

A Computational Pipeline for Sepsis Patients' Stratification and Diagnosis

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Abstract: Sepsis is still a little acknowledged public health issue, despite its increasing incidence and the growing mortality rate. In addition, a clear diagnosis can be lengthy and complicated, due to highly variable symptoms and non-specific criteria, causing the disease to be diagnosed and treated too late. This paper presents the HemoSpec platform, a decision support system which, by collecting and automatically processing data from several acquisition devices, can help in the early diagnosis of sepsis.

1 INTRODUCTION

Infectious diseases and sepsis are a problem worldwide whereby the immune system overreacts and turns against itself. Sepsis is a poorly acknowledged public health priority with increasing incidence, high mortality and a high health-economic burden (Gaieski et al., 2013; Fleischmann et al., 2016). Sepsis emerges as a major complication of an infection acquired either among patients hospitalized in an Intensive Care Unit or among patients admitted to the emergency department (Walkey and Wiener, 2014). The mortality of sepsis ranges from 7% in less severe cases to almost 50% in cases of septic shock (Whitaker et al., 2015). The cornerstone of efficient treatment is early recognition and beginning appropriate therapy. However, in many cases clinical signs are not conclusive and diagnosis is difficult. Even nowadays, a clear diagnosis of sepsis is hindered by highly variable symptoms and non-specific criteria (Singer et al., 2016; Neugebauer et al., 2014). Hence, sepsis is often diagnosed and treated too late. However, early diagnosis is necessary for optimal selection of treatment for the highly heterogeneous group of sepsis patients.

In the HemoSpec project¹, a multidisciplinary team develops an innovative technological platform for early, fast and reliable medical diagnosis of infectious diseases using only minimal amounts of patients' blood. HemoSpec combines in one device three key enabling technologies: automated microflu-

idic sample handling with integrated holographic blood count (Schröder et al., 2017), simultaneous multiplex fluorescence biomarker sensing and detailed Raman spectroscopic leukocyte characterization (Neugebauer et al., 2016). In this project, the HemoSpec platform (HSP) has the overall objective of integrating data generated in the various distinct modules. This integrated multiplex analysis platform is being validated in two clinics specialized in hospital-acquired and community-acquired sepsis, respectively. Ultimately, we expect that the HSP results can help to administer the right therapy to the right patient at the right time, reducing costs in the health care sector.

2 SYSTEM REQUIREMENTS

The HSP architecture and its development was guided by a set of general requirements, in terms of connectivity, security, storage and user interaction (Silva et al., 2017). Some of those can be highlighted, namely:

- connect the different physical devices;
- exchange data following a single protocol and data format;
- secure data communication, avoiding access by third parties;
- managing and logging the different physical devices' activities and functionality;

¹<http://www.hemospec.eu>

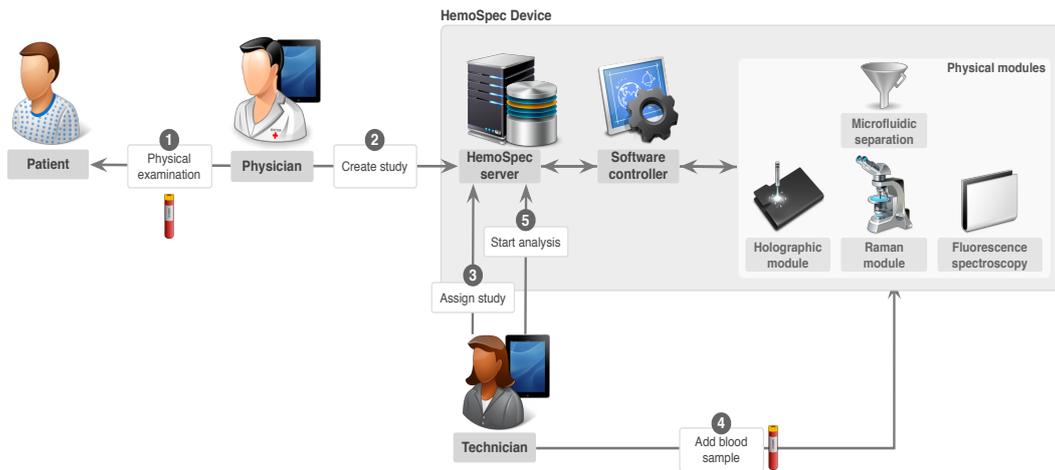


Figure 1: HemoSpec sepsis diagnosis interaction workflow.

- store the generated data in a structured resource, enabling processing by computers and easy understanding by humans;
- support physicians decisions regarding sepsis diagnosis;
- clear and simplified interaction workflow between the various actors;
- access to information from any device at any time.

Figure 1 illustrates the diagnosis workflow that we addressed in the requirements phase. In this diagram, the HSP is composed of the *HemoSpec server* and the *Software controller* modules.

During the patient examination (1), and in case of suspected severe infection, the physician starts the process by requesting a new study in the HSP (2). This will trigger a notification to HSP technician(s) who will be responsible for leading the study (3), collecting and adding the blood sample to the physical models (4) and starting the analysis (5). Through the HSP user interface, the technician has full control of the process, accessing detailed preliminary results and statuses, also being able to stop or restart the process if desired. After processing the blood sample, the device makes the results immediately available to all the actors involved in the patients treatment. When the technician validates the results, the HemoSpec device performs a background data-mining process to automatically organize the collected data and infer a knowledge-based decision, which will help the physician in the final decision. Finally, physicians can get the results, in real time, ensuring an anticipated patient diagnosis and suitable treatment. This workflow intends to reduce the procedure time, the risk of errors in the process of exchanging data and guarantee that the patient receives, on time, the proper treatment.

3 THE HSP ARCHITECTURE

The technological infrastructure of the HSP, which enables the previous requirements, is composed of two main blocks (Figure 2):

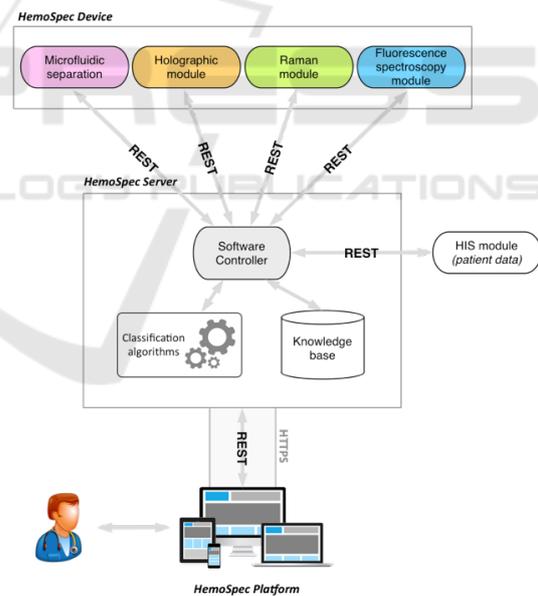


Figure 2: Technological infrastructure of HSP.

- **Server:** responsible for controlling the various physical modules, storing the generated data, and supporting sepsis diagnosis;
- **Web Platform:** the entry point for HemoSpec users, enabling data visualization and interaction with devices.

Overall, every physical module must be connected to the HSP Server through the Software Controller,

which will be responsible for controlling all modules' actions and for collecting the generated data. Such data will be stored in the Knowledge Base, which will keep all patients' history together with the results obtained from each module on each performed study. Finally, the HSP allows all users to have access to all the generated information, providing simplified interfaces to support data analysis and decision making, together with the ability to control modules' actions and blood sample processing workflows.

To develop the infrastructure that fulfils all the requirements of the HemoSpec project, we created three logical components, some of which will be described in the following sections:

- **Communication:** how to enable heterogeneous communication between devices and the software controller.
- **Data integration:** how to combine data from several devices in a single knowledge base and support sepsis diagnosis.
- **User interaction:** how can users access patients data and interact with the device.

3.1 Technical Framework

In the HSP architecture, the client-side is responsible for the direct interaction with users through their web-browsers, and the server-side is responsible for storing and processing all generated data. Both sides exchange data through a secured and encrypted channel using authenticated and authorized services.

The client-side was developed targeting compatibility and performance, through the application of standard web technologies, i.e., HTML, CSS and JavaScript, which are supported by most commonly used web-browsers on both desktop and mobile devices. The application of such web standard technologies also delivers information quickly. Thus, together with simple and fast client-side algorithms, we enable loading and presentation of information rapidly, providing smooth and sophisticated navigation and interaction with the system.

The server-side is responsible for storing all information in a unique resource, as well as providing the services to interact with that same data. All users, patients, devices and configurations are stored in a MySQL² relational database. Every processing task is available as a REST web-service (Lin, 2007), enabling easy and fast integration in any development platform, such as web, desktop and mobile. Moreover, those web-services are secured by requiring specific authentication and authorization per user. Ad-

²<https://www.mysql.com>

ditionally, to guarantee complete protection of exchanged data, the communication between client and server sides is performed through a secured and encrypted channel using HTTPS.

3.2 Data Model

The database was carefully designed targeting high flexibility, high performance and high scalability. It contains a hierarchical and structured representation of organizations that support multiple users, devices and patients. Moreover, each patient may have multiple studies with several measurements attached.

An organization contains multiple users who can be administrators, physicians and technicians. Users may be in more than one organization, enabling project supervisors to constantly monitor and analyse the work progress in each geographically distant institution. The organization has devices that can be controlled by the users within the same organization. This modular structure enables each institution to acquire new devices at any given time, while granting access and control by the organization's users at all times. Lastly, each organization has specific information stored about all its patients, which allows the overview and control of every patient diagnosis and their study progress.

3.3 Disease Prediction

Our goal is to provide a rapid solution for sepsis classification, namely:

- **Sepsis:** predict if the patient has sepsis or not;
- **Sepsis categorization:** predict the patient's type of sepsis;
- **Survival:** predict if the patient will survive after a specific number of days;
- **Organ failure:** predict if the patient will have any type of organ failure;
- **infection:** predict if the patient has an infection or not; if patient has an infection, predict the type of infection.

To develop the decision algorithms inside the HSP, we incorporated the following machine learning (ML) techniques, which provide a wide coverage of the supervised techniques available: Naive Bayes; Random Forests; Support Vector Machines (SVMs); Logistic Regression; Hidden Markov Models (HMMs); and Neural Networks (NNs).

Using several training datasets and these ML algorithms, we developed an advanced data analysis framework to automatize:

- Feature selection and replacing;
- Cross-validation;
- Hyper-parameters optimization per ML model;
- Collecting the best results considering the stratification criteria.

Incorporation of the classification models into the HSP allows predicting the type of sepsis according to the incoming parameters from the various devices and in an incremental way, as new data comes in.

Besides the models already integrated in the HSP, a specially developed component allows users to provide their own datasets to train and evaluate new ML models. The following features are provided:

- Upload files in text format with input data, allowing the specification of a field separator to support CSV or TSV file formats; From the input data, the target class field must be selected;
- Specify the training procedure, using cross validation or simple dataset split;
- Select the target ML model and its hyper-parameters;
- Evaluate results;
- Store or download the model for further use.

3.4 User Interface

The HSP was designed to be simple and easy to use, while keeping the information organized in such a way that the user has direct access to the most important data. For this purpose, the interface was divided in three main areas: Patients, Devices and Management. Management contains all administrative tools that are used to configure the platform and organizations. The other two sections contain specific data about patients and devices available in each organization. Furthermore, if a user is associated with more than one organization it is possible to switch between workspaces, gaining access to all data. In the following paragraphs, a more detailed description of each section of the interface is presented and discussed.

Once a user successfully logs into the system, the patient's overview page is displayed (Figure 3).

This view provides a list of the institution's patients with the ability to sort and search according to different criteria, for example search by study date, study status or patient details. On the left side of this view, the available search filters are organized in groups to make the search task simple. In the central section, a table containing a list of patients that meet the search criteria is displayed, containing relevant information that helps to identify the patient as

well as the number of studies and the status of the latest study requested for each patient. If no search criteria are specified, the list of all patients is displayed. A summary of important information helps to identify patients and studies that require a technicians attention in cases where the study was requested or a physicians attention when the studies have already retrieved data for the physician to analyse. In this example (Figure 3), each patient listed contains one associated study. While the study of the first listed patient is in a status where the technician must analyse and validate the device results, the second requires the physician to decide about the patient diagnosis.

Each personal page contains clinical information about the patient, the operations available to the user, and a list of the studies performed. The most recent study is highlighted to enable faster access. Here, the physician can request a new study for the patient. When taking this action, the physician is prompted to introduce some optional information about the patient, such as temperature or blood pressure. After submitting these data, a study pipeline is initialized and the study can be managed by the technician. During the study, a workflow page is available displaying the five steps of the pipeline (Start, Status, Validation, Classification, Decision), which allow tracking the study progress. In the first stage, the view gives the indication that the technician must undertake the required procedures to prepare the device to process a blood sample. If any error is detected by the platform, a notification is shown and the Start study button is disabled. Otherwise, as soon the device is ready, the technician may proceed and start the study.

In the next step (Figure 4), it is possible to keep track of the device processing, visualizing at any time the operation status of each module. As each device finishes processing and has results available, the HSP downloads the data from the devices into its database and makes it available through the web interface, so that the technician can begin validating these values, thus speeding up the reporting process. When every module finishes processing, the study advances to the next step where the technician must submit a report.

In this stage, the technician is responsible for analysing the results from the device and verifying that no errors have occurred during the blood sample processing. When the process finishes without errors the technician must then validate the data and submit the report, which will be then accessible by the physician. Otherwise, if it lacks quality, a new study may be requested cancelling the current study and starting a new one.

At this point, the platform combines the data provided by the physician with the one returned by the

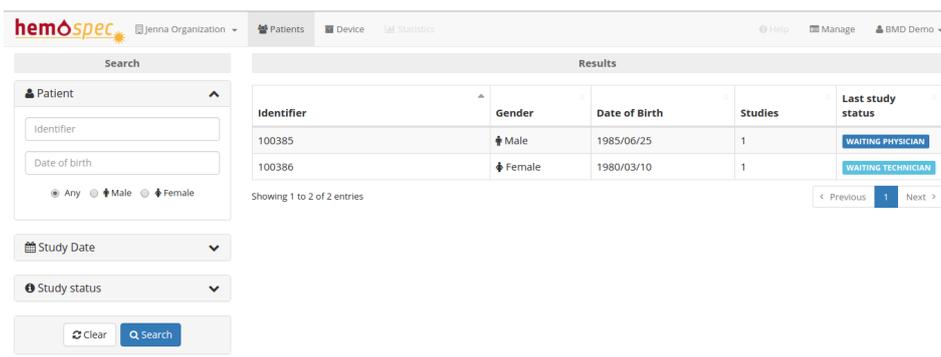


Figure 3: Patient page.

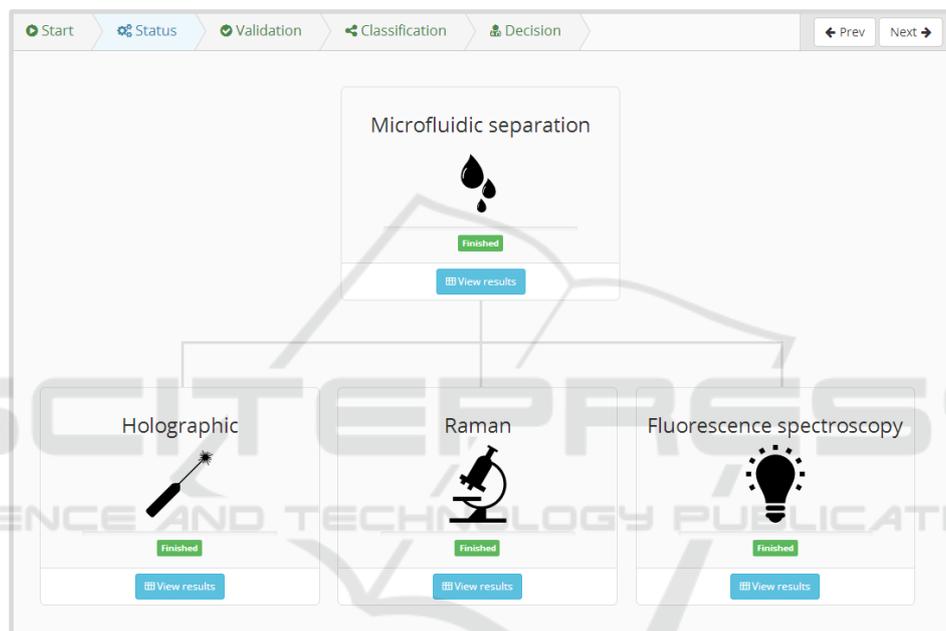


Figure 4: Device status and study overview.

device, to compute an automatic prediction of the diagnosis. This prediction is performed by one of the trained models that were previously uploaded into the platform. In this view (Figure 5), the physician has access not only to the data generated by the platform, but also to all data collected in the previous steps of the study.

Finally, in the last step of the study process pipeline, a view is displayed containing the diagnosis provided by the platform and a field for the physician to submit the final report of the current study. After the physician’s decision and submission of this report, the study is concluded.

4 CONCLUSION

We have presented a computational system (HSP) able to collect and classify information provided by different data acquisition equipment, which performs distinct analysis and measurements from small blood samples from sepsis patients. This system consists of: 1) a master-slave communication architecture based on REST web-services, responsible for communication with the devices; 2) a data mining engine for patients stratification with models trained previously from clinical records, and 3) a web portal for device management, patient follow-up and diagnoses. Besides this platform, we have been building machine learning models to incorporate in the HSP, using several clinical datasets, so that they can be used for patients’ stratification in intensive care units.

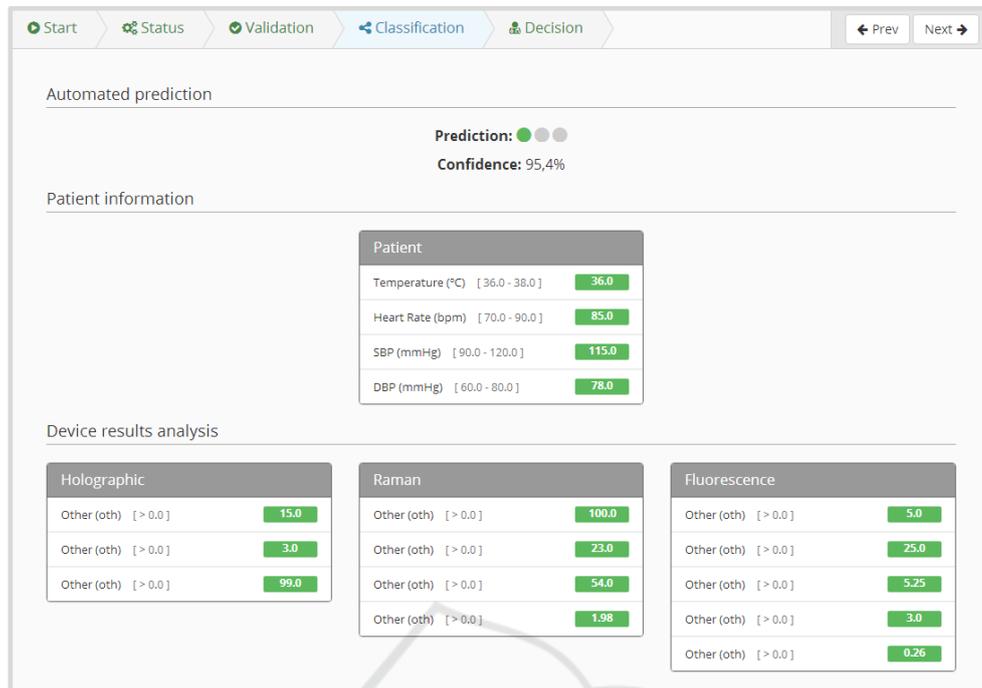


Figure 5: Summary of data retrieved by the platform and its diagnosis prediction (where data attributes were blinded).

5 ACKNOWLEDGEMENTS

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