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Predicting the neuro-cardio-haemodynamic outcomes of sepsis and its pharmacological interventions: Get to the future through numerical equations

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Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. It is a global health burden that is particularly prevalent in equatorial regions, such as sub-Saharan Africa, South Asia, East Asia and Southeast Asia. In 2017, 49 million incident cases of sepsis and 11 million sepsis-related deaths were documented worldwide, accounting for 19.7% of all global deaths (Rudd *et al.* 2020). Despite the significant reduction in the incidence of sepsis and sepsis-related mortality over the last 20 years, the management of sepsis remains challenging, partly due to the complex pathomechanisms of sepsis and the rapid progression from minutes to hours, lowering the effectivity of current treatment modalities. As a consequence, sepsis often deteriorates, resulting in multi-organ dysfunction and haemodynamic impairment, leading to septic shock and death.

Multiscale mathematical modelling of various organs has progressed over the past decades and now advances towards personalised medicine. In many fields of medicine, multiscale mathematical modelling has emerged as a powerful tool to better understand biological complexities. For example, in cardiology, mechanistic modelling from subcellular to organ and system levels is employed to unravel the complex pathophysiological underpinning of cardiovascular diseases and to predict the outcome of clinical interventions. These models integrate diagnostic data from various clinical modalities in personalised heart simulations on the basis of widely accepted physical and physiological principles (Niederer *et al.* 2019). Similar approaches may be employed to improve the understanding of sepsis pathophysiology, estimate its progression and predict the effectivity of treatment regiments for sepsis.

In recent years, several mathematical models operating on the system level have been developed to better understand the cellular determinants of sepsis and to predict the effects of pharmacological agents (McDaniel *et al.* 2019; Yamanaka *et al.* 2019; Zhao *et al.* 2019). The model by Yamanaka *et al.* (2019) focused on elucidating the impact of inflammation on cardiovascular dynamics during sepsis, incorporating the core elements of blood pressure (BP), such as stroke volume and vessel properties (i.e. lumen size and permeation), and sympathetic nervous system. This model was validated against the data from sepsis and non-sepsis patients, and was employed to investigate the effect of pharmacological agents for sepsis, such as antibiotics and vasopressors (i.e. noradrenaline), as well as to predict the disease progression. However, the immune component of this model did not include the changes on inflammatory mediators, hindering any investigation of the effect of inflammatory cytokine modulation in sepsis. Meanwhile, McDaniel *et al.* (2019) developed a comprehensive, whole-body mathematical model using the BioGears Engine, an electric-circuit analogue characterizing the fluid dynamics of the cardiopulmonary system, to compare sepsis treatment regimens. Interestingly, the inflammation model in BioGears was optimised using murine data employed for human predictions, which is problematic because murine inflammatory pathways are different from those found in humans (Dobreva *et al.* 2021). Next, Zhao *et al.* (2019) developed a mathematical model of septic shock, integrating a previously published endotoxin-induced human inflammation model with epigenetic regulatory loops. They employed the model to investigate the effects of interleukin (IL)-10 modulation during septic shock and subsequently compared the results with clinical data and experimental data obtained in mice. However, the modified model was not revalidated and this model only focused on immune system modulation in sepsis. Importantly, these pre-existing models did not include sepsis-induced changes on neurological and thermal regulations, limiting their future clinical applications.

In a recent study published in the *The Journal of Physiology*, Dobreva *et al.* (2021) developed a mathematical model simulating the response to one-time bacterial endotoxin lipopolysaccharide (LPS) injection. The system-level model integrated three submodels: the inflammatory response to endotoxin; the effect of inflammation on temperature, pain perception and nitric oxide (NO); and their impact on the cardiovascular system. The inflammatory component included pro-inflammatory cytokines [i.e. tumour necrosis factor (TNF)α, IL-6 and IL-8] and anti-inflammatory IL-10, whereas the cardiovascular model consisted of small and large vessels of the systemic circulation, and accounted for BP and heart rate (HR) changes over hours (Fig. 1). To determine the interactions between components of these three submodels, previously published physiological data were integrated in the model, including the link between LPS-induced inflammation and fever, as well as pain perception threshold (PPT), temperature- and BP-dependent modulation of HR, changes in vascular resistance following the modulation of pain perception, and inflammation-induced NO production, which further affected BP by reducing peripheral vascular resistance. The system-level model was parameterised and calibrated to published data from 20 healthy young adults (18–35 years) who received a low bolus of LPS, and further validated against published independent data from 10 human subjects (18–40 years) receiving similar low bolus dose of LPS. This model was employed to simulate the response to sustained endotoxemia and to test the available treatments for endotoxemia and sepsis (i.e. antipyretics, LPS adsorption and vasopressors).

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The model nicely reproduced patients' inflammatory cytokines (TNFα, IL-6, IL-8 and IL-10), temperature, PPT, BP and HR data over 0–8 hours (h) after a single transient LPS injection. Both the patients' data and the model showed a rise in inflammatory cytokine concentrations within 2 h after LPS injection, reaching a peak concentration 2–4 h after injection and starting to subside after 4 h. Similarly, the temperature increased in the first 4 h before reaching its peak and recovered thereafter. The HR also consistently showed an increasing trend in the first 4 h before attaining its peak HR. Interestingly, the PPT data showed diverse patterns with a reduction in the first 2 h, followed by an increase or a sustained reduction for the entire observation period. The BP curves were highly variable over time, which was reproduced by the model.

The sustained endotoxemia simulations mimicking the inability to eliminate endotoxin-producing pathogens indicated an earlier activation of inflammatory mediators with higher peak concentrations, which was accompanied by a second wave of activation and a reduction to baseline after 2 h despite the presence of persistent endotoxin concentration. Consistently, this increase was followed by a rise in temperature which also recovered after 12 h of observation. By contrast, the PPT declined after 2 h and did not recover to baseline after 12 h. The HR increased and stayed high for the rest of observation and the BP fluctuated with an initial increase followed by a decrease to a hypotensive state. The LPS adsorption diminished the second wave of inflammatory activation, which facilitated faster recovery of temperature, PPT and BP, although HR remained high. Interestingly, antipyretics, although not directly affecting inflammation, promoted partial recovery of temperature, PPT and BP. Meanwhile, vasopressors reduced hypotension, allowing the BP to normalise, at the same time as keeping the HR high. Finally, the combination of those drugs was superior to their individual performances in controlling inflammation, neurological (pain), thermal and cardiovascular consequences of sustained endotoxemia.

Dobreva *et al.* (2021) elegantly demonstrated how system-level mathematical modelling could elucidate the complex inflammation, neurological, cardiovascular and haemodynamic interactions following transient and sustained endotoxemia, which could provide new insight into the management of sepsis, including the discovery of new druggable targets. They employed the perfect control and observability offered by mathematical modelling to untangle the individual contributions of sepsis determinants. Moreover, an important strength of their study is the use of two independent datasets obtained in humans for calibration and validation, highlighting the robustness of the model in simulating the (patho)physiological response of endotoxemia in diverse populations. The study effectively showed that sustained endotoxemia could explain the hypotensive state of sepsis, possibly through elevated NO, which could be compensated by increasing HR using vasopressors, antipyretics and/or agents fostering LPS adsorption.

Nevertheless, in contrast to the well-validated response to transient endotoxemia, the (patho)physiological response to sustained endotoxin is yet to be validated on human data. Moreover, the model identified several relevant questions for future research, including how antipyretics increase HR and BP, why the inflammatory mediators returned to

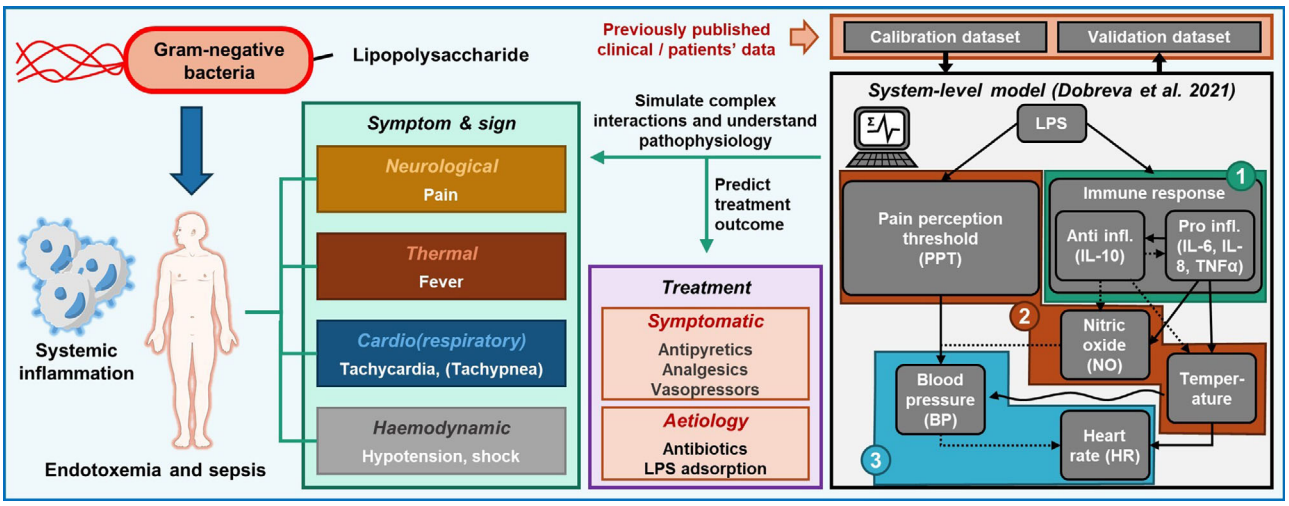

Figure 1. The role of mathematical modelling in improving the management of endotoxemia and sepsis
Bacterial endotoxin LPS injection results in the activation of systemic inflammation, leading to endotoxemia and sepsis. Such a systemic inflammatory syndrome affects multiple organs and causes a wide range of clinical consequences, including neurological, thermal, cardiorespiratory and haemodynamic impairments. Current treatments for sepsis include symptomatic and aetiological treatments aiming to eliminate sepsis-inducing pathogens or toxins. A system-level mathematical model is designed to incorporate complex physiological data and integrate multiple submodels (1–3) to reproduce patient-specific clinical observations. Subsequently, mathematical modelling is used to simulate complex multi-organ interactions and to better understand the disease pathophysiology. Moreover, the intent is to predict the outcome of pharmacological treatments of sepsis. [The model by Dobreva *et al*. (2021) did not include a respiratory submodel, thus limiting any investigation of the respiratory consequences of endotoxemia].

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baseline during sustained endotoxemia, the possible contribution of other unexplored inflammatory mediators (e.g. NLRP3 inflammasome) in the later stage of endotoxemia, as well as why the HR did not increase in response to sustained endotoxemia-induced hypotension, whereas pharmacological agents could increase HR to compensate the low BP. Such questions will stimulate more in-depth scrutiny of the model and possibly demand additional *in silico* and *in vivo* experiments. Additionally, although the model overcomes some of the limitations of previously developed mathematical models for sepsis (McDaniel *et al*. 2019; Yamanaka *et al*. 2019; Zhao *et al*. 2019), it will still require further improvements, including the incorporation of positive/negative feedback of the model components as physiological adaptive mechanisms and the integration of pharmacokinetics/pharmacodynamics models to better simulate the acute and chronic effects of certain drugs.

Overall, the *in silico* study conducted by Dobreva *et al*. (2021) exemplifies the value of mathematical modelling in identifying major determinants of a complex disease state (e.g. sepsis) and potentially providing an opportunity to support clinical decision-making processes. Finally, mathematical modelling has potential to be a novel quantitative modality for the early detection and treatment of complex diseases, providing a low-cost, low-risk, rapid, integrative and objective analysis of a patient's condition (Niederer *et al*. 2019).

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Additional information

Competing interests

The authors declare that they have no competing interests.

Author contributions

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