93.31	56.21	179.35

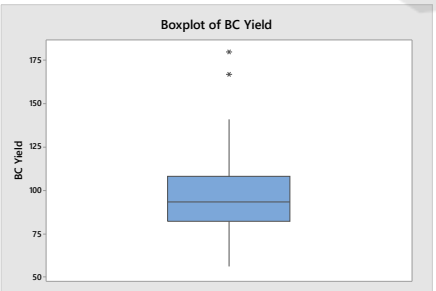

Figure 2: Boxplot of platelet yield for n=84 buffy coat units.

Summary statistics for buffy coat unit volume appear below.

Table 2: Summary statistics for buffy coat unit volume (ml).

N	Mean	St Dev	Median	Min	Max
84	47.738	1.223	48.0	44.0	50.0

Distributions were fit to both buffy coat unit volume and buffy coat unit platelet yield. A normal distribution [Normal (47.7, 1.223)], was fit to the buffy coat unit volume sample. See Figure 3.

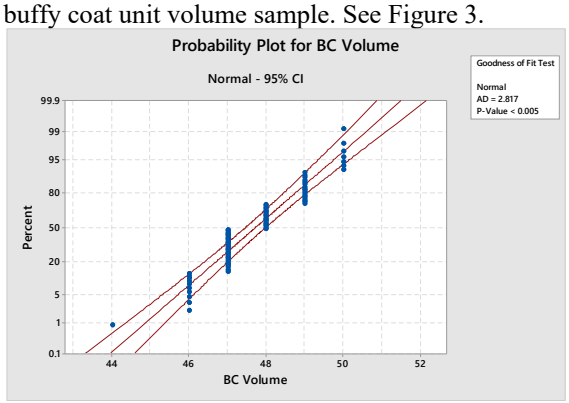

Figure 3: Probability plot for sampled buffy coat (BC) volumes (in ml) compared to a normal probability distribution.

A Johnson transform was found to provide the best fit for the buffy coat unit platelet yield data. In the simulation, therefore, an N(0,1) distribution is used to generate buffy coat platelet yield and the inverse of the Johnson transform is used to return a value in the original data space. See (Law, 2006) for more detail. For the data appearing in Figure 4, the Johnson transform parameters are A = -1.201, B = 1.593, C = 73.874, and D = 21.989.

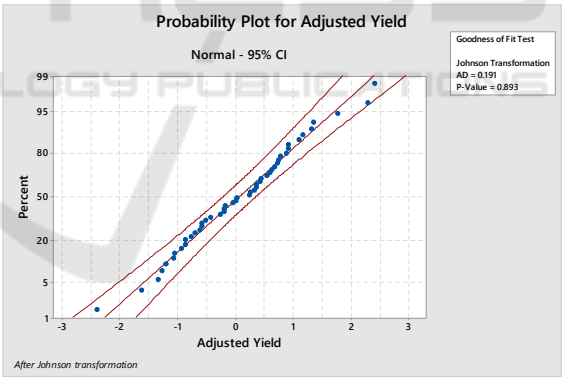

Figure 4: Johnson transformed buffy coat platelet yield plotted against an N(0,1) distribution.

Once buffy coat units are pooled and platelets are extracted, a platelet additive solution is added to the pool. The process causes both the volume of the pooled platelet unit and its platelet count to vary from the sum of the input buffy coat units. A Normal(0.991, 0.037) distribution was found to represent adequately the scale change in volume of the output unit from the sum of input buffy coat pools; a Normal(0.864, 0.041) was found to represent the scale change in platelet yield in the pooled unit as measured from the sum of the input unit yields.

6 ANALYSIS

6.1 Overview

Experiments were conducted using both a bin sort and an optimal sort algorithm with different levels of WIP at the end of the production line available to build a pool. The experiments estimate the volume and yield of input buffy coat pools and determine the impact, in terms of output product metrics, including post-illumination quality control, of implementing a sort algorithm for input units.

6.2 Model Verification

To verify the simulation, tests were conducted with the model and the results were compared to the historical dataset used to build the input distributions listed in **§ Data**. The purpose of the verification was to ensure that the model returns values matching input pilot project data.

In Table 3 the pooled platelet volume (ml), after buffy coat units are pooled identified during the pilot project, is compared to simulation output using a t-test; Table 4 compares the pooled platelet yield from the data set to simulation output using a Mann-Whitney test, since the underlying data is not normally distributed. As may be seen from the simulation, there is no data to disprove the null hypothesis that the mean/median of the simulation output is the same as mean/median of the data used to build the model.

Table 3: T-test comparison of pooled platelet volume in the pilot project dataset and the simulation results.

	Pilot Project Data	**Simulation**
Mean	331.2	331.1
Standard Deviation	12.5	12.1
n	7	300
p-value	0.99	

Table 4: Mann-Whitney comparison of pooled platelet yield in the pilot project dataset and the simulation results.

	Pilot Project Data	**Simulation**
Mean	573.3	580.0
Median	592.06	573.88
n	7	300
p-value	0.978	

6.3 Sorting Experiments

Experiments were conducted with the simulation to evaluate the ability of the process to meet input processing requirements as well as CSA standards for completed units. The simulation model was run under the assumption of no sorting for buffy coat units prior to forming a pool; employing a bin sort algorithm having 3, 5, or 7 bins prior to forming a pool; and employing an optimal sort prior to forming a pool. For both sort algorithms, differing amounts of WIP (7, 14, 21, or 28 units) were tested. In each instance, the simulation was run for 5 replications of 1000 batches of 7 buffy coats. The results of the experiments appear below.

In Table 5, the results from a run without any sorting algorithm in place are presented. From the table it may be seen that the pooled platelet volume is expected to meet acceptable PR input volume (300-375 ml) and input platelet yield ($250x10^7$ – $700x10^7$ platelets) restrictions without a sorting algorithm and only marginal losses in production; approximately 0.4% of batches would exceed input volume restrictions and 2.13% of batches would exceed input platelet yield limits.

However, without a sort in place, some pooled units would have a platelet count below $480x10^7$, the CSA dictated minimum number of platelets that must appear in 75% of the units sampled for quality control (QC) purposes, if applied to double pools (2 units at $240x10^7$ apiece). Note: In our analysis, we add $41x10^7$ platelets to the minimum pool requirement to account for losses in lines when a double unit is split into two single units. Since quality control samples typically consist of ten units of randomly sampled platelets, it can be calculated, via the binomial distribution, that 33.43% of sampled batches would be fall below minimum CSA efficacy standards if 19.6% of pooled units have a platelet yield of $521x10^7$ or less, as reported by the simulation.

Table 5: Expected process metrics if no sorting algorithm is used.

No Sort	
% pools with volume below 300 ml	0.4%
% pools with volume above 375 ml	0.00%
% pools with platelet yield below $521x10^7$	19.6%
% pools with platelet yield below $250x10^7$	0.00%
% pools with platelet yield above $700x10^7$	2.1%
Simulated pool volume (Mean, St Dev) in ml	(331.59, 3.24)
Simulated pool yield (Mean, St Dev)*10^7	(568.81, 54.12)

6.3.1 Bin Sort

Experiments were conducted with a bin sort algorithm, using 3, 5, or 7 bins and WIP inventory available for sorting set at 7,14, 21, and 28 units (or 1, 2, 3, or 4) pools. Several output metrics were recorded in the simulation, but this report focuses on the proportion of pools expected to have yield below $521x10^7$ and the number of quality control batches, of size 10 units, expected to fall below minimum CSA standards.

Table 6: Simulated results showing the number of pools with a platelet yield below $521x10^7$ as bin size and WIP is varied assuming a bin sort algorithm.

% pools below $521x10^7$		WIP			
		7	14	21	28
# of Bins	3	19.6%	12.5%	11.4%	10.8%
	5	20.3%	8.6%	8.2%	7.7%
	7	19.5%	8.3%	9.0%	6.6%

Table 7: Simulated results showing the number of the proportion of quality control batches of size 10 expected to be blow CSA standards as bin size and WIP is varied assuming a bin sort algorithm.

% pools not meeting CSA standards		WIP			
		7	14	21	28
# of Bins	3	31.1%	12.1%	9.5%	8.5%
	5	33.2%	4.8%	4.3%	3.7%
	7	30.8%	4.5%	5.5%	2.5%

As may be seen in Table 6, the proportion of pools below a platelet count of $521x10^7$ per unit decreases at the number of designated bins increases. The impact of WIP available to build a batch, beyond 14 units, on the proportion of batches not meeting the $521x10^7$ platelets per unit standard is modest, but statistically significant across the set of experiments. It is particularly evident that the impact of WIP on batch yields is quite modest if the number of bins used in the sort is greater than three. An analysis of variance (ANOVA) conducted on the experimental results for platelet yield under the assumption of a bin-sort algorithm, show that the number of bins is significant (DOF = (2,30), $F_{Crtical}$ = 3.15, p = 0.005), as is the WIP level for the entire experiment set.

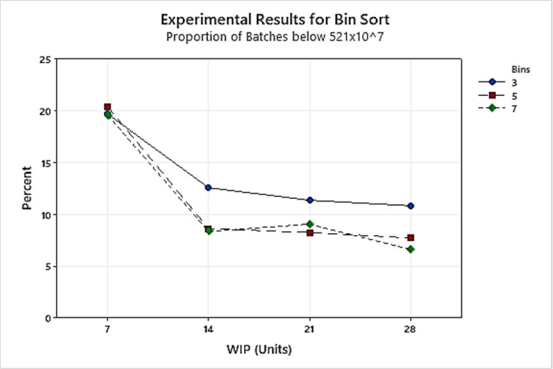

Figure 5: Interaction plot illustrating the results from the bin sort experiments. Plot shows the proportion of units expected to have a platelet yield below $521x10^7$.

Figure 5 illustrates the results for the bin sort experiments. It shows that an inventory of 7, equating to a random sort, is inferior to a sort with any number of bins. Figure 5 also shows that any bin sort with more than three bins will produce similar results for platelet yield, all of which are superior to a 3-bin sort. Finally, it was found that if the 3-bin sort and all experiments with 7 units of WIP (i.e., a random sort) are eliminated from the comparison, there is no statistical significance, for either the number of bins or the amount of WIP available to assemble a batch, on platelet yield.

6.3.2 Optimal Sorting

Experiments were also conducted using an optimal sort algorithm. In this set of experiments, only one algorithm is employed (the optimal sort algorithm), while the amount of WIP available to build a pool is varied between 7, 14, 21, and 28 units. The simulation was run for 5 replications of 1000 batches of size 7 to get a measure of variability. Results appear below.

Table 8: Simulated results showing the number of pools with a platelet yield below $521x10^7$ as WIP is varied assuming an optimal sort algorithm. Note that there are no bins in the optimal sorting algorithm.

WIP			
7	14	21	28
29.6%	7.2%	5.7%	6.2%

Experimental results, confirmed by an ANOVA (DOF = (2,8), $F_{Crtical}$ = 4.45, p = 0.63), show that inventory has no effect on the proportion of pools not meeting CSA standards, so long as at least 14 units are available to build batches. See Table 9. Similarly, it is evident from Table 8 and Figure 6 that larger WIP

Table 9: Simulated results showing the number of the proportion of quality control batches of size 10 expected to be blow CSA standards as WIP is varied assuming an optimal sort algorithm. Note that there are no bins in the optimal sorting algorithm.

WIP			
7	14	21	28
31.1%	3.1%	1.6%	2.0%

inventory does not lead to reductions in the proportion of buffy coat pools with less than $521x10^7$ platelets, if at least 14 units are available to build batches.

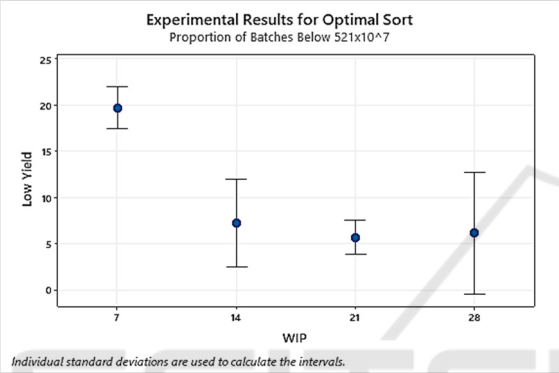

Figure 6: Interaction plot illustrating the results from the optimal sort experiments. The plot shows the proportion of units expected to have a platelet yield below $521x10^7$.

6.3.3 Sort vs. No Sort

A comparison of the simulation results with sort algorithms in place vs. no sort was conducted using an analysis of variance. The ANOVA indicated a statistically significant difference between the sort and no-sort scenarios. A Dunnett's test and analysis of means, indicates that the no-sort algorithm produces a statistically larger fraction of QC batches not meeting CSA standards. The bin sort algorithms produce fewer non-conforming QC batches than not sorting, but there were no statistically different results with increasing number of sort bins. The ANOVA (DOF = (2,45), $F_{Crtical}$ = 3.20, p = 0.335) showed, however, that an optimal sort algorithm outperforms both the 3 and 5 bin sort scenarios and the no-sort scenario, with respect to the proportion of non-conforming batches. Finally, the analysis suggests that, if a bin sort algorithm is used, the impact of the number of bins on the proportion of QC batches of size 10 that do not meet $521x10^7$ in 75% of units, is unaffected by the actual number of bins. See Figure 7.

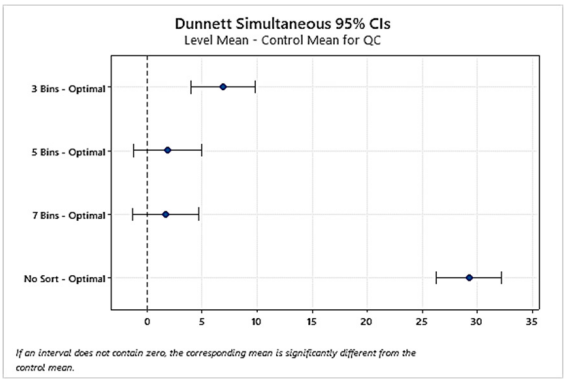

Figure 7: Comparisons fraction of pooled units not meeting minimum CSA standards by sorting algorithm.

7 CONCLUSION

This study estimated the impact of the process used to assemble input buffy coat units into buffy coat pools prior to illumination in a pathogen reduction system. The benefit that could be achieved by sorting input buffy coat units to ensure consistent input pools for the PR process was evaluated.

A Monte-Carlo simulation model was built, populated with experimental data from a pilot project, and verified. Experiments were conducted using different sorting algorithms (no sort, bin sort, and optimal sort) and differing levels of WIP used to build pools (7, 14, 21, 28 units).

The simulation shows that, even without a sort algorithm in place, more than 97.5% of pooled platelet units would be expected to meet input restrictions for both volume (300-375 ml) and platelet yield (200 – $700x10^7$). However, approximately 20.4% of all pools would have a platelet yield below $521x10^7$ and that 31.1% of quality control batches of size 10 assembled from such units would fail to meet a minimum efficacy standard of $521x10^7$ platelets in 75% of the units sampled.

Implementing any sort of sorting algorithm with a minimum of 14 units of WIP will result in a statistically significant reduction in low yield units and will improve the acceptance rate for quality control batches. A simple bin sort using, 3, 5, or 7 bins will produce a more consistent input platelet pool for the PRT system. However, the simulation results were not statistically different between the bin sorts employing different numbers of sorting bins. Thus, should a bin sort be implemented, a 3 or 5 bin sort might well be as effective as a 7-bin sort.

The simulation shows, as is expected, that the most consistent input pools are provided by an

optimal sort algorithm. Furthermore, the results suggest that an optimal sort algorithm, using a WIP of at least 14 units, results in the most consistent input pools. An optimal sort algorithm using a WIP of at least 14 units would result in less than 3% of all quality control samples falling below the CSA minimum. The simulation shows that an optimal sort is statistically similar to a 7-bin sort, but superior to a 3 or 5-bin sort, when compared over all WIP levels and measured in terms of meeting minimum CSA standards.

Thus, it may be concluded that a sort algorithm, of any kind, will improve the acceptance rate of platelet pools coming from the PR process described in this paper. Optimal sort algorithms, clearly, provide the best result, but would be complex to implement in a production environment. A simpler bin-sort algorithm was found to perform similarly to an optimal sort, if the number of bins was greater than or equal to 5. The impact of increasing WIP on QC acceptance rates was found to be modest, so long as 14 units were available. Thus, it is practical to suggest that a simple 5 bin sort algorithm could be used to ensure the most efficacious units are delivered by the PR process.

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