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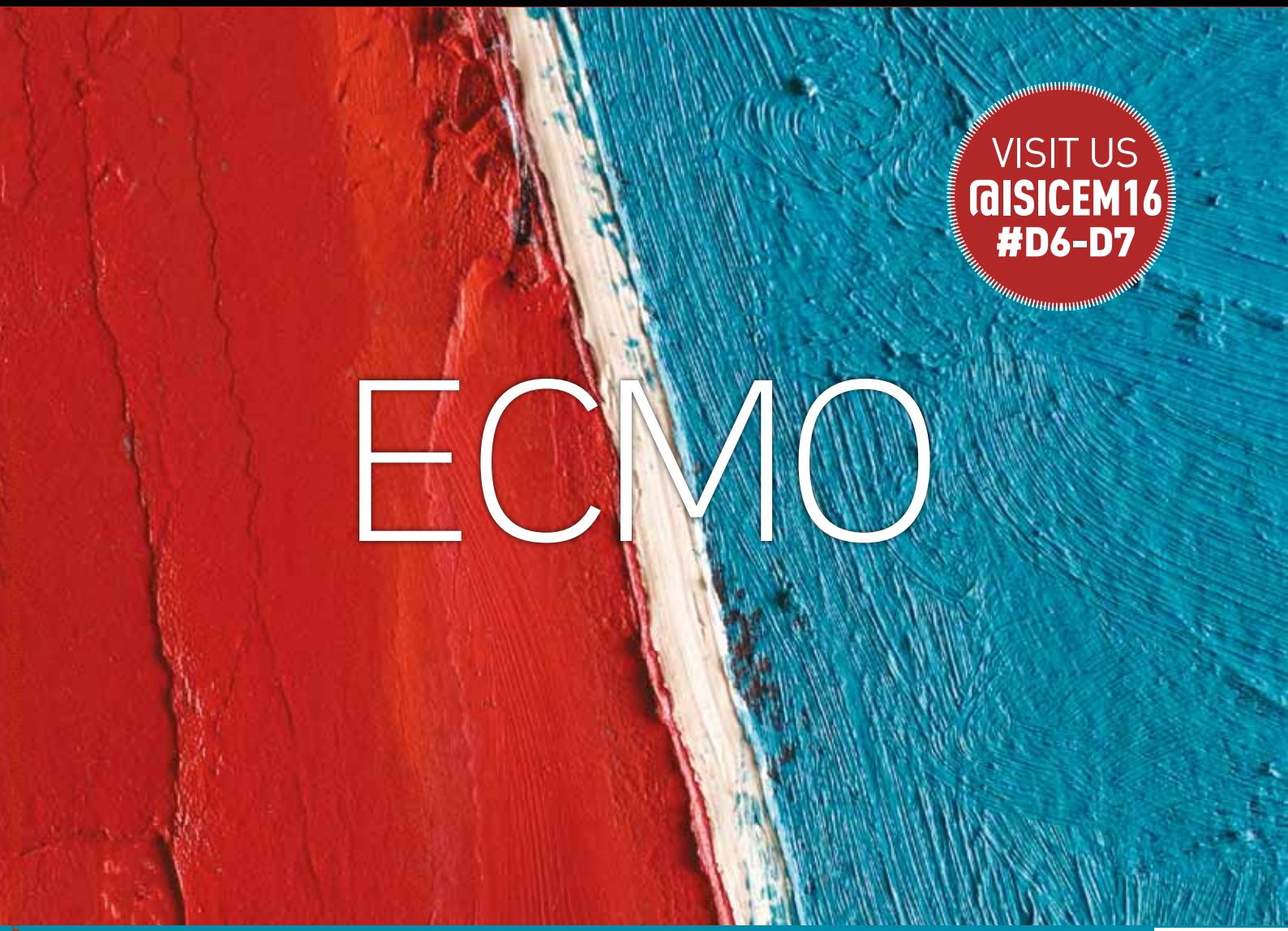

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TRANSFORMING MEASUREMENT INTO UNDERSTANDING

QUANTITATIVE BEDSIDE DECISION SUPPORT

Intensivists today are faced with a growing deluge of quantitative data, along with demands to implement evidence-based protocols of increasing number and complexity. The tools to support such implementation, including computerised decision support, have, however, seen only incremental development over the past decades. This article will attempt to provide an analysis of the underlying causes and suggest possible structural and technological remedies.

Quantitative Data Sources

Since its inception, intensive care medicine has been one of the fields of medicine with the highest density of quantitative data derived from direct physiological measurement, as well as methods used across most clinical domains, such as laboratory and imaging results. Measurement technology has evolved continuously, with recent developments in molecular biology and medical technology promising a plethora of additional quantitative data sources from novel biomarkers, high throughput -omics technologies, quantitative imaging and innovative physiological sensors. Integration of these data sources into a patient-specific decision support framework may help to realise the potential of the "precision medicine" of tomorrow (Celi et al. 2014; Mertz 2014).

Data Deluge: Challenges in Translating Measurement to Understanding to Outcome Improvement

The traditional approach to transforming quantitative data into beneficial clinical decisions has been based on assimilation and integration of all data by the responsible physician in a largely qualitative fashion. For example, quantitative lab results are typically evaluated based on their relationship to statistical result distributions in the healthy population ("normal values"), and possibly their qualitative trends. A similar approach is taken to guiding therapy based on continuous physiological measurements such as arterial blood pressure. For long-established haemodynamic parameters, such as central venous pressure, this approach has been demonstrated to be largely ineffective for guiding fluid management (Marik et al. 2008). Furthermore, studies of the effects of established haemodynamic measurement techniques of unquestionable pathophysiological relevance such as the Swan-Ganz catheter have failed to demonstrate positive effects on outcome (Harvey et al. 2005; Rajaram et al. 2013). Appropriate patient selection and data interpretation have been identified as a key issue in these contexts (Vincent et al. 2008). The systematic translation of quantitative measurements into effective clinical decisions is an important current challenge in intensive care medicine, which will only become more daunting as our ability to measure continues to expand.

Medical science has provided numerous approaches to post-processing the available measurements to obtain more directly interpretable and relevant data to support effective clinical decisions. In the haemodynamic monitoring field, these include simple but effective dynamic markers of fluid responsiveness and the well-developed field of pulse contour analysis of arterial blood pressure, some of which have recently been recommended for usage in the management of circulatory shock (Cecconi et al. 2014). Another example is the wide field of physiological variability quantification, the potential of which in the critical care setting has long been recognised (see, e.g. Buchman et al. 2002). Technically more challenging is the utilisation of mechanistic mathematical models of (patho-)physiology for clinical data interpretation, prediction, and control (Zenker 2009; Zenker et al. 2007), in particular when addressing the safety-critical issue of uncertainty quantification. This holds the promise of not only meaningfully incorporating pathophysiological knowledge from centuries of physiological science, but also enabling the application of powerful techniques from the engineering domain to quantitative decision support in medical settings.

Translating Scientific Progress to the Bedside: Technological Developments, Market Structure and Regulatory Environment

Status Quo

Even though numerous approaches to making more of available measurements have been developed and prospectively validated, the level of available evidence to support their use and routine availability at the bedside is still limited. This may partially be attributed to the fact that although many innovative derived parameters can be computed from routine measurements, they are typically made accessible in the form of a separately sold "box", (or a new model of a general-purpose patient monitoring system), which encapsulates a vendor-specific implementation of the post-processing algorithm. This situation has several consequences:

- The innovation cycle of available post-processing algorithms is largely determined by the hardware life cycle, rather than the software and knowledge innovation cycle.
- The cost of bringing innovative techniques to the beside is exacerbated, since software innovation is, often unnecessarily, tied to

hardware replacement and unnecessary hardware redundancy often requiring additional disposable materials, contributing to the already significant resource utilisation in intensive care medicine.
- A large variety of vendor-specific implementations of very similar ideas with undefined differences in practical behaviour and applicability are marketed, leading to an inefficient dispersion of resources available for vendor-independent validation of their utility satisfying the criteria of evidence-based medicine.

There appear to be at least two major factors contributing to this situation:

a) Routine use of any technology at the bedside requires commercially available solutions. Development of such solutions is driven by their revenue potential, which, in the medical device market, has traditionally been concentrated in hardware and particularly in the disposable segment.
b) The regulatory environment has traditionally focused on the single manufacturer providing a medical device as a closed system (either a single "box" or an integrated system of devices including the connectivity infrastructure, as was typically the case for monitoring systems with distributed alarm functionality). The manufacturer guarantees a specified functionality for the intended use of the medical device and takes responsibility for managing risks associated with the system according to the state of the art as defined by norms such as ISO 14971: 2007, *Medical devices -- Application of Risk Management to Medical Devices* (ISO 2007), among others.

With regard to a), the increasing market penetration of electronic documentation systems in intensive care has forced increasing integration of the medical device infrastructure with the hospital information technology (IT) infrastructure. Such documentation systems, in particular with a view to integrating decision support functionality, may themselves be classified as medical devices/products (typically of risk class IIa in the German market) (Mania 2012). They are thus subject to associated regulatory requirements with regard to implementing state-of-the-art operational procedures (European Commission 2012; Council Directive 1993). However, the challenges of achieving reliability levels typical of medical device setups for more generic data streams relevant to therapeutic decision making involving various IT subsystems (such as lab results) remain largely unaddressed. Key components of the data processing chain are typically not classified as medical devices and, consequently are not subjected to the same level of quality assurance and risk control procedures. To add to the overall complexity of the current situation, economic as well as technological constraints have led to a wider implementation of traditional medical device solutions (distributed alarm systems again providing a prominent example) that piggyback on regular IT infrastructure by, e.g., using the hospital IT network for inter-device connectivity and alarm propagation. This is the other side of the coin of IT/medical technology convergence. Such setups require a different approach to managing the risks associated with their operation, since no single manufacturer can be held responsible for the functionality of the system as a whole. The relatively recent norm IEC 80001 (ISO 2010-2015), *Application of risk management for IT-networks incorporating medical devices* (ISO 2010), provides guidance for risk management of IT networks incorporating medical devices and addresses key properties such as safety, effectiveness and data and system security. As opposed to the traditional "box" situation, the "responsible organisation" (typically the hospital) now bears responsibility for managing the risk of the entire setup in a structured fashion. Each manufacturer of medical device components of the system is obliged to provide customers with sufficient device-specific information to enable structured risk management. These often unrecognised and unaddressed responsibilities entail both challenges and opportunities.

A key challenge in implementing such state-of-the-art risk management is the additional effort and highly qualified personnel required, which entails additional cost at a time when economic constraints already affect healthcare delivery.

Turning Challenge into Opportunity

Since hospital-side structured risk management of complex interconnected IT and medical device systems from various vendors may now be required anyway, a fundamental hurdle to restructuring the entire information processing pipeline incorporating both medical device data sources and other clinically relevant quantitative data such as laboratory results and imaging data towards a more robust, flexible and dynamic model that would enable more effective and efficient translation of scientific insight into computer-supported bedside decision support integrating all these data, can now be addressed proactively.

An obvious approach for such restructuring, using intensive care patient monitoring as an example, would be modelled on the concept of modularity and open interface standardisation. This concept is hugely successful in almost all areas of engineering and technology. In this case it would be designed specifically to enable a structured risk management approach to the system as a whole. Naturally the conceptual framework extends to the entire quantitative data flow surrounding patient care. Risk management becomes more central as physicians have to, for practical purposes, often exclusively rely on information that has been processed in a chain of interconnected devices and IT subsystems currently not subject to structured risk management as established in the traditional medical device sector.

> **"highest density of quantitative data derived from direct physiological measurement"**

For example, if, in the haemodynamic monitoring domain, physiological measurement and signal conditioning, digital postprocessing and visualisation were decoupled and connected via standardised interfaces (Zenker et al. 2012), several advantages could be reaped:

- The threshold to market entry for postprocessing technology would be lowered since "software only" solutions would become marketable, increasing the breadth of potential contributors of innovative postprocessing solutions.
- The incentive to produce vendor-specific modifications of existing approaches with unproven or incremental benefit would be reduced:
- The whole breadth of downstream processing would become available as validated stan-

dard modules from specialised manufacturers (which of course could be identical with the hardware manufacturers);
- Competition of hardware vendors could focus on core competencies such as providing optimal signal quality, device reliability, and usability at competitive prices.
- Available public resources for vendor-independent evidence-based clinical validation of post-processing and visualisation technology could concentrate on reference implementations with significant innovation potential, thus increasing the evidence base for available and relevant tools.
- The innovation cycle for postprocessing and visualisation technologies could approach the fast cycles typical of the software industry.
- Broad availability of state-of-the-art post-processing and visualisation technology at the bedside could become affordable. Innovative functionality would become available at the cost of rolling out highly standardised software modules along with established structured risk management procedures rather than buying and installing new hardware.

Recent efforts of established vendors of data analytics solutions have yielded systems with some of the desired functionality, which have been deployed in academic settings (see e.g., Sow 2015). However, the implementation of modular systems that allow adequate structured risk management with the required level of automation of quality assurance procedures (automated unit tests at interfaces etc.) to keep risk control efforts under control in clinical settings critical to patient safety would require a concerted effort of medical device manufacturers, analytics providers, users and regulators. This should include interface standardisation that is sufficiently specific, with interoperability across these standardised interfaces included in the intended use of the medical device/software. In the current globally heterogeneous regulatory environment, a promising practical near-term solution to make progress in this direction may be for large manufacturers of medical devices or software to open up their closed systems to certified "app"-like analysis and visualisation components produced by third parties, similar to the way the mobile device industry has catalysed a massive innovation boost by creating a standardised application software "ecosystem" in which third parties can offer novel functionality with a relatively low market entrance threshold. Obviously, certification requirements for such medical "apps" would have to be more demanding than in the mobile device market, likely including formal validation steps and provision of manufacturer support for structured user-side risk management of the resulting setup. However, the obstacles appear technically surmountable and the potential yield with regard to enabling rapid and affordable translation of scientific insight to improved patient care appears high. Standardisation of the interfaces for such an "app" ecosystem across manufacturers would naturally be desirable, although if such a market were to gain momentum, de facto standards based on individual vendor specifications might emerge, as could repeatedly be observed in the digital audio signal processing industry over the past decades.

With regard to data streams currently viewed as lying outside of the medical device domain and the associated regulatory constraints, establishment of an infrastructural basis that would enable reliability and structured risk management comparable with the medical device sector, adequate for the emerging usage scenarios of potentially safety-critical bedside decision support beyond what the unaided human can implement, would serve to make explicit and supportable the already inevitable technological convergence of the medical device and software sectors. It would establish a solid and safe basis for implementing advanced clinical decision support technology without compromising patient safety. To keep risk management efforts manageable, a modular architecture that incorporates meaningful structured risk management by design and complies with regulatory constraints (which may also require adaptation in the long run) appears of critical importance.

Conclusions

A modular architecture for medical data acquisition, processing, and visualisation, based on open interface standards with associated structured risk management procedures incorporating at least partially automated quality assurance procedures evolved from existing standards in the medical device industry would enable implementation of state-of-the-art clinical decision support based on all available data that pushes beyond what the unaided human can achieve without compromising patient safety. In the absence of sufficiently detailed and provably workable interface specifications that would enable regulatory enforcement, incentives for implementation by manufacturers, aside from the intrinsic motivation of improving patient care, may come from the hugely successful examples provided by the mobile device industry, along with the commercial potential of a new market for providing risk management packages as a service to healthcare providers.

Failing that, it will be left to customers to demand meaningful structural innovation that enables state-of-the-art patient care at affordable cost and manageable risk.

Conflict of Interest

SZ is PI of the "AcuWave" project supported by the Dräger foundation, which aims at improving bedside availability of advanced postprocessing algorithms at the ICU bedside. ■

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