Optimal Donor Management in a Public Stool Bank

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Abstract

Motivated by the recent opening of a public stool bank that enables fecal microbiota transplantation for the treatment of Clostridium difficile infection, we develop and optimize a mathematical model that tracks the flow of stools from donation to sales. To prevent the spread of infectious diseases, donors are periodically tested and donated stools are not released for sale until a donor passes a subsequent test; donors and their recently donated stools are permanently ejected from the system after a failed test. We choose the testing frequency and a policy for introducing new donors into the system to minimize the long-run expected average costs due to paying donors, processing and testing stools, and holding and backordering finished goods inventory. This problem is a variant of a continuous review inventory problem where items (i.e., donors) are continuously producing product and are failure-prone, and lead times are controllable. Instead of using approximate dynamic programming to deal with the unwieldy size of the state space, we apply heavy traffic results for multiclass infinite-server queues to approximately optimize within a specified class of base-stock policies, which maintains the expected inventory position at a constant level. This policy outperforms a policy that maintains a constant number of donors.

Key Words—stochastic inventory theory; heavy traffic approximations, controllable lead times, fecal microbiota transplantation

1 Introduction

Due to recent scientific advances, modern biology views a human being as an ecosystem consisting of human cells and many microbial species (Costello et al. 2012). In particular, the gut (i.e., intestinal) microbiota impacts human health and disease, playing a crucial role in autoimmune diseases, obesity and psychiatric disorders (Blaser et al. 2013). These ideas have entered the clinic via the treatment of Clostridium difficile infection (CDI), which causes 30,000 deaths (Lessa et al. 2015) and $4.8B in hospital costs (Dubberke and Olsen 2012) annually in the U.S., primarily due to the high and increasing failure rate of the antibiotics metronidazole and vancomycin (van Nood et al. 2013). Fecal microbiota transplantation (FMT), i.e., stool transplanted from a healthy donor that recolonizes the intestinal tract of the recipient, achieves a 90% cure rate in cases that previously failed antibiotic treatment (Kassam et al. 2013) and is now approved by the Food and Drug Administration for these recurrent cases.

This dramatic success has led to ongoing clinical investigations of FMT for other microbiota-associated conditions. To satisfy the demand for FMT, a nonprofit organization, OpenBiome, has built a public stool bank. This organization recruits and screens potential donors in the Boston, MA area, processes and tests donated stool, and sells the final product to hospitals. As of March 2016, their stool has been distributed to over 350 clinical institutions in 48 U.S. states and six countries (OpenBiome 2016).

In this paper and its companion (Kazerouni et al. 2015), we build, calibrate and optimize a mathematical model that tracks the process flow of stool in OpenBiome’s operations, from donation to sales. OpenBiome’s most important and difficult logistical challenge is to screen potential donors and actual stool donations
to prevent recipients from either contracting infectious diseases or becoming more susceptible to chronic conditions such as obesity or autoimmune disorders (Smith et al. 2014). OpenBiome addresses these risks in two ways. First, it carries out a rigorous initial screening consisting of an on-site clinical assessment and stool and blood testing, where 97% of potential donors are turned away (OpenBiome 2016). Second, once a donor starts donating stool (typically several times per week), he undergoes a set of 27 blood and stool assays every 60 days; if he passes this screening then his donated stool from the previous 60 days is released to finished goods inventory, and if he fails the screening (i.e., an infectious agent is detected) then he is ejected from the system and his donated stool from the previous 60 days is discarded.

Our mathematical model contains two types of decisions that need to be addressed by OpenBiome’s managers: when to release a new donor into the system and how often to test donors. It is prohibitively expensive to test donors frequently, but a long inter-testing time increases the likelihood that donor stool will be discarded. These decisions are chosen to minimize the sum of traditional holding and backorder costs, and the cost of processing (e.g., donors are paid for each donation) and screening stools.

1.1 Related Literature

To our knowledge, Kazerouni et al. (2015) is the only other study that addresses this problem. Kazerouni et al. (2015) consider an exponentially-increasing deterministic demand, which is appropriate during OpenBiome’s startup phase, whereas we consider a stochastic time-homogeneous demand that is appropriate after the CDI market has been saturated. As explained in §6, Kazerouni et al. (2015) also considers several refinements that are ignored here.

Although the context is new, our model has some connections to the operations research and operations management literature. First, our FMT model is quite different than the models for organ transplants (e.g., Zenios and Wein 2000) because each FMT donor can serve multiple recipients. It is also different from blood transfusions (e.g., Pierskalla 2005): the FMT problem is more difficult in that stool donors continuously produce stool, but is simpler in that stools are not perishable, and, under the current state of knowledge, there are not compatibility issues for FMT as there are with transfusing different blood types.

Our model is a variant of an inventory model (Zipkin 2000), where we are attempting to match supply (i.e., donated stool) to stochastic demand to minimize backorder and holding costs, but it has several distinctive features. First, each unit of supply (i.e., donor) generates product (i.e., stool) in an ongoing manner and can satisfy the demand of multiple customers. Second, there is imperfect quality, which we do not learn about (via the stool and blood screening) until the units are about to be placed into finished goods inventory. Third, our model has a controllable lead time, in that we can decide how frequently to test donors, and hence how frequently to place salable stool into finished goods inventory. Moreover, the yield (i.e., the proportion of donated stool that passes the tests) is functionally related to the controllable lead time via a survival model for the time until donor failure. Taken together, the number of salable items from each unit of supply (i.e., donor) is both random and partially controllable.

Turning back to the inventory theory literature, there are many studies with imperfect quality (reviewed in Chapters 3, 7 and 9 of Zipkin 2000), and many studies with controllable lead times (motivated by just-in-time manufacturing, reviewed in Sarkar et al. 2015), but few where the two are intricately intertwined, as in our model. Perhaps the closest work in spirit, if not in modeling approach, to ours is Porteus 1986 and Sarkar et al. 2015, where controllable investments in process quality bring a machine back in control after it has been producing defective items in a lot-sizing setting. In addition to the details of the models being different (e.g., EOQ vs. continuous review setting), in our model the discarding of a donor is decoupled from the release of a new donor; i.e., instead of bringing a process back into control, in our model it may not be optimal to release a new donor when an existing donor fails a test.

In a dynamic programming formulation of this problem, the state of the system (assuming that all donors have the same stool production rate) is the current finished goods inventory level and, for each current donor, the amount of time since the last test. While progress has been made in solving inventory problems with multi-dimensional state spaces (see Sun et al. 2014 for a recent review) using results from approximate dynamic programming (Farias and Van Roy 2003), we do not attempt to find a near-optimal solution to this problem, and instead settle on approximately optimizing over a class of base-stock policies that naturally
arises in this problem. Although the $M/G/\infty$ queue has been widely used to analyze base-stock policies in inventory systems ($\S 7.2$ in Zipkin (2000)), the release process is not a Poisson process for our base-stock policy. However, we show that the release process satisfies a functional central limit theorem, which allows us to employ the multiclass $G/G/\infty$ heavy-traffic approximation of Glynn and Whitt (1991). This asymptotic approximation assumes that the demand rate is very large, which is applicable in our setting because OpenBiome is attempting to singlehandedly satisfy the nationwide demand for FMTs. The model in Glynn and Whitt (1991) is particularly well suited to our problem because each class has deterministic service times, which is satisfied in our model due to the fixed inter-testing time. In addition, this approximation allows for a compound (the compounding aspect is due to each transplant requiring multiple grams of stool) renewal demand process and leads to relatively tidy results.

The rest of this paper is organized as follows. We formulate the problem in $\S 2$ and show that the constant-donor policy, which is how OpenBiome currently operates, leads to unbounded system cost in heavy traffic in $\S 3$. The proposed base-stock policy is formulated and analyzed in $\S 4$, and a numerical example is provided in $\S 5$. We offer concluding remarks in $\S 6$.

2 The Model

The model is depicted in Figure 1. The first set of decisions in our continuous-time model is the control process $R \triangleq \{R(t), t \geq 0\}$, where $R(t)$ is the cumulative number of donors released into the system up to time $t$. We implicitly assume that an ample number of prescreened potential donors are available for release into the system. OpenBiome’s prescreening involves three steps (Kazerouni et al. 2015): a fully automated donor registry process, a 109-question clinical assessment to rule out risk factors, and a set of 27 stool-based and serological assays for detection of infectious agents. The first two prescreening steps occur very quickly. Although there is currently a 12-day delay to obtain results from the stool test (Kazerouni et al. 2015), OpenBiome is in the process of bringing testing in-house, which will dramatically reduce the testing delay, thereby eliminating testing delays as a salient feature in the model. Hence, we assume that these test results are available immediately.

Upon release into the system, a donor begins the first of a random number of donation cycles, and the length of the donation cycle, $D$, is the second decision variable in our model; we refer to $D$ as the inter-testing time. In each cycle, a donor donates stool at a deterministic rate of $s$ grams per day for $D$ days. This assumption is made for mathematical simplicity: donors actually donate several times per week on average, and the stool production rate varies among donors (Kazerouni et al. 2015). At the end of the donation cycle, the donor undergoes screening (i.e., the 27 stool and blood assays) to make sure that he did not become infected over the previous $D$ days. If the donor fails the test, he is permanently ejected from the system and his produced stool during this donation cycle (i.e., the previous $D$ days) is discarded. If the donor successfully passes the test, his produced stool over the previous $D$ days is placed into the finished goods inventory and the donor immediately starts a new donation cycle.

Based on a statistical analysis of testing results from OpenBiome’s donors (Kazerouni et al. 2015), we assume that a donor’s failure time – i.e., the time until he gets infected – is exponential with parameter $\eta$. 

Figure 1: The stool bank operation.
Hence, the probability that a donor passes the test at the end of a donation cycle is
\[ p = e^{-\eta D}. \] (1)

Stool demand is modeled as a stochastic process \( \{\Lambda(t), t \geq 0\} \), where \( \Lambda(t) \) is the cumulative demand for stool (in grams) up to time \( t \). Because each customer requires sufficient stool for a FMT, we assume that \( \Lambda(t) \) is a compound renewal process with interdemand times that have mean \( \mu_d^{-1} \) days and squared coefficient of variation \( \text{variance divided by the square of the mean} \) \( \sigma_d^2 \), and batch sizes with mean \( \mu_b \) grams and square coefficient of variation \( \sigma_b^2 \). We denote the mean demand rate by \( \lambda = \mu_d \mu_b \) grams/day.

Three stochastic processes appear in our objective function: \( Q \equiv \{Q(t), t \geq 0\} \), where \( Q(t) \) is the number of donors in a donation cycle (i.e., currently donating) at time \( t \); \( Z \equiv \{Z(t), t \geq 0\} \), where \( Z(t) \) is the number of donors who finish a donation cycle at time \( t \); and \( I \equiv \{I(t), t \geq 0\} \), where \( I(t) \) is the finished goods inventory level at time \( t \). To construct these processes, we also need the stochastic process \( \{Y(t), t \geq 0\} \), where \( Y(t) \) is the number of donors who both finish a donation cycle and pass the associated test at time \( t \). Furthermore, we let the increasing sequence \( f_1 < f_2 < f_3, \ldots \) be the times at which at least one donor finishes a cycle (i.e., times \( t \) at which \( Y(t) \neq 0 \)). Hence, for each \( j = 1, 2, \ldots \), \( Y(f_j) \) is a binomial random variable with parameters \( Z(f_j) \) and \( p \), which we denote by
\[ Y(f_j) \sim \text{Bin}(Z(f_j), p) \quad \text{for} \ j = 1, 2, \ldots. \] (2)

Similarly, we let \( r(t) \) be the number of donors released into the system at time \( t \), and let the increasing sequence \( a_1 < a_2 < a_3 < \cdots \) be the release times (i.e., times \( t \) at which \( r(t) \neq 0 \)), which allows our control process to be expressed as
\[ R(t) = \sum_{j: 0 \leq a_j \leq t} r(a_j). \] (3)

Then the process \( Z \) is given by
\[ Z(t) = r(t - D) + Y(t - D) \quad \text{for} \ t \geq 0, \] (4)
where by convention, all the processes are defined to be zero at negative times. The processes \( Q \) and \( I \) can be expressed as
\[ Q(t) = \sum_{j: t - D < a_j \leq t} r(a_j) + \sum_{j: t - D < f_j \leq t} Y(f_j) \quad \text{for} \ t \geq 0 \] (5)
and
\[ I(t) = sD \sum_{j: 0 \leq f_j \leq t} Y(f_j) - \Lambda(t) \quad \text{for} \ t \geq 0. \] (6)

The model includes five cost parameters: the prescreening cost \( c_r \) (in $/donor) associated with releasing a prescreened potential donor into the system, which includes the costs incurred for potential donors who fail prescreening; the daily donor cost \( c_d \) (in $/donor/day), which includes the costs of paying donors and processing their stool, the screening cost \( c_s \) (in $/donor) incurred at the end of each donation cycle, and the finished goods inventory holding and backorder cost parameters \( h \) and \( b \), respectively, (in $/gram/day). The optimization problem is to choose the nondecreasing donor release process \( R \) and the nonnegative inter-testing time \( D \) to minimize the long-run expected average system cost, which can be formulated as
\[
\min_{D \geq 0, \ R} \limsup_{T \to \infty} \frac{1}{T} \mathbb{E} \left[ c_r R(T) + \int_0^T [c_d Q(t) + c_s Z(t)] dt + \int_0^T [h I(t)^+ + b I(t^-)] dt \right],
\] (7)
subject to \( R \) is nondecreasing,
(8)
where \( x^+ = \max(0, x) \) and \( x^- = \max(0, -x) \).

Although problem \( (7)-(8) \) can be formulated as a dynamic program that, at any time \( t \), keeps track of the finished goods inventory level and the length of time each donor has spent in his current donation cycle, the space-state of the problem is prohibitively large to allow for direct computation of the optimal policy. Rather than pursue recent approximate dynamic programming methods for inventory problems with multi-dimensional state spaces \cite{Sun2014}, we use heavy traffic asymptotics to analyze the constant-donor policy that is currently used by OpenBiome, and a base-stock policy that naturally arises in heavy traffic.
3 The Constant-Donor Policy

Under the constant-donor policy, the number of active donors in the system is maintained at a constant level by releasing a new donor whenever an existing one is ejected from the system. In this section, we show that such a policy incurs an unbounded system cost.

Consider a policy that keeps \( K \) active donors in the system at all times. To prevent a linearly growing inventory level, the constant level \( K \) should be set such that the production rate matches the demand rate; i.e., \( Ksp = \lambda \), which yields

\[
K = \frac{\lambda}{p_s}.
\]

In this section, we conservatively assume that \( \lambda, p \) and \( s \) are such that \( K \) is integer-valued. Without loss of generality, we assume that all \( K \) donors are released into the system at time \( t = 0 \), which implies that the number of donors who go through the test at any time \( t \) is

\[
Z(t) = \begin{cases} 
K & \text{if } t = mD \text{ for some } m \in \mathbb{N}; \\
0 & \text{otherwise}.
\end{cases}
\]

By (6), the inventory level is

\[
I(t) = sD \sum_{i=1}^{\lfloor \frac{t}{D} \rfloor} Y_i - \Lambda(t) \quad \text{for } t \geq 0,
\]

where the \( Y_i \)'s are independent and identically distributed (iid) random variables distributed as \( \text{Bin}(K, p) \).

To analyze the performance of the constant-donor policy in the heavy traffic limit, we consider scaled versions of the demand and inventory processes. Consider a sequence of systems as above indexed by \( n \in \mathbb{N} \) and define

\[
\Lambda^n(t) = \frac{\Lambda(nt)}{\sqrt{n}} \quad \text{for } t \geq 0,
\]

\[
I^n(t) = \frac{I(nt)}{\sqrt{n}} \quad \text{for } t \geq 0,
\]

as the demand and finished goods inventory process in the \( n \)th system, respectively; this is the same scaling used in §4.3. According to (10), the inventory process in the \( n \)th system can be represented as

\[
I^n(t) = \frac{1}{\sqrt{n}}sD \sum_{i=1}^{\lfloor \frac{n t}{D} \rfloor} Y_i - \Lambda^n(t) \quad \text{for } t \geq 0.
\]

Let \( \hat{I}(t) = \lim_{n \to \infty} I^n(t) \) be the heavy traffic limit of the scaled finished goods inventory process in (12), and let \( \Rightarrow \) denote weak convergence (see Billingsley (1968) for technical details). The following proposition characterizes \( \hat{I}(t) \).

Proposition 1. With the above definitions, we have

\[
\hat{I}^n(t) \Rightarrow \hat{I}(t) = \sigma_f W(t),
\]

where \( \{W(t), t \geq 0\} \) is a standard Brownian motion and

\[
\sigma_f^2 = \lambda s(1 - p)D + \lambda \mu_b (v_d^2 + v_b^2).
\]

Proof of Proposition 1. Based on the functional central limit theorem (FCLT) for renewal-reward processes with finite variances (Theorem 7.4.1 in Whitt (2002)), we have as \( n \to \infty \),

\[
\Lambda^n(t) \Rightarrow \lambda \sqrt{nt} + \sqrt{\mu_d \mu_b} \sqrt{v_d^2 + v_b^2} W_1(t),
\]

where
and
\[
\frac{1}{\sqrt{n}} sD \sum_{i=1}^{\lfloor nt \rfloor} Y_i \Rightarrow K_p s \sqrt{nt} + \sqrt{K s^2 (1-p)} \bar{D} W_2(t),
\]
where \( W_1(t) \) and \( W_2(t) \) are two independent standard Brownian motions. The statement then follows from (9) and (12).

Proposition 1 implies that
\[
E[\hat{I}(t)] = E[\bar{I}(t)] = \frac{\sigma_f \sqrt{T}}{\sqrt{2\pi}}.
\]
Therefore, the inventory cost of the system in the heavy traffic limit can be expressed as
\[
\limsup_{T \to \infty} \frac{1}{T} \int_0^T \left( E[h \hat{I}(t)^+ + b \bar{I}(t)^-] - h \right) \frac{\sigma_f}{\sqrt{2\pi}} \limsup_{T \to \infty} \frac{1}{T} \int_0^T \sigma_f \sqrt{T} dt,
\]
\[
= \frac{2}{3} (b + h) \frac{\sigma_f}{\sqrt{2\pi}} \limsup_{T \to \infty} \sqrt{T},
\]
\[
= \infty.
\]
Thus, the inventory cost of the system – and hence the total system cost – is unbounded when a fixed-donor policy is followed. Although such a policy matches the production rate with the demand rate, it cannot bound the inventory costs because it does not directly attempt to control the finished goods inventory level. Hence, a more sophisticated family of policies is required to achieve finite system costs.

4 The Base-Stock Policy

In this section, we describe a specific base-stock policy in 4.1, convert the model under this policy into a queueing system in 4.2, analyze this queueing system in heavy traffic in 4.3, and solve the heavy-traffic version of problem (7)-(8) within this class of base-stock policies in 4.4.

4.1 Description of the Base-Stock Policy

As is standard in inventory management problems without fixed ordering costs, we look for a solution to problem (7)-(8) within a family of base-stock policies. A base-stock policy tries to keep the inventory position, i.e. the inventory on hand plus the inventory on order, at a constant base-stock level by ordering more units whenever the inventory position falls below this level. Unlike usual inventory management problems (Zipkin 2000), here we do not observe the inventory on order (and hence the inventory position) because a donor's lifetime is not observable until he fails a test and is ejected from the system. Therefore, we look for a base-stock policy in which the expected inventory position (which is observable at all times) is kept at a constant level.

Due to the memoryless property of the exponential failure time of donors, any donor who is present in a donation cycle produces an average future amount of \( sDp \) grams of salable stool, regardless of what cycle the donor is in. Hence, the expected inventory on order at time \( t \) is
\[
J(t) = \frac{sDp}{1-p} Q(t) \quad \text{for } t \geq 0,
\]
and the expected inventory position at time \( t \) is
\[
\frac{sDp}{1-p} Q(t) + I(t).
\]
Note that there are three types of events that change the inventory position: a new demand reduces the finished goods inventory level \( I(t) \), a failed test reduces \( Q(t) \) by one and hence reduces \( J(t) \) by \( \frac{sDp}{1-p} \), and a passed test increases \( I(t) \) by \( sD \).
We make two simplifying assumptions in order to obtain a reasonably accurate estimate of the base-stock level \( B \), which is respect to the expected inventory position in (14). Because the heavy-traffic scaling is too crude to capture the fact that the cumulative number of released donors into the system needs to be an integer, we ignore the integrality constraint on \( \{R(t), t \geq 0\} \), although we re-impose this constraint in the numerical example in §5.2. Hence, the base-stock policy continuously monitors the expected inventory position \( J(t) + I(t) \) and when it falls below the base-stock level \( B \), sufficiently many (possibly fractional) donors are released into the system to raise \( J(t) + I(t) \) back to the level \( B \). In addition, we relax the constraint that the control process \( \{R(t), t \geq 0\} \) is nondecreasing. Note that this relaxation should not significantly affect the problem because the scaled control process has a large positive drift in the heavy traffic limit and hence it would only be rarely decreasing. Thus, the number of donors released at time \( t \) is assumed to be

\[
r(t) = \frac{(B - I(t) - J(t))}{sD \pi} \quad \text{for } t \geq 0.
\]

and the release process is given by (3).

The optimization problem in (7)-(8) now reduces to deriving the optimal base-stock level \( B \) and the optimal cycle length \( D \) that minimizes the long-run expected average inventory and donor-related costs. To analyze this policy in heavy traffic, we first map this model into a queueing system.

4.2 A Queueing Model for the Number of Donors in the System

By (14), the key to analyzing the long-run expected average cost in (7) under the base-stock policy is to derive the steady-state distribution of \( Q \), which is the number of donors currently donating. In this subsection, we show that under the base-stock policy described in §4.1, the process \( Q \) in (5) can be modeled as the number of customers in a multiserver \( G/G/\infty \) queue.

We classify the donors based on the number of donation cycles that they survive in the system. Specifically, for \( i = 0, 1, 2, \ldots \), a class \( i \) donor is one who goes through \((i + 1)\) donation cycles in the system before getting ejected. Therefore, the service time of a class \( i \) donor is

\[
x_i = (i + 1)D \quad \text{for } i = 0, 1, \ldots,
\]

and – because the donation during his last cycle is discarded – a class \( i \) donor adds a total of \( isD \) grams of salable stool to the inventory during his lifetime in the system. Note that the class of a donor is not observable until he fails a test. Therefore, classifying the donors based on their lifetime is only a modeling tool to quantify the cost in (7) and is not used in the base-stock policy described in §4.1.

For \( i = 0, 1, 2, \ldots \), define \( R_i \triangleq \{R_i(t), t \geq 0\} \), where \( R_i(t) \) is the cumulative number of class \( i \) donors released into the system up to time \( t \). The exponential failure time implies that a released donor is of class \( i \) (i.e., passes exactly \( i \) tests) with probability

\[
\pi_i = (1 - p)^i \quad \text{for } i = 0, 1, 2, \ldots,
\]

independent of other donors. It follows that the vector of release processes \( \{R_0, R_1, \ldots\} \) is a multinomial process with parameters \( R(t) \) and \( \pi_i \) at time \( t \); i.e., if for \( j = 1, 2, \ldots \), we define \( \phi_{ij} \) to equal 1 with probability \( \pi_i \) and 0 otherwise, then the arrival process of class \( i \) customers to the \( G/G/\infty \) queue is

\[
R_i(t) = \sum_{j=1}^{R(t)} \phi_{ij} \quad \text{for } t \geq 0,
\]

where the release process \( R \) is defined in (3) and (15).

Let \( Q_i(t) \) be the number of class \( i \) donors in the system at time \( t \), which can be expressed as (page 191 of Glynn and Whitt [1991])

\[
Q_i(t) = R_i(t) - R_i(t - x_i) \quad \text{for } t \geq 0.
\]
Then the total number of donors in the system at time $t$ in (5) can be re-expressed as

$$Q(t) = \sum_{i=0}^{\infty} Q_i(t) \text{ for } t \geq 0. \tag{20}$$

In §4.3 we will also need the long-run average donor release rates, which are the arrival rates to the $G/G/\infty$ queue. Because each released donor produces an average amount of $\frac{sDp_1 - p}{s}$ grams of salable stool during his lifetime, and because the long-run average production rate of salable stool must equal the long-run average demand rate $\lambda$ under the base stock policy in (15), it follows that the long-run average release rate, $\rho = \lim_{t \to \infty} \frac{R(t)}{t}$, satisfies

$$\rho = \frac{\lambda(1 - p)}{sDp}. \tag{21}$$

Consequently, the long-run average release rate of a class $i$ donor is

$$\rho_i = \pi_i \rho = \frac{\pi_i \lambda(1 - p)}{sDp}, \text{ for } i = 0, 1, 2 \ldots. \tag{22}$$

### 4.3 The Queue Length Distribution in Heavy Traffic

The goal of this subsection is to derive the steady-state distribution of $Q$ in (20) in the heavy traffic limit. We rely on results in Glynn and Whitt (1991), which considers a sequence of systems indexed by $n$, where the arrival rates in the $n$th system are increased by a factor of $n$. In Glynn and Whitt (1991), the authors derive a functional law of large numbers (FLLN) for this queue length process divided by $n$, and a FCLT for $\sqrt{n}$ times the difference between the queue length process divided by $n$ and the fluid limit from the FLLN.

To streamline the presentation, we work directly with the $\frac{nt}{\sqrt{n}}$ scaling, for which their results directly apply. To this end, for a sequence of systems indexed by $n = 1, 2, \ldots$, we define the scaled demand process

$$\Lambda^n(t) = \frac{\Lambda(nt)}{\sqrt{n}} \text{ for } t \geq 0, \tag{23}$$

the scaled release process based on the base-stock policy from (15),

$$R^n(t) = \frac{R(nt)}{\sqrt{n}} \text{ for } t \geq 0, \tag{24}$$

the scaled release process for each donor class $i = 0, 1, \cdots$,

$$R^n_i(t) = \frac{R_i(nt)}{\sqrt{n}} \text{ for } t \geq 0,$$

and

$$= \frac{R^n(t)}{\sqrt{n}} - \frac{R^n_i(t - x_i)}{\sqrt{n}} \text{ by (18)}.$$ 

the scaled queue length process for each donor class,

$$Q^n_i(t) = \frac{Q_i(nt)}{\sqrt{n}} \text{ for } t \geq 0,$$

and

$$= R^n(t) - R^n_i(t - x_i) \text{ by (19) and (24)},$$

and the scaled total queue length process

$$Q^n(t) = \frac{Q(nt)}{\sqrt{n}} \text{ for } t \geq 0,$$

and

$$= \sum_{i=1}^{\infty} Q^n_i(t) \text{ by (20)}.$$
The classical heavy traffic limit for a $G/G/\infty$ queue relies on a FCLT assumption for the arrival process (Glynn and Whitt [1991], Pang and Whitt [2010]). However, the arrival process in our model is a controllable process governed by the base-stock policy. To apply the results of Glynn and Whitt [1991], we prove in Theorem 2 that the release process in (3) dictated by the base-stock policy in (15) indeed satisfies a FCLT.

**Theorem 2.** The release process $\{R(t), t \geq 0\}$ defined in (3) and (15) satisfies

$$
\frac{R(nt) - \rho nt}{\sqrt{n}} \Rightarrow \hat{R}(t) = \nu_r W(t) \quad \text{as } n \to \infty,
$$

where $W(t)$ is a standard Brownian motion and

$$
\nu_r^2 = \frac{\lambda}{p^2} \left[ 1 - \frac{p}{sD} + \frac{(1 - p)^2}{s^2D^2} (\nu_d^2 + \nu_b^2) \right].
$$

Furthermore, for any $i = 0, 1, \ldots$,

$$
\frac{R_i(nt) - \rho_i nt}{\sqrt{n}} \Rightarrow \hat{R}_i(t) = \pi_i \nu_r W(t) + V_i(\rho t) \quad \text{as } n \to \infty,
$$

where $\{V_i(t)\}_{i=0,1,\ldots}$ is a zero-drift, $\infty$-dimensional Brownian motion independent of $W(t)$ with covariance matrix $\Gamma = [\gamma_{ij}]$ given by

$$
\gamma_{ij} = \begin{cases} 
\pi_i(1 - \pi_i) & \text{if } i = j; \\
-\pi_i \pi_j & \text{if } i \neq j.
\end{cases}
$$

The proof of Theorem 2 appears in the Appendix.

Theorem 2 allows us to derive the heavy traffic limit for the scaled queue length process $\{Q^n_i(t), t \geq 0\}$ in terms of the limiting scaled release process, $\{\hat{R}_i(t), t \geq 0\}$.

**Theorem 3.** Given $\hat{R}_i(t)$ in (28), for $i = 0, 1, 2, \ldots$, we have

$$
\lim_{n \to \infty} \left( Q^n_i(t) - \sqrt{n} \rho_i \left[ t - (t - x_i)^+ \right] \right) \Rightarrow \hat{R}_i(t) - \hat{R}_i(t - x_i).
$$

Theorem 3 is a direct consequence of Theorem 1 of Glynn and Whitt [1991] except that the latter considers a finite number of classes. However, Theorem 3 follows directly from Theorem 3.2 of Pang and Whitt [2010], which treats a countable number of classes.

In the remainder of this subsection, we derive the approximate steady-state distribution for the unscaled total queue length process $\{Q(t), t \geq 0\}$ that is suggested by Theorems 2 and 3. These theorems imply that for sufficiently large $n$,

$$
Q^n_i(t) \approx \sqrt{n} \rho_i \left[ t - (t - x_i)^+ \right] + \nu_i \nu_r [W(t) - W(t - x_i)] + [V_i(\rho t) - V_i(\rho(t - x_i))] \quad \text{for } i = 0, 1, 2, \ldots.
$$

That is, $Q^n_i(t)$ is approximately normally distributed with mean $\sqrt{n} \rho_i \left[ t - (t - x_i)^+ \right]$ and variance $\nu_i^2 \nu_r^2 + \pi_i(1 - \pi_i) \rho x_i$ for $i = 0, 1, 2, \ldots$. The two theorems and (30) also imply that

$$
\text{cov}(Q^n_i(t), Q^n_j(t)) = \pi_i \pi_j \nu_r^2 \rho_x \rho_{x_j} \quad \forall i \neq j,
$$

where $x \wedge y = \min(x, y)$.

For sufficiently large $t$, equations (25) and (30)-(31) imply that $Q^n(t)$ is approximately normally distributed with mean

$$
\sqrt{n} \sum_{i=0}^{\infty} \rho_i x_i = \frac{\sqrt{n} \lambda (1 - p)}{sDp} \sum_{i=0}^{\infty} \pi_i i x_i \quad \text{by (22)},
$$

$$
= \frac{\sqrt{n} \lambda (1 - p)}{sDp} \sum_{i=0}^{\infty} (i + 1) D(1 - p)^i \quad \text{by (16) - (17)},
$$

$$
= \frac{\sqrt{n} \lambda}{sp},
$$

(32)
and variance
\[
\sum_{i=0}^{\infty} \left( \pi_i^2 + \pi_i (1 - \pi_i) \rho \right) x_i + 2 \sum_{i=0}^{\infty} \sum_{j=i+1}^{\infty} \pi_i \pi_j (v_r^2 - \rho)(x_i \land x_j),
\]
\[
= (v_r^2 - \rho) D \left[ \sum_{i=0}^{\infty} \pi_i (i+1) \left( \pi_i + 2 \sum_{j=i+1}^{\infty} \pi_j \right) \right] + \rho D \sum_{i=0}^{\infty} \pi_i (i+1) \text{ by (16)},
\]
\[
= (v_r^2 - \rho) D \left[ \sum_{i=0}^{\infty} p_i' (1-p) (i+1) \left( p_i' (1-p) + 2 \sum_{j=i+1}^{\infty} p_j' (1-p) \right) \right] + \rho D \sum_{i=0}^{\infty} p_i' (1-p) (i+1) \text{ by (17)},
\]
\[
= (v_r^2 - \rho) D \left[ \sum_{i=0}^{\infty} p_i' (1-p) (i+1) \left( p_i' (1-p) + 2 p_i'^{i+1} \right) \right] + \rho D \sum_{i=0}^{\infty} p_i' (1-p) (i+1),
\]
\[
= (v_r^2 - \rho) D \left[ \sum_{i=0}^{\infty} p_i' (1-p) (i+1) \left( p_i' (1-p) + 2 \right) \right] + \rho D \sum_{i=0}^{\infty} p_i' (1-p) (i+1),
\]
\[
= (v_r^2 - \rho) (1-p^2) D \sum_{i=0}^{\infty} p_i'^2 (i+1) + \rho D \sum_{i=0}^{\infty} p_i' (1-p) (i+1),
\]
\[
= \frac{(v_r^2 - \rho) D}{1-p^2} + \frac{\rho D}{1-p},
\]
\[
= \frac{\lambda (1-p)}{s(1+p)p^2} \left[ \frac{\mu_0}{sD} (v_g^2 + v_h^2) + 1 \right] + \frac{\lambda}{ps} \text{ by (21) and (27)}. \tag{33}
\]

Finally, when the demand rate \( \lambda \) and hence the release rate \( \rho \) is large, reversing the scaling in equation (25) suggests that the steady-state distribution of the total queue length process is well approximated by a normal distribution with mean \( \frac{\lambda}{sp} \) by (32) and variance given in (33). We use this approximation in the following subsection to derive the optimal base-stock level and cycle length.

4.4 The Optimal Base-stock Level and Cycle Length in Heavy Traffic

In this subsection, we approximate the cost function in (7) using the heavy traffic approximation for the steady-state distribution of \( Q \) in (4.3). The optimization is performed in two steps: we first derive a closed-form solution for the optimal base-stock level in terms of the cycle length \( D \), and then reduce the solution for \( D \) to a one-dimensional optimization problem.

Under the base-stock policy in (15), the expected inventory position satisfies \( I(t) + J(t) = B \) for all \( t \geq 0 \). Recalling that \( Q(\infty) \) is approximately normal with mean \( \frac{\lambda}{ps} \) and variance given in (33), equation (13) implies that the steady-state expected inventory on order satisfies \( J(\infty) \sim N(\theta, \alpha^2) \), where
\[
\theta = \frac{\lambda D}{1-p}, \quad \alpha^2 = \frac{\lambda \mu_b D (v_g^2 + v_h^2) + \lambda sD^2 (1+p^2)}{1-p^2 (1-p)} \tag{34}.
\]

Little’s Law implies that \( E[Z(\infty)] = \frac{1}{\theta} E[Q(\infty)] \). Hence, the long-run expected average system cost in (7) can be approximated by
\[
C = c_r \rho + \left( c_d + \frac{c_s}{D} \right) E[Q(\infty)] + hE[(B - J(\infty))^+] + bE[(B - J(\infty))^-],
\]
\[
= c_r \frac{\lambda (1-p)}{psD} + \left( c_d + \frac{c_s}{D} \right) \frac{\lambda}{ps} h \int_{(B-x)} (B-x) \frac{1}{\alpha} \phi \left( \frac{x - \theta}{\alpha} \right) dx + b \int_{B}^{\infty} (x-B) \frac{1}{\alpha} \phi \left( \frac{x - \theta}{\alpha} \right) dx \text{ by (21) and (34)},
\]
\[
= c_r \frac{\lambda (1-p)}{psD} + \left( c_d + \frac{c_s}{D} \right) \frac{\lambda}{ps} h (B-\theta) + (b+h) \int_{B}^{\infty} (x-B) \frac{1}{\alpha} \phi \left( \frac{x - \theta}{\alpha} \right) dx,
\]
\[
\text{ (35)}
\]
where \( \phi(\cdot) \) is the probability density function of the standard normal distribution. Setting \( \frac{dC}{dt} = 0 \) yields
\[
h - (b + h) \int_{-\infty}^{\infty} \frac{1}{\alpha} \phi\left( \frac{x - \theta}{\alpha} \right) dx = 0,
\]
or
\[
\Phi\left( \frac{B - \theta}{\alpha} \right) = \frac{b}{b + h},
\]
where \( \Phi(\cdot) \) is the cumulative distribution function of the standard normal distribution. Therefore, the optimal base-stock level is given by
\[
B^* = \theta + \alpha \Phi^{-1}\left( \frac{b}{b + h} \right),
\]
where \( \theta \) and \( \alpha \) are given in (34).

Defining \( z = \Phi^{-1}\left( \frac{b}{b + h} \right) \) and substituting the optimal base-stock level \( B^* \) from (36) into the long-run expected average cost function in (35) gives
\[
C(D) = c_r \lambda (1 - p) + \left( c_d + \frac{c_s}{D} \right) \lambda + h z \alpha + (b + h) \int_{\theta + z \alpha}^{\infty} (x - \theta - z \alpha) \frac{1}{\alpha} \phi\left( \frac{x - \theta}{\alpha} \right) dx.
\]
Substituting (1) in for \( p \) and simplifying yields
\[
C(D) = c_r \frac{\lambda (1 - e^{-\eta D})}{ps} + \left( c_d + \frac{c_s}{D} \right) \frac{\lambda}{se^{-\eta D}} + \frac{b + h}{\sqrt{2\pi \alpha e^{-z^2}}},
\]
where \( \alpha \) is given in (34).

Although (37) is a complicated function of \( D \) (note that \( \alpha \) is a nonlinear function of \( D \)), \( C(D) \) is a function of a single variable and hence can simply be optimized over \( D \geq 0 \), e.g., by plotting. Once the optimal cycle length \( D^* \) is obtained, the optimal base-stock level \( B^* \) is given by (36).

5 A Numerical Example

In this section, we perform a computational analysis to assess the accuracy of our heavy-traffic approximation in §4, and to compare the constant-donor and base-stock policies.

5.1 Parameter Estimates

Some of our parameter values are taken from Kazerouni et al. (2015), and were estimated in conjunction with OpenBiome’s managers and using their data: \( s = 87.2 \) grams/day/donor, \( \eta = 0.0106 \) day, \( c_d = $18 \) day/donor, and \( c_s = $835 \) /test. The prescreening cost \( c_r \) is also derived from Kazerouni et al. (2015). From Table 1 in Kazerouni et al. (2015), we have that the cost of a clinical assessment is $50, the cost of initial serum and stool screening is $775 (this differs from \( c_s = $835 \) because donors are paid $60 to get a serum test), 35.1% of applicants pass the clinical assessment and move on to the initial serum and stool screening, and 44.4% of these people pass these serum and stool tests. Hence, the cost to produce a prescreened donor is
\[
c_r = \frac{50}{0.351(0.444)} + \frac{835}{0.444} = $2066.3/donor.
\]

Kazerouni et al. (2015) model demand as deterministic – and hence there was no need to consider holding and backorder costs – and exponentially increasing, which captures the startup environment. Here, we consider a stochastic time-homogeneous demand, which is intended to represent a stable environment after the FMT market is saturated. We assume demand for treatment is Poisson (i.e., \( v_d = 1 \)), and assume a standard treatment size of 25 grams (Kazerouni et al. 2015), implying that \( \mu_b = 25 \) grams, \( v_b = 0 \). To estimate the average demand rate, we note that the demand rate that corresponds to 10% of the recurrent
<table>
<thead>
<tr>
<th>Type of Cost</th>
<th>Simulation-Optimal Policy</th>
<th>Heavy-Traffic Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily Cost</td>
<td>% of Total</td>
</tr>
<tr>
<td>Prescreening</td>
<td>3099</td>
<td>31.12</td>
</tr>
<tr>
<td>Processing</td>
<td>3117</td>
<td>31.30</td>
</tr>
<tr>
<td>Testing</td>
<td>3711</td>
<td>37.28</td>
</tr>
<tr>
<td>Inventory holding</td>
<td>20</td>
<td>0.20</td>
</tr>
<tr>
<td>Inventory backorder</td>
<td>10</td>
<td>0.10</td>
</tr>
<tr>
<td>Total</td>
<td>9,957</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 1: The breakdown of the simulated mean daily cost for the simulation-optimal policy \((D_s, B_s)\) and the proposed heavy-traffic policy \((D^*, B^*)\).

The CDI market in the U.S. is 685 grams/day \cite{Kazerouni2015}. In addition, approximately 80% of OpenBiome’s current production is devoted to CDI, with the remainder allocated to research applications \cite{Burgess2016}. Assuming that OpenBiome captures the U.S. CDI market and continues to expand their research volume, we use the round number of 10,000 grams/day as the average demand rate, which yields \(\mu_d = \frac{10,000}{25} = 400/\text{day}\).

Finally, we estimate the holding and backorder costs, \(h\) and \(b\). We assume that \(h\) is the product of the interest rate and the variable cost. We compute the variable cost by the expected lifetime cost per donor divided by the expected salable stool over a donor’s lifetime, which is

\[
\frac{c_r + \frac{c_e}{1 - e^{-\eta D}}}{(1 - e^{-\eta D}) - 1} s D = 0.6525/\text{gram}
\]

after substituting in OpenBiome’s current cycle length of \(D = 60\) days. We assume an annual interest rate of 0.3, which corresponds to a daily rate of \(1.3^{1/365} - 1 = 7.2 × 10^{-4}\). Combining these two values gives a holding cost rate of \(h = 7.2 × 10^{-4}(0.6525) = 4.7 × 10^{-4}/\text{gram/day}\).

The backorder cost parameter is difficult to estimate. While OpenBiome’s main out-of-pocket cost for being backordered is to pay an additional $50 (or $2/gram) for expedited shipping, their primary concern is failing to provide timely service for a life-threatening disease \cite{Burgess2016}. As a typical estimate that represents a high service level, we choose \(b = 19h = 0.0089/\text{gram/day}\), which corresponds to a critical ratio of \(\frac{b}{b+h} = 0.95\).

### 5.2 Computational Results

Substituting our parameter values into \(36\) and \(37\) gives a proposed inter-testing time of \(D^* = 40\) days and a proposed base-stock level of \(B^* = 1.3248 \times 10^9\) grams, for an optimal cost of $10,038/day.

Recall that the base-stock policy in \(15\) does not require us to release an integer number of donors. In our numerical study, we operationalize this policy by releasing \([r(t)]\) donors into the system at time \(t\), where \([x]\) is the smallest integer that is greater than or equal to \(x\). The preference for rounding \(r(t)\) up rather than rounding it down stems from the fact that the per unit backorder cost is larger than the per unit holding cost.

Our first goal is to assess the accuracy of the heavy-traffic approximation, in terms of both cost and the decision variables. We simulate the system for 10 years (truncating the results from the first 5 years), and do this with the same stream of random numbers for different values of \(D\) and \(B\). This gives us the simulation-optimal decision variables, the simulated cost under this policy, and the simulated cost under the proposed heavy-traffic policy. We repeat this entire procedure 10 times to calculate the simulation-optimal policy, \((D_s, B_s)\), the average simulated daily cost (along with a 95% confidence interval) under
the simulation-optimal policy, $C(D_*, B_*)$, and the average simulated daily cost under the proposed policy, $C(D^*, B^*)$. This procedure yields $(D_*, B_*) = (39, 1.1848 \times 10^8)$, $C(D^*, B^*) = $10,018 ± 79/day; and $C(D_*, B_*) = $9,957 ± 49/day, which translates to a cost suboptimality of 0.61% for the proposed heavy-traffic policy.

To assess whether the accuracy of the heavy-traffic approximation improves as $\lambda$ gets larger, we repeat this entire procedure with a demand rate of $\lambda = 10^6$ grams/day, which is 100-fold larger than in the base case. In this scenario, $(D^*, B^*) = (40, 1.1872 \times 10^8)$, $(D_*, B_*) = (41, 1.1906 \times 10^8)$, and the cost suboptimality is reduced from 0.61% to 0.09%, suggesting that the heavy-traffic approximation is highly accurate when the demand rate is very large.

Returning to our base-case demand rate of $\lambda = 10^4$ grams/day, we provide a breakdown of the simulated average daily cost for the simulation-optimal and proposed heavy-traffic policies in Table 1. Under both policies, the inventory costs make up <1% of the total cost and the remaining cost is fairly evenly distributed among the prescreening, processing and testing costs. The heavy-traffic policy overestimates the optimal base-stock level and hence incurs nearly all of its inventory costs via holding, whereas the simulation-optimal policy has comparable holding and backorder costs. The heavy-traffic policy also has a slightly larger inter-testing time than the simulation-optimal policy, which leads to lower testing costs and higher prescreening and processing costs.

In addition, we find that the first of the two terms in $\alpha^2$ in (34) comprises only 0.17% of the total value of $\alpha^2$, implying that nearly all of the safety stock is due to hedging against random yield, not random demand (even though the demand is a compound Poisson process and hence quite variable).

We also run simulations to compare the performance of the constant-donor policy and the proposed base-stock policy over a five-year period, again using the same random number stream for each policy, and then repeating this procedure for 10 random number streams. We consider two variations of the constant-donor policy: the simulation-optimal pair $(D_*, K_*) = (50, 195)$ and the pair $(D, K) = (60, 217)$, where $K = 217$ is the optimal number of donors under OpenBiome’s current inter-testing time ($D = 60$ days). The simulation-optimal constant-donor policy incurs a cost of $12,539 ± 711/day (Table 2), which is 26% higher than the simulated cost of the simulation-optimal base-stock policy. Moreover, the $(D, K) = (60, 217)$ constant-donor policy, which is an optimistic (i.e., assuming that the optimal number of donors is used) version of OpenBiome’s current policy, incurs a cost of $12,949 ± 755/day, which is 30% higher than the simulated cost of the simulation-optimal base-stock policy. The cost increases incurred by the constant-donor policies are primarily due to large increases in the backorder costs (Table 2), which occurs because these policies do not monitor the finished goods inventory level. Although the inventory backorder and holding costs are predicted to grow as the square root of time in Table 2, these costs are somewhat stable over the five-year period of the simulation model.

<table>
<thead>
<tr>
<th>Type of Cost</th>
<th>$(D_<em>, K_</em>) = (50, 195)$</th>
<th>$(D, K) = (60, 217)$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily Cost</td>
<td>% of Total</td>
</tr>
<tr>
<td>Prescreening</td>
<td>3277</td>
<td>26.13</td>
</tr>
<tr>
<td>Processing</td>
<td>3510</td>
<td>27.99</td>
</tr>
<tr>
<td>Testing</td>
<td>3214</td>
<td>25.63</td>
</tr>
<tr>
<td>Inventory holding</td>
<td>4</td>
<td>0.04</td>
</tr>
<tr>
<td>Inventory backorder</td>
<td>2534</td>
<td>20.21</td>
</tr>
<tr>
<td>Total</td>
<td>12,539</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 2: The breakdown of the simulated mean daily cost for the simulation-optimal constant-donor policy $(D_*, K_*) = (50, 195)$ and the constant-donor policy with $(D, K) = (60, 217)$. 

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6 Concluding Remarks

We analyze a novel operation – the world’s first public stool bank [Amirtha 2016] – and uncover an interesting variant on the traditional inventory management problem: donors produce stool at a constant rate and get infected at a random time, stool cannot be placed into finished goods inventory until a test confirms that the donor is still uninfected, and donors found to be infected are permanently ejected from the system. The problem is one of joint quantity- and quality-control: when to release new donors into the system and how frequently to test current donors in order to minimize processing, testing and finished goods inventory costs.

We first consider a constant-donor policy, which is what OpenBiome is currently using to manage its system. In contrast to a traditional inventory system, the inventory on order – i.e., the amount of salable stool that the current donors will produce in the future – is not observable because we cannot anticipate when donors will get infected. Due to the exponential failure time of donors, the constant-donor policy can be viewed as a base-stock policy for the expected inventory on order. We find that this policy leads to unbounded costs, even if the number of donors can be chosen such that the production rate of salable stool exactly equals the stool demand rate, because it does not account for the current finished goods inventory level. Consequently, we consider a base-stock policy in which the expected inventory position, which is the expected remaining number of salable grams of stool produced by all current donors during their time in the system plus the current finished goods inventory level, is kept at a constant level. While our proposed base-stock policy may not be optimal, we believe that its intuitive simplicity makes it an attractive candidate for practical implementation. Under this policy, the stochastic process for the current number of donors in the system maps directly into a model that has been previously studied in heavy traffic [Glynn and Whitt 1991]: a multiclass $G/G/\infty$ queue with possible service times that are multiples of the inter-testing time $D$. Applying their results, which first requires us to show that the donor-release process satisfies a FCLT under the proposed base-stock policy, generates a rather concise solution, while also allowing for compound renewal demand for stool.

In our numerical study, which uses parameter values based on OpenBiome’s data, the inter-testing time $D$ and the base-stock level $B$ derived from our heavy-traffic analysis lead to a cost suboptimality of 0.61% compared to the optimal values derived by searching $(D,B)$ space via simulation. Despite the use of a compound Poisson demand process, the safety stock in the proposed policy is used almost entirely to hedge against random yield, not random demand. The proposed inter-testing time of $D^* = 40$ days is considerably smaller than the value of $D = 60$ days that is in current use at OpenBiome, and is reasonably close to the value of $D^* = 36$ days derived in Kazerouni et al. (2015), which ignores the statistical variability in demand and yield, and incorporates a 12-day testing delay. The $(D,K) = (60, 217)$ constant-donor policy, which is an optimistic version of the policy used by OpenBiome, incurs a mean daily cost that is 30% larger than the proposed base-stock policy, with the cost increase due primarily to an increase in backorders.

As noted earlier, this study complements Kazerouni et al. (2015) by considering a stochastic time-homogeneous demand rather than a deterministic time-varying demand, where the latter demand model represents the startup environment and the former demand model represents a stable scenario after nationwide CDI demand is satisfied. While it may be possible to generalize these results to the stochastic nonhomogeneous demand case using results from Pang and Whitt (2010), we do not view this as a practically important extension for OpenBiome because the stochastic uncertainty in interarrival times in the nonhomogeneous setting is dwarfed by the uncertainty in the future demand rate, which is quite sensitive to factors that are exogenous and unforeseen, such as published scientific studies and media coverage (e.g., Eakin (2014)). Kazerouni et al. (2015) study two refinements of the model that were of interest to OpenBiome management, both of which were found to reduce costs: using donor-specific inter-testing times, where donors with a high stool production rate are screened more frequently than donors with a low production rate, and interim testing, where a $120 test for two common infectious agents (rotavirus and Clostridium difficile) is performed in between two consecutive regular $775 tests.

A statistical analysis of data in Kazerouni et al. (2015) suggests that the time to donor failure is well modeled by an exponential distribution. This assumption implies that the expected inventory on order is linear in the number of donors (see [13]), which simplifies the analysis. If future data suggest that the donor failure time is not exponential, then a more complicated analysis would be required.
While our focus is on managing a public stool bank, it is possible that our model and analysis could be a useful starting point in other settings where failure-prone machines are operated in a make-to-stock setting. In particular, our analysis suggests that there may be other scenarios in which a constant-machine policy (akin to our constant-donor policy) may be inherently unstable.

Acknowledgment

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A Proof of Theorem 2

Proof. As mentioned in §4.1 of the main text, three events can change the expected inventory position at time \( t \): demand at time \( t \), a failed test at the end of a cycle at time \( t \), and a passed test at the end of a cycle at time \( t \). Beginning with the first event, because the demand process is a compound renewal process, it can be written as

\[
\Lambda(t) = \sum_{j:d_j \leq t} L_j \quad \text{for } t \geq 0,
\]

(38)

where \( l_j \) is the arrival time of the \( j \)th demand and \( L_j \) is its batch size. If we define \( l^n_j = \frac{l_j}{n} \) and \( L^n_j = \frac{L_j}{\sqrt{n}} \) for \( j = 1, 2, \ldots \), then

\[
\Lambda^n(t) = \sum_{j:d_j \leq nt} \frac{L_j}{\sqrt{n}} \quad \text{for } t \geq 0 \quad \text{by (23)},
\]

\[
= \sum_{j:d_j \leq t} L^n_j.
\]

Let

\[
d^n(t) = \begin{cases} 
L^n_j & \text{if } t = l^n_j \text{ for some } j; \\
0 & \text{otherwise},
\end{cases}
\]

(39)

be the demand at time \( t \) in the \( n \)th system, so that the scaled finished goods inventory \( I^n(t) = \frac{I(nt)}{\sqrt{n}} \) drops by \( d^n(t) \) due to demand at time \( t \). Note that with this definition, we have

\[
\Lambda^n(t) = \sum_{j:d^n_j \leq t} d^n(l^n_j).
\]

(40)

Also note that since \( \Lambda(t) \) is a renewal reward process, then from Theorem 7.4.1 in Whitt (2002), it follows that

\[
\Lambda^n(t) \Rightarrow \lambda\sqrt{nt} + \sqrt{mu_b} \sqrt{v^2 + v^2_0} W_1(t),
\]

(41)

where \( W_1(t) \) is a standard Brownian motion.

Let \( Y^n(t) = \frac{Y(nt)}{\sqrt{n}} \) and \( Z^n(t) = \frac{Z(nt)}{\sqrt{n}} \) be the scaled processes defined via equations (2)-(4) in the main text, which represent the number of donors passing a test and finishing a cycle at time \( t \) in the \( n \)th system, respectively. Also, the finishing times (times at which at least one donor finishes a cycle) in the \( n \)th system are \( f_1^n = \frac{L_1}{n}, f_2^n = \frac{L_2}{n}, \ldots \), where \( f_1, f_2, \ldots \) are the finishing times in the original system. The released number of the donors in the \( n \)th system at time \( t \) is \( r^n(t) = \frac{r(nt)}{\sqrt{n}} \) and the release times (times at which \( r^n(t) \neq 0 \)) are \( a^n_1 = \frac{a_1}{n}, a^n_2 = \frac{a_2}{n}, \ldots \), such that

\[
R^n(t) = \sum_{j:a^n_j \leq t} r^n(a^n_j).
\]

(42)

Turning to the second and third events that can change the expected inventory position, we note that if a donor fails a test at time \( t \), then the expected inventory on order decreases by \( \frac{sDp}{\frac{1-p}{p}} \) grams, and if a donor passes a test at time \( t \) then the finished goods inventory level increases by \( sD \) grams. Consequently, if the expected inventory position is at the base-stock level \( B \) right before time \( t \), equation (15) implies that

\[
r^n(t) = \frac{d^n(t) + [Z^n(t) - Y^n(t)] \frac{sDp}{\frac{1-p}{p}} - Y^n(t)sD}{\frac{sDp}{\frac{1-p}{p}}} \quad \text{for } t \geq 0,
\]

\[
= \frac{d^n(t)}{\frac{sDp}{\frac{1-p}{p}}} + [Z^n(t) - \frac{1}{p}Y^n(t)].
\]

(43)

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Now, we define the auxiliary random process \( U(t) = Z(t) - \frac{1}{p} Y(t) \) in the original system, which is nonzero only at times \( t = t_1, t_2, \ldots \). Because \( Y(f_j) \sim \text{Bin}(Z(f_j), p) \) for any \( j = 1, 2, \ldots \), then \( \mathbb{E}[U(f_j)] = 0 \) for any \( j = 1, 2, \ldots \) and \( \text{cov}(U(f_{i_1}), U(f_{i_2})) = 0 \) for any \( i_1 \neq i_2 \). Also note that for any \( f_j \), we have

\[
\text{var}(U(f_j)) = \mathbb{E}[(U(f_j))^2]
\]

\[
= \mathbb{E}[(Z(f_j) - \frac{1}{p} Y(f_j))^2]
\]

\[
= \mathbb{E}[(Z(f_j))^2 - \frac{2}{p} Z(f_j) Y(f_j) + \frac{1}{p^2} (Y(f_j))^2 | Z(f_j)]
\]

\[
= \mathbb{E}[(Z(f_j))^2] - \frac{2}{p} \mathbb{E}[Z(f_j) | Z(f_j)] + \frac{1}{p^2} \mathbb{E}[(Y(f_j))^2 | Z(f_j)]
\]

\[
= \mathbb{E}[(Z(f_j))^2] - \frac{2}{p} \mathbb{E}[Z(f_j)] + \frac{1}{p^2} \mathbb{E}[(Y(f_j))^2] + \frac{1}{p} Z(f_j) p (1 - p)
\]

\[
= \frac{1 - p}{p} \mathbb{E}[Z(f_j)].
\]

Because

\[
Z^n(t) = \frac{1}{p} Y^n(t) = \frac{1}{\sqrt{n}} (Z(nt) - \frac{1}{p} Y(nt)) = \frac{U(nt)}{\sqrt{n}},
\]

we can express (43) as

\[
r^n(t) = \frac{d^n(t)}{s D_p} + \frac{U(nt)}{\sqrt{n}}.
\]

In addition, by Theorem 7.4.1 in Whitt (2002), we have

\[
\frac{1}{\sqrt{n}} \sum_{j: f_j \leq t} U(n f^n_j) = \frac{1}{\sqrt{n}} \sum_{j: f_j \leq nt} U(f_j) \Rightarrow \lim_{j \to \infty} \frac{\text{var}(U(f_j))}{\mathbb{E}[f_j - f_{j-1}]} W_2(t) = \lim_{j \to \infty} \sqrt{\frac{1 - p}{p} \mathbb{E}[Z(f_j)]} W_2(t),
\]

where \( W_2(t) \) is a standard Brownian motion. On the other hand, \( \psi = \lim_{j \to \infty} \frac{\mathbb{E}[Z(f_j)]}{\mathbb{E}[f_j - f_{j-1}]} \) represents the asymptotic rate at which donors finish their tests. Because a fraction \( p \) of these donors are re-injected into the system, we have \( \psi = \rho + p \psi \), which yields \( \psi = \frac{\rho}{1 - p} \). This, by equation (22) in the main text, gives \( \psi = \frac{\lambda}{s D_p} \) which together with (46) gives

\[
\frac{1}{\sqrt{n}} \sum_{j: f_j \leq nt} U(f_j) \Rightarrow \sqrt{\frac{\lambda(1 - p)}{p^2 s D}} W_2(t),
\]

Putting things together, we have

\[
R^n(t) = \sum_{j: a^n_j \leq t} r^n(a^n_j)
\]

\[
= \frac{1 - p}{s D p} \sum_{j: f^n_j \leq t} d^n(t^n_j) + \frac{1}{\sqrt{n}} \sum_{j: f^n_j \leq t} U(n f^n_j)
\]

\[
= \frac{1 - p}{s D p} \Lambda^n(t) + \frac{1}{\sqrt{n}} \sum_{j: f_j \leq nt} U(f_j)
\]

\[
\Rightarrow \frac{1 - p}{s D p} \left( \lambda \sqrt{nt} + \sqrt{\mu_d \mu_b} v_d^2 + v_b^2 W_1(t) \right) + \sqrt{\frac{\lambda(1 - p)}{p^2 s D}} W_2(t)
\]

\[
= \rho \sqrt{nt} + \sqrt{\frac{\lambda}{p^2} \left[ \frac{1 - p}{s D} + \frac{(1 - p)^2 \mu_b}{s^2 D^2} (v_d^2 + v_b^2) \right]} W(t),
\]
where \( W(t) \) is a standard Brownian motion. Rearranging both sides of the last equation in (48) gives

\[
\frac{R(nt) - \rho nt}{\sqrt{n}} \Rightarrow \nu_t W(t),
\]

where

\[
v_t^2 = \frac{\lambda}{p^2} \left[ \frac{1 - p}{sD} + \frac{(1 - p)^2 \mu_b}{s^2D^2} \left( v_d^2 + v_b^2 \right) \right].
\]

Equations (28)-(29) in Theorem 2 follow immediately from Theorem 9.5.1 of Whitt (2002) and the discussion thereafter, noting that \( R_i(t) \) is a splitting process with respect to \( R(t) \) with iid splits. \( \Box \)