Flexible Services and Manufacturing Journal
https://doi.org/10.1007/s10696-025-09645-2

Production of blood components from donated units: literature review, areas for improvement, and research perspectives

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Received: 2 August 2024 / Accepted: 21 November 2025

Abstract
In several countries, most whole blood units donated by healthy volunteers are separated into their components (mainly red blood cells, plasma, and platelets). However, despite its importance, the production of blood components has been studied only marginally in the literature dealing with the blood supply chain (BSC). In fact, no scheduling approach has been developed specifically to address this production in detail. In this study, we provide a description of the BSC production phase from a scheduling perspective by considering the European system in particular. We also consider the specific features of this production system in light of the broad classes of chemical processing and disassembly systems, relying on the idea that a whole blood unit is broken down, or processed, into specific components. We review the literature on management and scheduling systems in these contexts to identify insights or methodologies that could inform future research in formulating a scheduling problem for blood component production. Finally, on the basis of these analyses, we suggest future research directions for improving the management of the BSC production phase.

Keywords Blood component production · Scheduling · Chemical processes · Disassembly processes · Research perspectives

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Published online: 19 January 2026

1 Introduction

Blood is a vital fluid for patients during many health care operations, but at the same time, it is a limited resource that can only be obtained from donations from healthy individuals.

According to several national laws, blood can be used as such through whole blood transfusion, which is employed as a blood supply during surgery (Ajmani 2020; Gammon et al. 2024) or for resuscitation in the case of severe traumatic hemorrhage (Cap et al. 2018). However, it is almost always preferred to transfuse individual blood components, including red blood cells (RBCs)—also called erythrocytes—, plasma, platelets, and cryoprecipitates (Osorio et al. 2015). In fact, each component can serve different purposes in different patients. For example, RBCs are used to treat anemia or blood disorders, plasma and cryoprecipitates are used to treat blood clotting deficiencies, and platelets are required in cancer treatments and organ transplant procedures (AmericanRedCross 2024). Each blood component has a specific shelf life, for example, up to 5 days for platelets, up to 42 days for RBCs, and up to 3 years for plasma if stored under optimal conditions (European Directorate for the Quality of Medicines & Healthcare 2023).

Blood donation can be done in two different ways: whole blood donation and apheresis. In whole blood donation, blood is collected in its entirety, and its components are subsequently separated with specific procedures and equipment. Indeed, more than 90% of donated whole blood units are separated into their components in most European and American countries (World Health Organization 2021, 2024). Dedicated facilities collect the whole blood units, produce the blood components, and supply them to the centers where they are needed. By contrast, apheresis is a specialized process in which a machine separates and directly collects blood components, returning the rest of the blood to the donor (Greening et al. 2010; Ekici 2018).

The blood donation system is responsible for providing adequate units of whole blood and blood components to meet demand. The blood supply chain (BSC), required to ensure the production and distribution of blood components, consists of different entities organized into four main phases, which can be classified according to the main life stages of a donated blood unit: collection, production, inventory, and distribution (Osorio et al. 2015).

The BSC must be managed effectively and efficiently to respond quickly to blood demand and minimize operational costs. BSC management is made even more complicated by the limited availability of blood, the significant uncertainty surrounding blood component demand, donation volumes, and the limited shelf life that results in discarded blood components. As evidence of these complexities, it was reported that 23% of discarded blood donations were due to exceeding the expiration date (World Health Organization 2021).

In the literature, there are several classifications of the main decisions made in the BSC. For example, Pierskalla (2004) classified such decisions according to the planning level. Strategic decisions include the location of blood banks, the allocation of donation areas to blood centers, and the coordination of supply and demand, whereas processes such as blood collection, blood component production, inventory management, and distribution are considered at the tactical and operational levels. A

more detailed classification was made by Osorio et al. (2015) in terms of breaking down each echelon of the BSC into corresponding decision levels: strategic, tactical, and operational. Building on this, Torrado and Barbosa-Póvoa (2022) addressed the decision levels from the sustainability perspective with the aim of providing a framework that incorporates social, financial, and environmental aspects. In a more recent study, an integrated framework for BSC management through an operations research perspective was provided by Meneses et al. (2023b), focusing mainly on the strategic and tactical planning levels.

The different BSC phases have been studied individually, or two or more phases have been investigated together, analyzing their interactions (Baesler et al. 2014; Habibi-Kouchaksaraei et al. 2018; Zahiri et al. 2018; Araújo et al. 2020). The production of specific blood components, such as platelets (Ensafian and Yaghoubi 2017; Stubbs et al. 2021), or the usage of blood components in specific contexts, such as disaster reliefs (Liu and Song 2019), have also been studied. However, some phases have received less attention than others. For example, collection has been less studied than storage and distribution (Baş et al. 2016; Baş Güre et al. 2018), while blood component production is the least studied and mostly neglected phase in the literature (Osorio et al. 2015; Imamoglu et al. 2023).

In this study, we address the BSC production phase by referring to the European system in particular. We first provide a description of this phase from a scheduling perspective. We then emphasize the research areas and needs that have not yet been addressed in the BSC literature regarding the production phase. In fact, although existing literature reviews analyze the BSC as a whole, including the production step, none has delved in depth into the topic to provide case studies or possible solution approaches from the optimization perspective. We also review the literature on management and scheduling systems in other contexts to identify insights or methodologies that could be leveraged for blood component production. Finally, on the basis of these analyses, we suggest future research directions to improve the management of the production phase.

Our analyses were also supported by a field analysis, which allowed us to interact with the Immunohematology and Transfusion Medicine Department of Niguarda Hospital in Milan, Italy, and with a company that manufactures separators and other blood processing equipment (Delcon Srl, Grassobbio, Italy). This allowed for clarifying discussions and validating comparisons between blood component production and the other systems considered.

In summary, the contributions of this review are as follows:

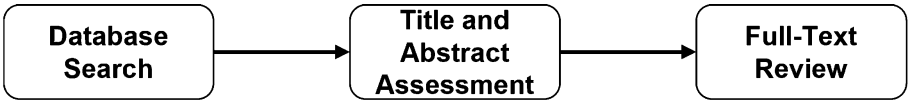
- To provide a detailed description of the specific BSC production step, mainly focusing on the operational aspects of the blood component production process;
- To highlight the gaps in the literature, which does not address scheduling problems for the BSC production of blood components and the consequent lack of available decision support systems (DSSs) for this production;
- To suggest future research directions for the development of DSSs that would meet the needs of blood component production, on the basis of similarities with scheduling approaches in other fields.

The remainder of this paper is organized as follows. The BSC is introduced in Sect. 2. Blood component production is detailed in Sect. 3 together with the associated requirements. The literature on the scheduling of blood component production, as well as that on the tools that support other systems sharing characteristics with blood component production, is then analyzed in Sect. 4. Areas in the literature other than the BSC were examined to find research on similar processes because of the lack of studies specifically addressing this process. The goal was to highlight scheduling approaches that may have relevance to blood component production and to draw insights into how the blood component production process can be optimized. Finally, discussions are made, and concluding remarks are reported in Sect. 5.

2 The blood supply chain

In this section, we provide an abridged, literature-rooted description of the main BSC phases, according to the classification of Osorio et al. (2015), and of the network as a whole. The goal is to position the BSC production phase—which is the focus of our analysis—among others, and highlight the interactions among them.

The search was performed on Web of Science, Scopus, and Google Scholar. Publications were considered if they were written in the English language, regardless of publication year. The keywords "blood donation", "blood supply chain", "blood components", "blood products", "fractionation", "separation", "schedule" and "network design" were used for the search. Titles and abstracts were initially assessed, and then a full-text review was conducted to include or exclude publications. The workflow is reported in Fig. 1.



Database Results		Duplicate Removal and Filtering	Title and Abstract Assessment	Final Selection After Full-Text Review
Web of Science	1346	762	132	58
Google Scholar	3440			
Scopus	4636			

Fig. 1 Flowchart of the literature search strategy, according to Durach et al. (2017) and Sauer and Seuring (2023)

2.1 Collection phase

The first phase of the whole BSC involves collecting and providing adequate and balanced amounts of blood to the entire BSC (Williams et al. 2020). At this stage, candidate donors are checked to assess their eligibility, and if eligible, they make the donation either as whole blood or through apheresis.

These activities are carried out at dedicated collection centers, which may be located inside or outside the health facilities that receive blood for processing. In addition, blood can be collected at temporary collection sites or mobile collection centers.

The literature is rich in studies addressing medical and biological issues related to donation. However, it is scant in studies concerning management aspects, such as scheduling blood collection, forecasting donor arrivals, and deciding on the collection method.

Although the blood collection phase has not been widely addressed in the past (Baş et al. 2016; Baş Güre et al. 2018), research on it has begun to gain popularity in recent years. For example, some studies have focused on appointment scheduling to meet donors' and production needs at the same time, to balance production, to reduce waiting times, and to respect donor preferences (Alfonso et al. 2015; Mobasher et al. 2015; Baş et al. 2018; Yalçındağ et al. 2020; Doneda et al. 2021). In this regard, the prediction of donor arrivals has also been studied to improve the organization of collection activities (Ding et al. 2023; Epifani et al. 2023; Argiento et al. 2024).

Other works have addressed mobile blood collection facilities (Şahinyazan et al. 2015), donation of specific components, such as platelets (Ghandforoush and Sen 2010), or collection in new contexts, such as home blood donation (Doneda et al. 2024; Bacci et al. 2024). Interactive communication strategies, through appropriate digital tools, have also been addressed to build effective relationships with donors and improve the process (Allamsyah and Mansur 2018), Finally, another area of study is the transportation of collected blood units between facilities before processing (Khameneh et al. 2023).

A key aspect of collection is the time spent during blood donation, which is also referred to as *bleeding time*. It determines the constraints on the possible blood components that can be produced from the collected whole blood unit. If the bleeding time exceeds certain values, as defined by law according to the country concerned, some blood components cannot be extracted, as they would be of too low quality. For example, in Europe, the European Committee on Blood Transfusion imposes a general limit of 15 min for platelet and plasma production (European Committee on Blood Transfusion 2023). Depending on the specific European country or region, the limits may then be further narrowed. In Italy, any type of blood component can be extracted from the donated unit if the donation takes less than 12 min. Otherwise, the blood unit should not be used for platelet production if the donation time exceeds 12 min, and the obtained plasma should be used only for industrial purposes, such as drug manufacturing, if the duration exceeds 15 min.

Finally, it is worth remarking that, along with the donated unit, donor blood samples are collected in one or more tubes so that the blood can be tested for blood type and the presence of various viruses, such as HIV and hepatitis B or C.

2.2 Production phase

In this phase, the collected blood is analyzed and separated into components. Different methods can be used to produce blood components from whole blood units, and each method can produce different amounts of blood components.

The separation of whole blood into components is typically a make-to-stock process, in which production decisions about which components to produce and in what quantities are made before the actual demand is known. Therefore, careful scheduling is needed to manage the separation process with a minimum rejection rate, meeting the uncertain demand for blood components, and in a cost-effective manner. Consequently, in the management literature, the main focus is on uncertain demands and arrivals of donated units.

Most studies employed a simulation approach (Katz et al. 1983; Sirelson and Brodheim 1991), sometimes combined with an optimization method (Haijema et al. 2007; Van Dijk et al. 2009; Haijema et al. 2009). In addition, production was usually studied together with inventory management, as it relates to stock replenishment (Haijema et al. 2007; Van Dijk et al. 2009; Haijema et al. 2009).

Some studies have analyzed the efficiency of blood component production (Veihola et al. 2006a, b; Baesler et al. 2011). Among them, Lowalekar and Ravichandran (2011) built a simulation model to decide the optimal amount of blood units to separate for a blood bank in India, although they did not consider the actual fractionation process or the related resources. Similarly, Baesler et al. (2011) built a simulation model for a blood center in Chile to investigate bottlenecks, resource utilization and the maximum capacity of the system under different arrival rates of blood units. Later, Baesler et al. (2014) extended the study to incorporate collection, inventory, and distribution while analyzing different inventory policies.

Finally, Li et al. (2022b) focused on different production methods to obtain components. Considering the perishability of components and the uncertainty of supply and demand, they proposed a daily plan over a weekly time horizon, including the inventory of blood components and a dynamic scheduling model that minimizes the total cost and shortage and waste penalties.

2.3 Inventory phase

This is the most studied phase of the BSC because of the perishability of blood and its components, as well as the need for cross-matching processes to assess the compatibility of blood products. Another challenge in blood component inventory concerns the uncertainties of blood component supply and demand, both in terms of quantity and type, over time (European Directorate for the Quality in Medicines & Healthcare 2022).

A key decision in this stage includes developing inventory policies. For example, some recent studies have proposed stochastic optimization models for deciding inventory strategies (Chen et al. 2021; Mallari et al. 2023; Meneses et al. 2023a), while others have followed a simulation-optimization approach (Dalalah et al. 2022; Hu et al. 2024) to tackle this problem. Of all blood products, platelets have the short-

est shelf life at only 5 days maximum; therefore some studies have focused solely on platelet inventory management (Rajendran and Ravindran 2019; Mallari et al. 2023).

In addition, as a part of inventory management, demand forecasting has been examined in several studies (Fortsch and Khapalova 2016; Li et al. 2021; Ben Elmir et al. 2023; Motamedi et al. 2024).

Lastly, some studies have also considered issuing policies (Abbasi and Hosseinifard 2014; Haijema 2014; Bozorgi and Najafi 2020).

2.4 Distribution phase

In the last BSC phase, blood components are distributed to the different demand points. Hospitals, hospital wards, and transfusion centers send their requests to blood banks, which are responsible for supplying an adequate amount of blood component units.

Available studies focus on strategies for the delivery of whole blood or components from blood centers to hospitals (Hemmelmayr et al. 2009), the preparation of blood for elective critical surgeries (Inamdar et al. 2021), and the transportation of blood components between blood centers and hospitals (Liu et al. 2020).

2.5 Network as a whole

Several works focus on network design, to coordinate phases and make them efficient in relation to the overall demand for blood and the availability of donors. Agac et al. (2024) recently reviewed the existing literature on BSC from a network design perspective, to highlight research gaps in this area.

Available studies proposed MILP models to make strategic and operational decisions (Yuesti et al. 2022), and to design appropriate BSC under uncertain conditions (Zahiri and Pishvaee 2017; Ramezanian and Behboodi 2017; Mohammadian-Behbahani et al. 2019; Haeri et al. 2020). Some of them also considered disruption in the network (Khalilpourazari and Hashemi Doulabi 2023).

3 Blood component production process

Blood component production from whole blood is a well-established process that uses dedicated equipment, such as centrifuges and extractors. However, the process varies from country to country, mainly because of regulations, supply and demand levels, and the technological infrastructure of the country.

We first describe the different components that can be obtained from whole blood in Sect. 3.1. Then, we discuss the alternative methods adopted in different countries to obtain the components in Sect. 3.2: we detail the typical production process in European countries in Sect. 3.2.1, and compare it with the U.S. system in Sect. 3.2.2.

The description of the European system is also supported by the analysis of the Immunohematology and Transfusion Medicine Department of Niguarda Hospital in Milan, Italy, which is a relevant example of this system. Furthermore, in describing the process, we consider the viewpoint of a company (Delcon Srl, Grassobbio, Italy)

that manufactures blood processing machinery and serves several facilities in both Europe and the U.S..

3.1 Blood components

Whole blood is primarily separated into the three main components: RBCs, plasma, and platelets. Plasma can be further processed to give cryoprecipitates (Fig. 2).

RBCs can be obtained in two variations based on leukocyte levels, depending on the country regulations. For example, residual leukocytes must be less than 5×10^6 cells per unit according to the Food and Drug Administration and less than 10^6 according to the European Council (Sharma and Marwaha 2010; Simancas-Racines et al. 2019). Leukoreduction refers to the removal of leukocytes using the gross removal method, whereas leukodepletion is the removal of leukocytes by means of specific filters or devices. In the latter case, the amount of leukocytes contained in RBCs is much lower and controllable, reduced by almost 99.99%. If required, RBCs can also be irradiated to further and completely block leukocytes in case the patient may develop an immune response against the transfused blood.

Plasma can be used both for transfusion, similar to the other components, and industrially for drug production. It can be rapidly frozen to give *fresh frozen plasma*, which is then thawed before transfusion. Additionally, it can be used to obtain cryoprecipitates, which contain clotting factors like plasma, but in higher concentrations. They are obtained from frozen plasma that thaws slowly.

Platelets can be kept together with RBCs, that is, they are not separated, or they can be separated to be transfused individually.

Each component has a specific shelf life until expiration, as well as specific storage conditions. Platelets are viable for up to 5 days between 20 and 24 °C and must be placed in a shaker to avoid coagulation. RBCs can be transfused up to 42 days after separation, and must be kept between 2 and 6 °C. Finally, frozen plasma and cryoprecipitates are viable for up to 1 year, but must be kept at −25 °C. Notably, the shelf life of frozen plasma can be extended to up to 5–7 years if stored at a temperature below −65 °C (Joint UK Committee, 2013).

Also the whole blood, if not separated into its components, has a shelf life. It must be kept between 2 and 6 °C for no more than 42 days. In any case, during this period, plasma loses its properties after 24 h, and platelet count decreases after 2 weeks (Hardwick 2020).

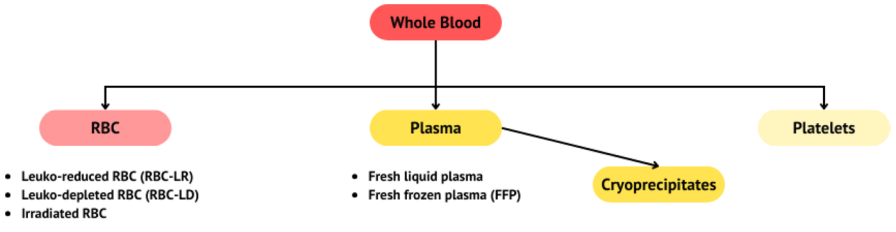


Fig. 2 Blood components produced from whole blood units

Blood components are also produced in small quantities for special purposes. The main ones are:

- RBCs and platelet units for pediatric patients, which are lesser in volume than the regular ones for adults;
- *Washed* RBCs and *washed* platelets, in which washing refers to eliminating plasma from these products. This is necessary for patients who may experience allergic reactions to plasma proteins. To reduce plasma proteins, RBCs and platelets are mixed with saline solution and centrifuged several times.

3.2 Whole-blood fractionation methods

Components can be produced by different fractionation sequences from whole blood, which also determine the volume of the different components produced. The possible sequences are depicted in Fig. 3, while the countries and regions in which they are used are shown in Table 1. Method 4 is mostly adopted by European countries (European Committee on Blood Transfusion 2023), as in the Niguarda Hospital, whereas Method 5 is more commonly employed in the U.S. and also China (Li et al. 2022b, Association for the Advancement of Blood & Biotherapies 2025).

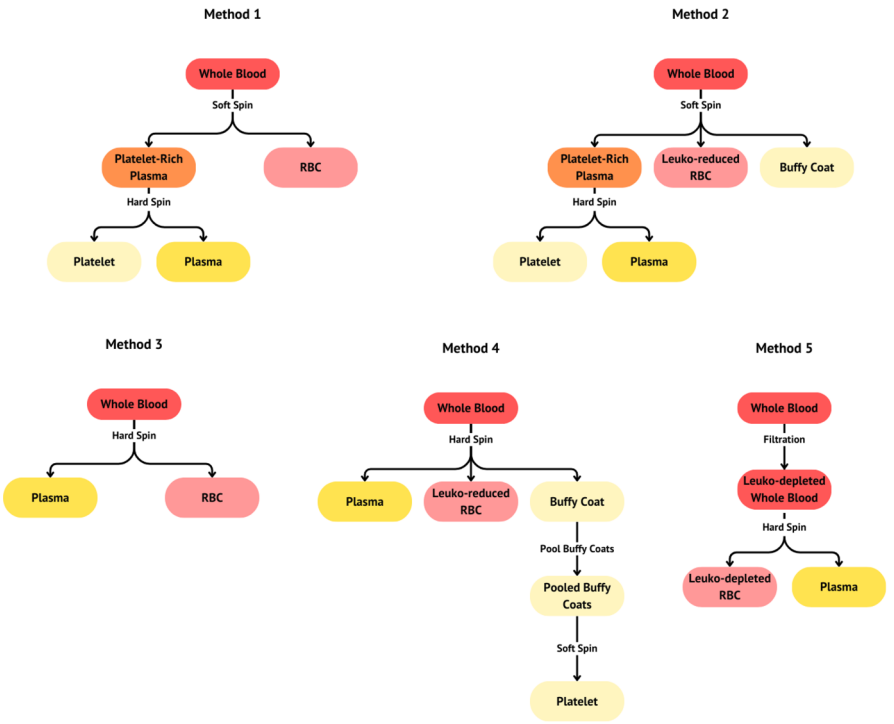


Fig. 3 Fractionation sequences and relative blood components that can be produced. Adapted from Li et al. (2022b)

Table 1 Main fractionation methods according to countries and regions

Country/region	Main fractionation sequences	References
Europe	Methods 4 & 5	European Committee on Blood Transfusion (2023)
North America	Methods 2 & 5	Association for the Advancement of Blood & Biotherapies (2025)
China	Methods 1 & 5	Li et al. (2022b)

All fractionation sequences share the idea of centrifuging blood, i.e., spinning the bags containing the donated blood units, to separate the different components according to density (Heaton et al. 1997). As a result, each major or intermediate component appears on a layer of the bag, according to its density. The components are then separated from one another by an extractor, and transferred to other bags.

Centrifugation among the different sequences differs mainly in spinning velocity, which determines the layers of components formed. Two layers appear if the whole blood unit is centrifuged at a low velocity: RBCs and platelet-rich plasma, which contains platelets and white cells (Method 1 in Fig. 3). RBCs, with a high density, sediment at the bottom of the bag, while plasma, with a low density, appears at the top. As the spinning velocity increases, the number of leukocytes and platelets separated from plasma and RBCs also increases. At high spinning velocities, an additional thin layer called *buffy coat* appears between the RBCs and plasma, which contains leukocytes and platelets (Methods 2 and 4 in Fig. 3).

Different types of blood bags exist, chosen according to the fractionation sequence adopted. They are primarily classified by the number of interconnected bags used during component production.

- *Single bags* include only the main bag that collects the blood and are typically used for autologous blood transfusion, but not for the production of components.
- *Double bags* consist of two attached bags. One collects the blood and keeps the RBCs after separation, while the other stores the separated plasma.
- *Triple bags* consist of three attached bags. One collects the blood and keeps the buffy coat after separation, while the others are used to store separated plasma and RBCs, respectively.
- *Quadruple bags* are similar to triple bags, but they also have a bag for preservation solution.

Triple and quadruple bags can be top-and-bottom (T&B) or top-and-top (T&T). T&B bags have one main outlet to connect bags at the top and one at the bottom of the main bag to allow simultaneous extraction of plasma and red cells. By contrast, in T&T bags, the outlets are both at the top of the main bag, and one component is pulled out at a time. The interconnected bags are detached only after separation, allowing each product to be handled independently thereafter. Additionally, some bags include a filter for leukodepletion. In all cases, bags include an anticoagulant (e.g., a citrate phosphate dextrose solution) and an additive to preserve RBCs (e.g., a saline adenine and glucose solution).

3.2.1 European process

Laboratories that separate whole blood units into blood components may be located within hospitals or in separate facilities. Daily units from each collection center arrive all together or in batches to the laboratory and are contained in suitable transport containers that can hold up to a certain number of units.

The production time of blood component units after whole blood collection is subject to some limitations. In several European countries including Italy, if plasma is obtained from whole blood, plasma must be frozen within 6 h, or within 18 h if the blood unit is refrigerated after donation and maintained at a temperature below 10 °C. Should these limits be exceeded, plasma can still be manufactured within 24 h but only for industrial use (e.g., pharmaceutical use). Concurrently, platelets must be produced within 24 h. As for RBC production, prestorage filtration of the RBC concentrate must be done up to 24 h after donation. Finally, cryoprecipitates can be produced from plasma at any time during storage, such as on demand when they are needed.

Upon arrival, the whole blood units are registered in the check-in area. If the laboratory is equipped with a digital tracking system, the units are scanned and logged automatically into the system. This step also includes weighing the units, especially if the weight has not been associated with the units in the collection center. Each blood unit must fall within specified upper and lower weight limits; those that do not meet these criteria are usually discarded.

The temperature of whole blood units is monitored initially from donation throughout transport to the blood-processing facility. In order to produce all three components (RBCs, platelets, and plasma), the temperature throughout transportation must be between 20 and 24 °C for no more than 6 h, or between 2 and 6 °C if the time is longer. However, in this case, platelets cannot be produced, and the plasma produced cannot be used for transfusions but only for drug production (NHS Blood and Transplant 2025).

Finally, the blood samples in the test tubes associated with each accepted unit are sent to a screening laboratory for analysis. The production of blood components starts even without the results of these tests in order to meet processing times.

The blood bags are placed into cups (i.e., the bags are *cupped*) to be centrifuged. Depending on the centrifuge, each cup may contain one or more bags. Centrifugation is performed using a device called a centrifuge, which has a given number of slots for cups. Cups of identical or very similar weights must be positioned on two diametrically opposite slots of the centrifuge to avoid unbalancing the motor shaft during spinning. The centrifuge can also start with empty slots, provided that the above-described balance is respected. Sometimes, weights or water-filled bags of the desired weight are added to the cups, to achieve balance.

As anticipated, depending on the desired blood components, blood bags are exposed to specific spinning velocities and times, and centrifugation is conducted at a specific temperature. Indeed, RBCs and platelet-rich plasma or, alternatively, RBCs, plasma and the buffy coat are obtained from a whole blood unit with centrifugation (Fig. 3).

Therefore, centrifuges can be adjusted to different settings, as required. Because of the different temperatures, there may be a setup period between two successive centrifugations if the programs (i.e., the products to be obtained) require different temperatures. No setup period is required if only the spinning velocity is changed.

After centrifugation, the bags are placed individually on an extractor, which squeezes the centrifuged bag, transferring each component into separate bags, as detailed in Sect. 3.2. Similar to the centrifugation process, extraction is programmed differently on the basis of the products to be extracted and the specific type of blood bag used.

After separation, the RBCs can be filtered. For leukodepletion, the bags are hung upside down to pass the RBCs through the dedicated filter. This process should last for a maximum of 12 min. If it lasts longer than 12 min, the RBC unit is checked individually to analyze the reason for such a long filtration process and, as needed, discarded. Alternatively, leukoreduction involves the removal of leukocytes using coarse removal methods but is currently less preferred compared with leukodepletion (Sharma and Marwaha 2010).

Despite these differences, it is important to note that a blood production center usually works with only one fractionation method. Therefore, the same parameters are set for centrifuges and separators, the same procedure is used for leukocyte reduction, and only one type of bag is used. This avoids a setup period.

Subsequently, the extracted components are stored under proper temperature conditions, as discussed in Sect. 3.1, until the results of the analysis conducted on the relevant test tubes are received. This stage of the process is called *quarantine* and usually takes place overnight.

If the test results reveal the presence of infectious diseases in a whole blood unit, the products derived from that unit are discarded. Otherwise, operations continue.

Additional processes are required to extract platelets from the buffy coat. Because the amount of platelets that can be produced from a single whole blood unit is not enough for transfusion, the buffy coats obtained from a fixed number of suitable units are pooled to reach the minimum amount of platelets needed for transfusion. To this end, buffy coat units are brought together by connecting the bags and hanging them upside down so that the buffy coats accumulate in one bag. Connections are made in a sterile manner by means of a specific machine that cuts and fuses the connecting tubes. Once pooled, the buffy coats undergo another centrifugation that separates the RBCs from the platelets. Finally, the platelets are transferred to their final bag using an extractor. A small sample of the produced platelets is analyzed to check whether their number is adequate, that is, above a specific threshold; if not, the unit is discarded.

Similarly, after quarantine, the frozen plasma must undergo additional steps if cryoprecipitates are to be produced according to demand. To produce them, centrifugation and extraction are carried out after the frozen plasma is thawed. Sometimes, as in the case of a buffy coat, the obtained cryoprecipitates are combined to reach the minimum amount for transfusion, although this is not the standard procedure. Alternatively, facilities can produce cryoprecipitates from plasma collected by apheresis by means of a specialized process in which a machine separates and directly collects some blood components, returning the rest of the blood to the donor.

Finally, all produced components are labeled with their final labels if they are eligible for use. The decision of whether the separated components can be used for transfusion is also determined by the constraints related to the blood donation duration (bleeding time), the time elapsed since donation, and the storage temperature, as discussed above. In particular, plasma units have different labels depending on their intended uses, clearly indicating whether they are suitable for transfusion or if they are to be sent to industry for drug production.

In case RBC units are irradiated to block the proliferation of leukocytes, it is mandatory to perform irradiation just before transfusion, as irradiation damages RBCs, and this damage increases over time. Therefore, units are irradiated on demand just before being transfused.

The blood components produced in small quantities for special purposes (e.g., for pediatric patients, as discussed in Sect. 3.1) usually have *high* priority, in which *high* means that, upon request, they must be produced within 24 h. Therefore, they can be produced during the day of demand when resources are available, without interrupting regular production. Alternatively, their production can be scheduled once or twice a week to prepare a small warehouse that is always available. In addition, requests for exchange transfusion, which refers to the replacement of most of an individual's blood (mostly performed on newborns in cases of blood incompatibility between mother and child), are considered extremely urgent. Therefore, the units are prepared immediately, interrupting regular production.

In general, production can be divided into two phases that take place at different time intervals during the day. This is mainly due to the waiting for the results of blood unit analysis, as mentioned earlier in this section. The diagram in Fig. 4 shows the activities grouped according to their execution times during the day. The first step of production begins in the afternoon and involves separating components from whole blood units as they arrive. Blood donations are mostly made in the morning, so this step occurs in the afternoon. Separated components are quarantined overnight, and the process continues with the second step on the morning of the next day, when the test results arrive. During the second phase, in the morning, secondary operations are performed on the buffy coats to produce platelets, and units are labeled with their final labels. Since the same equipment is used for both morning and afternoon operations, there might be a delay in the afternoon, depending on the morning activities, while the night represents a buffer long enough to separate activities when the system is sized well enough.

Different configurations of such a production system are possible. In particular, the assignment of groups of extractors to specific centrifuges and the management of queues, which may or may not be shared between centrifuges and between extractors, define the layout of the system. Two extreme cases for the first step up to quarantine are depicted in Fig. 5. The specific settings to adopt for maximizing the efficiency of the system can be chosen on the basis of several factors, such as the volume of supply and the available resources in terms of both machinery and human workforce.

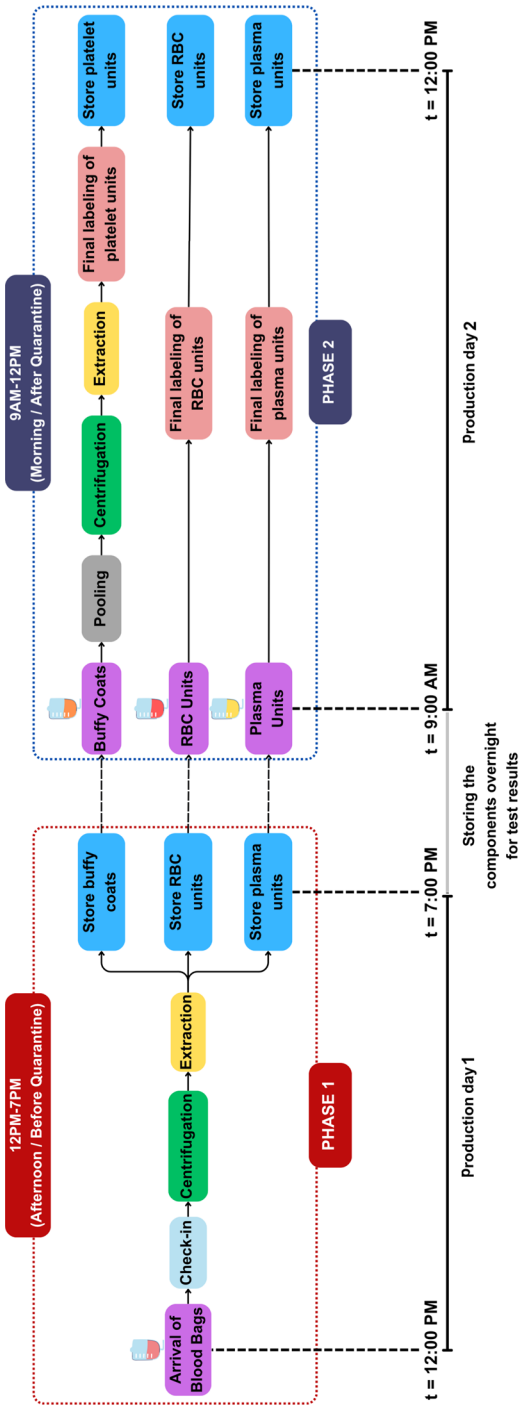


Fig. 4 Two steps of blood component production, with time intervals within a working day

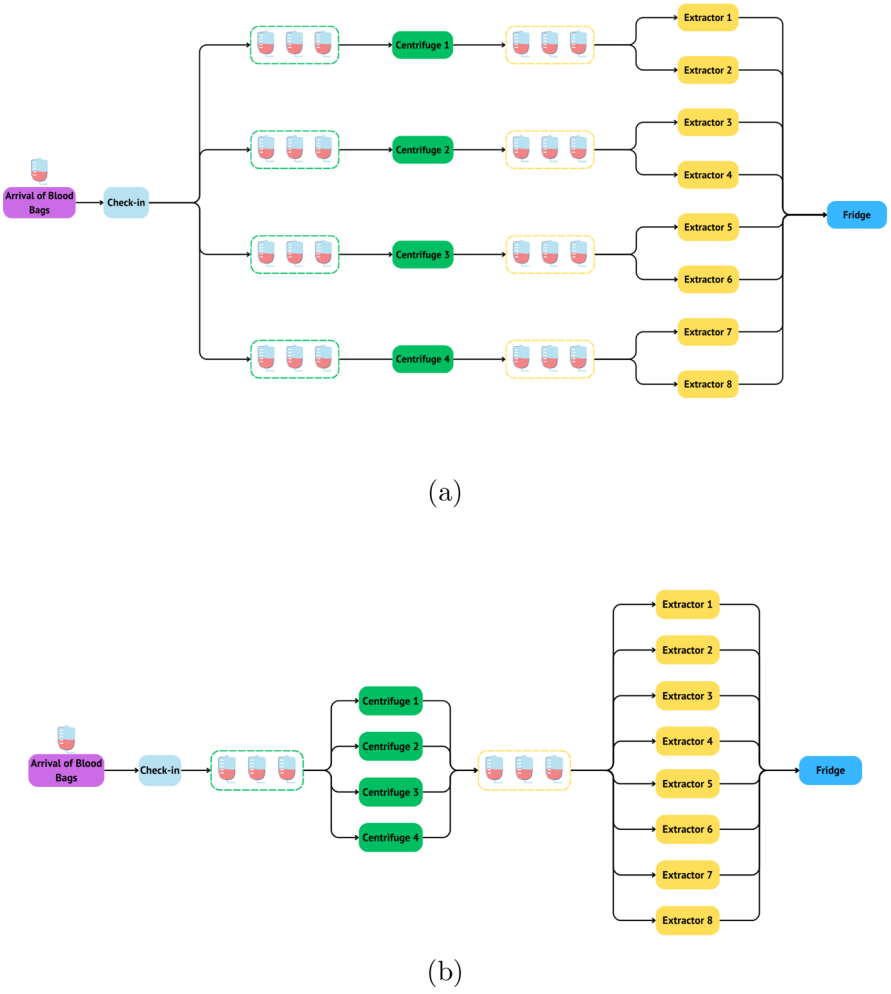


Fig. 5 Alternative settings for the first step of blood component production up to quarantine: with separated queues and extractors assigned to specific centrifuges (**a**); with a common queue for each operation and without extractor-to-centrifuge assignments (**b**)

3.2.2 Comparison with the U.S. system

Platelets are not separated from whole blood in the U.S., whereas they are in Europe, particularly at Niguarda Hospital. The motivation for this different practice is that platelets are collected through apheresis in the U.S., whereas in the European case, platelet production is carried out from the buffy coat originating from whole blood. In fact, in apheresis, a specialized machine separates and directly collects blood components, such as plasma and platelets, with the rest of the blood returned to the donor.

Therefore, the U.S. system differs from the European system. It can be considered a subset of the European one, in which the second part after quarantine is simply reduced to labeling, and the buffy coat is not separated when the whole blood unit is

centrifuged. In addition, it is worth mentioning that the U.S. system also differs from state to state.

Another difference is the maximum time that can elapse before components have to be produced, because of the different regulations that the centers are subject to. For example, in Europe, separation is required to be completed within 6 h of blood collection, while this time limit may vary in the U.S., even from state to state.

Moreover, the size of the production centers is generally larger in the U.S., so they receive blood from a larger area. Therefore, the transportation of whole blood units from collection to production centers consumes more time in the U.S., which implies that less time is available for the production of some components. Anyway, this is not an issue because platelets are not produced from whole blood in the U.S., but with apheresis. Therefore, the above-mentioned time limit does not apply because components are directly obtained during the collection phase.

Finally, there is generally a difference related to the use of technology and automation. For example, the Niguarda Hospital adopts Radio Frequency Identification technology to scan whole blood units and enter their information into the database during the check-in process, while in some U.S. centers, this operation is manual.

The main differences between the two systems are summarized in Table 2.

4 Literature on scheduling blood component and similar productions

As indicated in the introduction, we approach the topic of blood component production from a scheduling perspective. In this perspective, we aim to underline how scheduling can open new pathways for performance optimization by improving efficiency, reducing waste, and optimizing resource allocation. Scheduling blood component production plays a crucial role in enhancing the performance of the production process, especially given the scarcity of resources. It ensures that resources are used as effectively as possible, thereby maximizing the overall effectiveness and sustainability of the production system.

To this end, the literature on scheduling approaches for blood component production is first reviewed in Sect. 4.1. The literature analysis is then extended in Sect. 4.2 to include chemical processes and also disassembly processes, which share features with blood component production, and to frame blood component production within

Table 2 Summary of the main differences between the European and U.S. systems for blood component production

European system	U.S. system
Platelets are produced from buffy coats	Platelets are produced using apheresis
Time until separation must not exceed 6 h	Time until separation varies within the U.S
Relatively smaller production facilities	Larger production facilities
Greater reliance on automated systems and digital tools	Mostly manual processes and limited technological integration

these systems. Other frameworks available in the literature do not include the key features of blood component production and do not allow for easy repurposing.

4.1 Blood component production in the BSC literature

Blood component production from whole blood units is the least studied BSC phase in the literature (Osorio et al. 2015; Imamoglu et al. 2023). Below is a brief description of the few contributions that, to the best of our knowledge, specifically address this topic.

Baesler et al. (2011) proposed a simulation tool to determine the maximum production capacity of a blood production center and to determine the changes that can improve it.

Li et al. (2022b) proposed a dynamic programming model to optimize the preparation and inventory of blood components, accounting for uncertainty in the supply of whole blood and the demand for blood components. They considered five methods for producing components and included downward substitution among different blood types.

Finally, it is worth mentioning that quality monitoring strategies and statistical process controls are applied to monitor the production of blood components (Beckman et al. 2009).

4.2 Related productions outside the BSC literature

We investigate areas of research that include the separation of a main product into various by-products, with a focus on the resources, or equipment, that perform the operations.

The main decision for the blood component production process at the operational level is to determine the timing of each operation and the blood units to be processed while respecting various constraints, such as time limits because of component expiration, resource availability, and operation sequences. Previous studies in the BSC literature have already explored fractionation methods, but they have neglected the operational level. Therefore, we explore the literature available in other fields to find similarities to blood component production and frame a starting point for developing appropriate scheduling systems and DSSs for blood component production. We found two areas that include the separation of a main product into various subproducts: the main one concerns chemical processes (Sect. 4.2.1), while there also some similarities with disassembly processes (Sect. 4.2.2).

The same approach and workflow described in Sect. 2 were used to search within the literature outside the BSC context, aside from the keywords employed. This time, the keywords “scheduling” and “schedule” were always employed. Moreover, the keywords “separation”, “fractionation”, “process scheduling”, and “chemical process” were used to search within the chemical process literature, and the keywords “disassembly”, “demanufacturing”, and “remanufacturing” were adopted to search within the disassembly literature.

4.2.1 Blood component production as a chemical process

Blood component production can be viewed as a chemical process, which includes processing steps that absorb certain inputs and in return produce outputs that can be fed into subsequent activities as inputs for further processing. These operations are carried out by various machines with minimum and maximum capacities. Intermediate products and final products can be formed during the process and are subject to different storage policies.

There are *recipes* that describe the sequences of operations that need to be followed to produce a given product and support chemical process scheduling. A relevant representation, called the *state-task network* (STN), was proposed by Kondili et al. (1993). It has a network representation with two types of nodes: *states* and *tasks*. State nodes represent the inputs, or feeds, along with intermediate and final products, while task nodes represent operations that transform materials. STN representation was later extended by Pantelides (1994) with the *resource-task network* representation, in which the term "resource" is extended to cover not only equipment but also materials, allowing a focus on resources and their availability. MILP models have been proposed for both network representations.

Applications of chemical process scheduling can be seen in various areas, such as the oil industry, food processing, and waste water management (Gaglioppa et al. 2008). Among others, the fractionation process in oil refinery can be a close analogue to blood component production. Oil refinery operations are mainly composed of three stages: crude oil operations, production, and final product distribution (Wu et al. 2015). Oil tankers are docked into the station where they are unloaded to cylindrical storage tanks that allow oil transfer for distillation after oil settles for a certain amount of time for brine separation. The oil is then transferred into crude distillation units (CDUs) for separation into different products, such as naphtha, diesel, kerosene, and gas oil, using a series of chemical reactions that include heating of the oil. As oil is transferred via pipelines, oil refinery is a continuous process in which material flow and output yield are continuous throughout production. On the contrary, batch processes also exist in chemical production, in which materials are fully processed before moving on to the next step. Examples of such process types can be found in the food processing or paint industries.

Overall, the main connections between chemical fractionation and blood component production are as follows (Table 3):

Table 3 Comparison of items and steps between blood component production, chemical processes, and disassembly processes

Blood component production	Comparison with	
	Chemical processes	Disassembly processes
Whole blood units	Raw materials (feeds)	Root products
Intermediate products	Intermediate products	Intermediate (child) products
Centrifugation Extraction Filtration	Activities in CDUs	Disassembly activities

- The raw materials, or feeds, that undergo chemical processes correspond to whole blood units;
- Chemical reactions, or processing tasks, correspond to fractionation steps, such as centrifugation, extraction, and filtration;
- Intermediate products exist in both areas;
- As in blood component production, in batch chemical processes the products are moved across different equipment within bags.

Several works that address the operation aspects of fractionation in oil refinery (Jia et al. 2003; Yadav and Shaik 2012; Castro et al. 2015; Bayu et al. 2020), yogurt production (Kopanos et al. 2010), paint production (Vieira et al. 2013), and other chemical processes (Gao et al. 2022; Li et al. 2022a) are briefly presented in Table 4.

In this field, STN representation plays an important role in tracking down the transformed materials. Moreover, the constraints imposed in the model are similar to the restrictions and requirements of the blood component production process. For instance, the STN framework includes constraints for task-to-equipment allocations, capacity and storage restrictions, and material balances for the transformation of materials during the processes. Therefore, this framework can help capture the sequential nature of tasks and the connections between the products obtained during the process. Another potential benefit of adapting these frameworks to the context of blood component production is the ability to focus on the allocation of resources to tasks, while the available literature within the BSC does not focus specifically on manufacturing operations.

4.2.2 Blood component production as a disassembly process

In the literature, the term "disassembly" is used to describe processes in which a given product (root) is separated into its components (leaves), usually for the purpose of reuse (Colledani et al. 2014). Processing blood to extract its components can be conceptually likened to a disassembly task; although blood is not *assembled* in the traditional sense, the analogy holds because the goal is to start from a single entity (the blood unit) and separate it into distinct components through specific physical or chemical procedures, minimizing waste or inefficiencies (Table 3). Blood processing

Table 4 Characteristics of recent fractionation studies in chemical process scheduling (notation: B is batch, C is continuous, SC is semi-continuous, and MP is multi-product)

Reference	Capacitated	Uncertainty	Product	Process type	Solution	Perishability
Jia et al. (2003)	x		MP	C	MILP	
Kopanos et al. (2010)	x		MP	SC	MILP	x
Yadav and Shaik (2012)	x		MP	C	MILP	
Vieira et al. (2013)	x		MP	B	MILP	
Castro et al. (2015)	x		MP	B	MILP	
Bayu et al. (2020)	x		MP	C	MILP	
Li et al. (2022a)	x		MP	B	MILP	
Gao et al. (2022)	x	Processing times	MP	B	MILP	

and disassembly share challenges, such as sequencing operations, managing resource constraints, and ensuring the quality of the extracted components.

In disassembly, the main problem is deciding on the quantity and timing of products to be disassembled in order to meet demand. Studies in the disassembly literature also include other characteristics related to, for example, resource capacities (Gökgür et al. 2015; Cherkaoui et al. 2015; Piewthongngam et al. 2019; Yuan et al. 2022), the variety of root products to be disassembled (Kim and Xirouchakis 2010; Cherkaoui et al. 2015; Kang et al. 2016), process uncertainties (Slama et al. 2022), and the commonality of parts (Kim et al. 2018; Choi 2021; Darghouth and Abdel-Aal 2021).

In the disassembly process, a different number of operations can also be required to obtain the components (leaves); that is, there are different levels of disassembly. There may be intermediate components, called child products, and the question can apply to both these child products and the leaf components that cannot be further disassembled.

The objective function of disassembly scheduling problems is usually to minimize the total cost, which includes setup, operation, and inventory costs.

A recent review by Slama et al. (2019) analyzed the literature on disassembly scheduling problems and suggested future research directions.

One of the earliest studies dealing with disassembly scheduling was conducted by Gupta and Taleb (1994). They proposed a scheduling algorithm for a single product with a multilevel disassembly structure. Later, Taleb and Gupta (1997) extended their study to consider multiple products and parts commonality.

Below, we continue our review by considering the most relevant recent works. Their characteristics are summarized in Table 5.

Prakash et al. (2012) developed a constraint-based simulated annealing algorithm to determine the ordering and disassembly schedule, with the goal of minimizing inventory levels for products, taking into consideration part commonalities. Gökgür et al. (2015) proposed a mixed-integer linear programming (MILP) model for disassembling the schedule of multiple products with parts commonality. They included the assignment of disassembly operations to parallel capacitated resources, environmental costs, and a specific demand for each item. Kim et al. (2018) integrated disassembly leveling and disassembly lot sizing in a multi-period MILP model. Disassembly leveling was used to determine the disassembly structures to obtain the desired components, while disassembly lot sizing was used to determine the disassembly times and quantities and meet the demands of their components. The authors also proposed a two-phase heuristic to solve this integrated disassembly leveling and lot sizing problem. A similar study was conducted by Doh and Lee (2022), including different workstations and the reprocessing of disassembled parts. In another study, Darghouth and Abdel-Aal (2021) included the selection of the disassembly technique to optimize the cost and energy consumption of the disassembly system. Hrouga and Sbihi (2022) solved a MILP model with the goal of minimizing disassembly costs and lost sales, as well as inventory and holding costs and the possibility of defective parts. Finally, unlike the previously cited studies, Piewthongngam et al. (2019) included perishability and proposed a disassembly scheduling problem for a pork processing system in which the carcass is perishable and must be processed into meat cuts within 2 days.

Table 5 Characteristics of recent disassembly studies (notation: S is single period, M is multi-period, MP is multi-product, SP is single product, ML is multilevel, and SL is single level)

References	Capacitated	Uncertainty	Part commonality	Period	Product	Level	Solution method	Perishability
Prakash et al. (2012)				M	SP	ML	MILP, Heuristic	
Cherkaoui et al. (2015)	x			M	MP	SL	MILP, Heuristic	
Gökgür et al. (2015)	x		x	M	MP	ML	MILP	
Kim et al. (2018)			x	M	MP	ML	MILP, Heuristic	
Piewthongngam et al. (2019)	x		x	M	MP	ML	MILP	x
Choi (2021)		Demand	x	S	MP	ML	Stochastic IP, Heuristic	
Darghouth and Abdel-Aal (2021)	x		x	M	MP	SL	MILP	
Slama et al. (2022)	x	Lead time		M	SP	ML	Stochastic optimization	
Hrouga and Sbihi (2022)	x			M	MP	SL	MILP	
Doh and Lee (2022)	x			M	SP	ML	MILP, Heuristic	
Zhou et al. (2022)	x	Demand, Lead Time		M	MP	ML	LP, Heuristic	

Although not very common, some studies on disassembly processes have also focused on uncertain parameters. For example, Choi (2021) considered the uncertain demand for parts and proposed a stochastic integer programming model to solve the scheduling problem with the goal of minimizing setup and operation costs. Zhou et al. (2022) considered random demand and disassembly time for multiple product types and proposed a hybrid genetic algorithm to solve the mathematical model of the resulting scheduling problem. However, they assumed that there was no demand for intermediate items.

Blood component production can be considered a special disassembly process with specific constraints arising from the special type of production. In fact, the quantities to be extracted are almost decided once the fractionation sequence (Fig. 3) is decided, and timing is driven by the processing time limits imposed on unit processing and the related strict regulations.

Overall, we can conclude the following:

- Blood component production can be described as a problem with multiple root products (the whole blood units of different blood types) and multiple disassembly levels (see Fig. 3).
- Disassembly scheduling problems also include uncertainties in the arrival of root products and the demand for leaf products (i.e., the produced blood components).
- The study of Gökgür et al. (2015) stands out for its adaptability to the blood component production system. The proposed model allocates jobs to available resources in each period and considers the demand for intermediate products, consistent with the blood component production system. However, in its current state, the model does not reflect some of the important features of blood component production, as it neglects the uncertainty of supply and demand and the specific devices used.

Although the term "disassembly" may initially seem unconventional in this context, considering the similarities between the two systems, we believe that the scheduling approaches used in disassembly systems could serve as initial reference points for blood component production systems. In fact, the production structure underlying blood component production mirrors that of a disassembly problem, in which a product is separated into its components by some processing steps.

5 Discussion and research directions

In the literature, many studies have been conducted on how a BSC can be efficiently managed, given its importance in health care operations. Among the BSC phases, blood component production has received the least attention in the literature. Indeed, existing studies on the production phase have mainly focused on inventory replenishment, and have not addressed the process of separating blood units into the different blood components.

In this section, we suggest future research directions for the development of DSSs that would meet the needs of blood component production. They are based on the

three key activities we conducted in this work: (*i*) a review of the literature on the BSC, as well as on other contexts and approaches that might provide inspiration for further development; (*ii*) an in-depth field analysis of a real-world case in Europe, that is, the Immunohematology and Transfusion Medicine Department of Niguarda Hospital, during which we engaged directly with operators and experts, gathering valuable insights and practical knowledge; (*iii*) a series of discussions with Delcon Srl, a company that produces separators and other equipment for processing blood and that has customers all over the world, which allowed us to generalize our vision. The two latter activities were conducted in parallel with the first one to efficiently align the research progress with practitioners' perspectives.

This combination of theoretical exploration and practical investigation enabled us to identify three key areas for improvement and future research.

5.1 Role of decision support systems in the BSC

Existing blood component production systems are often not supported by DSSs. They usually have information systems to keep track of units and the current status of production, but they do not provide any scheduling or management support. However, a thorough analysis of the system from a management point of view is necessary to ensure the quality of blood components and the efficiency of the production system.

In this respect, a DSS for blood component production can leverage existing knowledge developed for other contexts. Our analyses show that fractionation processes first and disassembly processes to some extent are good starting points to tackle the problem, although the available methodologies need to be revisited for effective application to blood component production. The research in this direction would aim to adapt proven approaches to blood component production and support scheduling decisions and resource utilization.

From the point of view of tools, mathematical optimization models and simulation models emerge as the most important. On the one hand, an optimization model that schedules the required activities can prove relevant in deciding the optimal use of human and material resources, as well as the timing of processing of each blood unit, while optimizing metrics defined according to the needs of the facility. On the other hand, in consideration of the variability in the system (including the supply of whole blood units and the demand for blood products), a simulation model may enable *what-if* analyses to quantify the impact of any changes to the system. Both tools would be of great use in blood component production, in which efficiency is critical because products are perishable and scarce.

5.2 Production system configurations

The comparison of the European case with others (especially the U.S. case) allowed us to identify the configuration of the production system as a relevant factor in determining the performance of blood component productions. As is typical of the manufacturing context, production can be organized according to different paradigms, ranging from line production, in which activities are arranged in a sequential way, to cell production, in which activities and resources are organized in cells, each respon-

sible for the completion of the production (see also Fig. 5). Thus, exploring different configurations and improving their efficiency are essential. At the same time, analyzing bottlenecks is important in order to optimally decide which part of the process to strengthen when there are resources to invest.

The choice of the production layout also involves the ability to easily reconfigure it according to the specific production needs of a given period or context. As such, some facilities have centrifuges and extractors already configured with different settings so that the system can be easily reconfigured when required by supply and demand conditions.

The production stage can also be integrated with upstream and downstream BSC phases to provide a holistic perspective (Osorio et al. 2017; Samani et al. 2018; Xu and Szmerekovsky 2022).

All these analyses can be addressed with quantitative DSSs, such as simulation models or production schedulers.

5.3 The role of technology and information systems

Technology advancements can provide improvements in current blood component production processes at different levels. Considering the production process, improvements can be attained by implementing new separation technologies that reduce processing time and changeover, whereas considering the management process digitization of information can increase the efficiency and effectiveness of decision-making processes. In the latter perspective, we deem it is relevant to highlight how the design of appropriate DSSs, such as schedulers or simulation models, can provide relevant improvements. To the best of our knowledge, these needs have not been addressed thus far in the literature. Indeed, no DSS specific to blood component production, which specifically addresses this production in detail by considering internal operations and possible different workflows simultaneously, has been developed thus far. Available studies are mostly limited to determining production capacity or comparing inventory policies.

In parallel, appropriate information systems can improve blood component production processes and serve as a platform to efficiently implement decision support systems such a scheduler. On the one hand, the traceability of each blood unit is a key point, often mandated by law, to assess the quality of the system and ensure the correct implementation of any decision-making policy. This requires appropriate information systems that automatically record data on blood units and production steps in real time. On the other hand, the integration of the production phase with external information sources could automate and streamline the exchange of information with the rest of the BSC. This requires interoperable platforms connected to electronic blood bank registers and other databases relevant to the BSC, which can properly link the scheduler with the centers in charge of collecting the donated whole blood units and the centers where separated units are used.

6 Conclusions

The goal of this study was to explore the BSC production phase, with the aim of providing a detailed description of its operational aspects and highlighting relevant areas for the development of future research by combining an analysis of the existing literature and a field analysis.

This combination of theoretical exploration and practical investigation enabled us to identify three open methodological challenges still to be addressed in future research for the improvement of the production phase. First, the development of DSSs tailored to scheduling, resource utilization, and system variability could significantly improve production efficiency. Second, optimizing production system configurations, such as line or cell production layouts, would offer opportunities to address bottlenecks and adapt to fluctuating supply and demand. Finally, leveraging technological advancements, including new separation methods, digitized management processes, and traceability systems, could further enhance operational effectiveness and decision making. These findings pave the way for innovative solutions that address the unique challenges of blood component production. They would provide a more comprehensive view of the BSC, with the ultimate goal of avoiding blood shortages and wastages.

Available studies in the BSC literature do not consider the internal operations of the fractionation process and their management. On the contrary, approaches found in other production systems characterized by uncertainty and perishability could be exploited and repurposed.

From a practical point of view, the successful implementation of DSSs for the blood component production phase necessarily requires the availability of data and their management through appropriate information platforms. These platforms should ensure traceability of each blood unit and interoperability to integrate of the production phase with the rest of the BSC.

6.1 Limitations

A couple of limitations of our work arise from the specific perspective adopted in our study are worth mentioning. First, we relied on an Italian case as the primary source of field data. Although well representative of the practices across the European region, it may still reflect certain local adaptations or regulatory frameworks unique to Italy. These nuances could limit the generalizability of the research perspectives to regions with significantly different health care systems, operational practices, or blood supply chain structures.

Second, we focused on blood component production from whole blood, leaving out the apheresis process, as it introduces distinct operational challenges. By not addressing apheresis, our study provides a narrow scope of insights, potentially overlooking areas in which DSSs could also play a critical role in optimizing production processes.

Despite these limitations, we believe that our findings can provide a solid basis for further research that may expand the focus to include apheresis-based production methods.

Funding Open access funding provided by Università degli Studi di Bergamo within the CRUI-CARE Agreement.

Data availibility Not applicable.Being a discussion based on a literature review, only data coming from the review and the cited paper are reported.

Declarations

Conflict of interest The authors have no financial or nonfinancial interests that are directly or indirectly related to this work.

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