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Leveraging time series dependencies for clinical management of acute febrile illnesses using machine learning

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Clinical scenarios

- A 59 year old man has been admitted to hospital in the UK with abdominal pain and is awaiting investigations. On day 3 of admission, he develops a fever and becomes less responsive.
- A 24 year old woman develops fever and body aches in Vietnam, and attends the local hospital. Over the next 3 days she develops some gum bleeding but then makes a full recovery.

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Medical observation and patient dynamics

- Change in clinical state over time in the past is important for future prediction
- Methodologically, repeated measurements of different quantities a unique statistical challenge
- Pre-requisites: data of sufficient fidelity, linkage, fusion of data at different frequencies

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Aims of session and discussion:

- Discuss challenges in synthesising time series information for acute care of infections

- Multi-modal incorporation of diverse data (data fusion) and emergent themes

- Implementation of models to the clinical setting

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2 exemplar case studies

Bacterial bloodstream infections (BSI) using blood biomarkers

Dengue severity using pulse waveform and PPG

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Example 1: Bacterial bloodstream infections (BSI)

- Significant healthcare burden (2.91 million deaths in 2019)
- Positive predictive value of blood cultures ~ 7.5%
- Result turnaround time 24-48 hours
- Priorities in different settings – maximising NPV vs PPV

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Research question

Can the use of longitudinal patient information help predict BSIs and what is the added contribution of such time series data?

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Dataset – iCARE and EHR

- March 2014 – Dec 2021 at Imperial College NHS Trust
- 20,850 patients undergoing blood culture sampling
- Biomarker data up to 14 days prior (where available) extracted

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Microbiological definitions

- BSI state – according to WHO priority pathogens list [1] (18.5%)
- Non-BSI state – no growth at 5 days or isolation only of one of [2] (71.5%)

[1] *Escherichia coli*, *Klebsiella* spp., *Enterococcus* spp., *Pseudomonas* spp., *Proteus* spp., *Serratia* spp., *Citrobacter* spp., *Streptococcus* spp., *Staphylococcus aureus*.

[2] Coagulase negative *Staphylococcus* group, *Micrococcus* spp., *Corynebacterium* spp. excluding *Corynebacterium striatum.*

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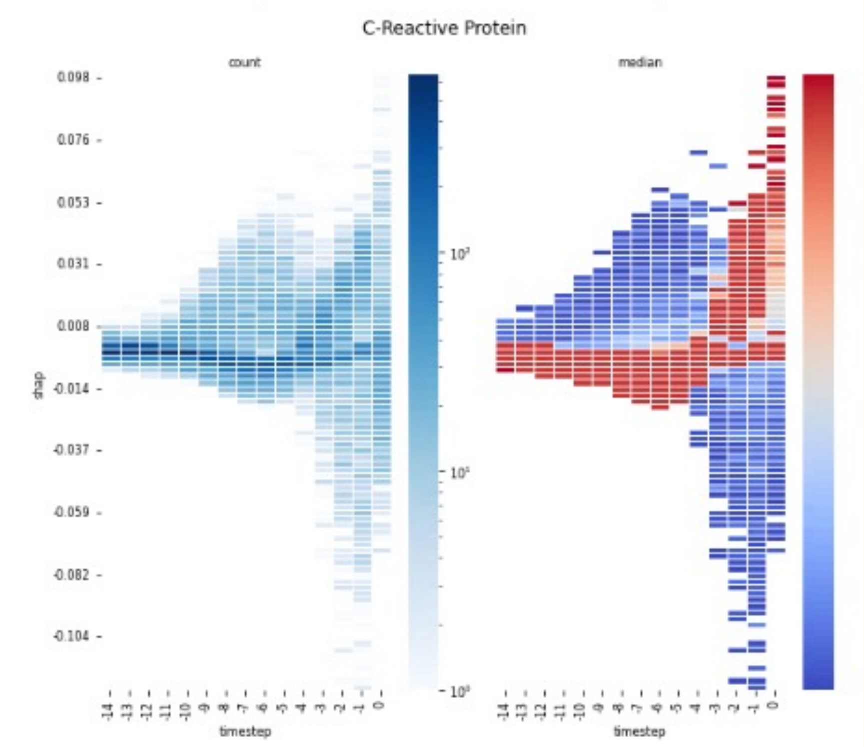
Data methods

- Initial training and hold-out set temporal split

Training (n=15,212) — March 2014 to Feb 2021

Test (n=5,638) — Feb 2021 to Dec 2021

- 5-fold cross validation
- Missing values forward filled where possible otherwise masked
- A long short-term memory (LSTM) approach for time series data, with logistic regression and feature engineering as baseline
- Tuning using Bayesian optimisation


C-Reactive Protein
count
median
0.098
0.076
0.053
0.031
0.008
-0.014
-0.037
-0.059
-0.082
-0.104
shap
timestep
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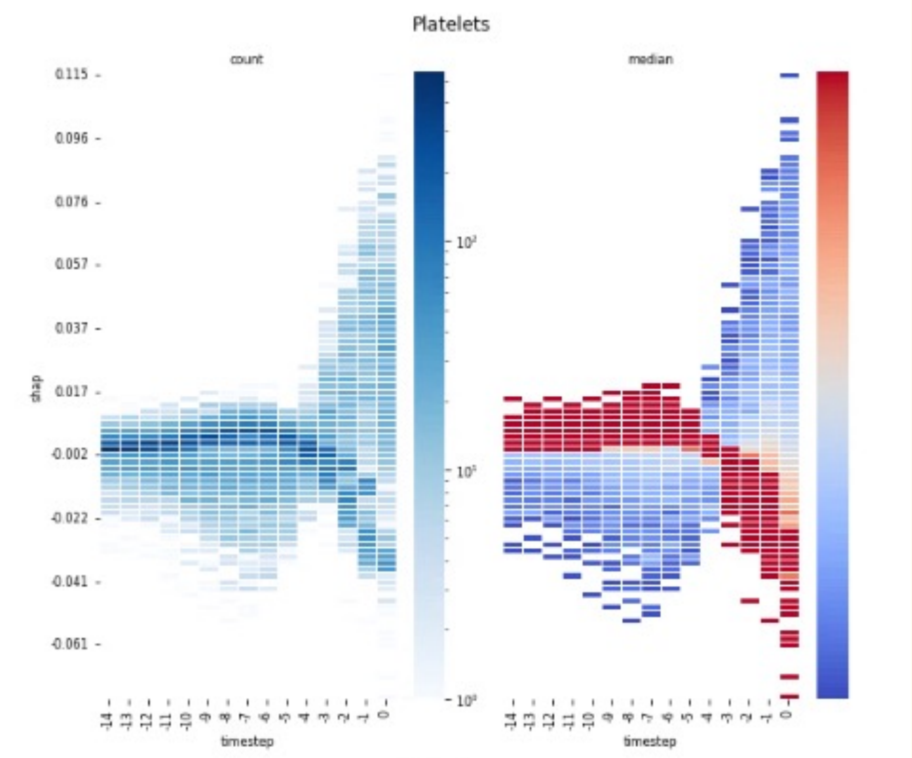
Platelets
count
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0

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Handling of missing data and MNAR

- The pattern of biomarker acquisition and measurement is reflective of clinical need
- Forward fill, interpolate, imputation, masking
- Models are built on the premise that local practices remain consistent

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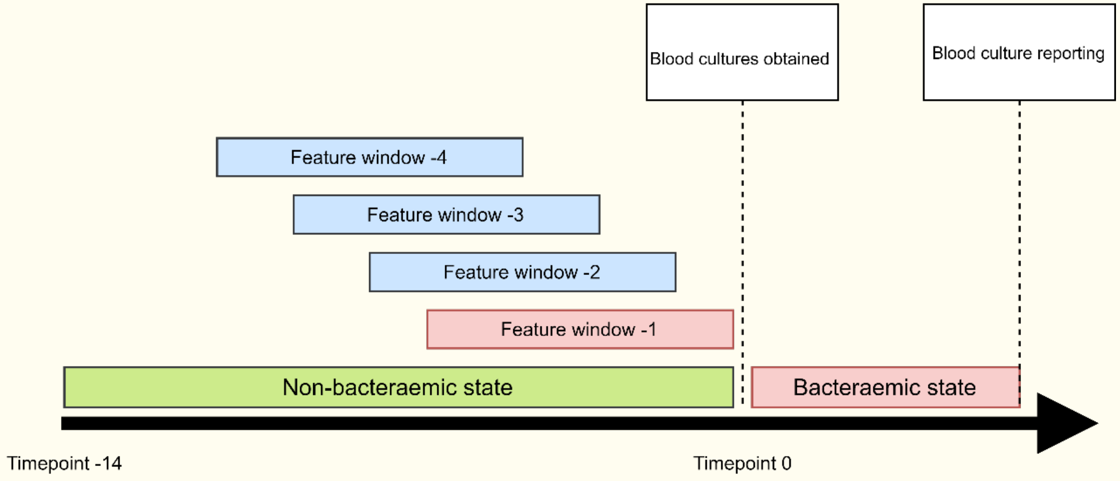
What about a real-time monitoring system?



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Synthesis of metadata to augment prediction

- Patient factors: immunosuppression status, risk factors, clinical assessment derived from natural language processing

- Laboratory metadata: time to positivity vs inoculum volume, information derived from MALID-TOF, use of adjunctive diagnostics e.g. sepsityper

- Fusion of data another challenge…

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Example 2 – dengue risk prediction

- Patients admitted to hospital fulfil dengue with warning signs (and are at increased risk)

- Tools for close monitoring of patients are lacking

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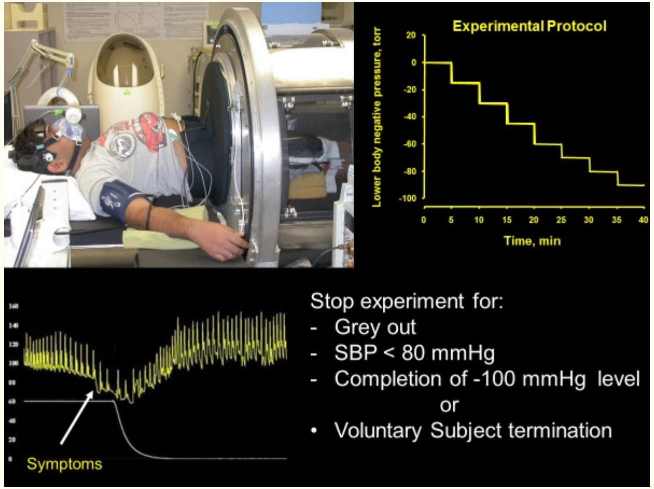
Wearables using photoplethysmography (PPG)

- Morphology of pulse waveform related to cardiovascular status

(and also derivation of pulse, SpO2, respiratory change)



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Research question

Can pulse waveform alone provide safe patient monitoring in dengue (and prediction of risk in) – and how can its performance be enhanced?

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Methods

- Prospective recruitment of 153 patients admitted to Ho Chi Minh City with acute dengue (2021-2022)

- PPG monitoring for 24+ hours alongside standard vital signs monitoring

- Approach using PPG signals and prediction of outcomes e.g. NEWS2, dengue shock, other relevant outcomes

- Can we incorporate relevant clinical data to the signal waveform too? Or synthesise with other machine learning models?

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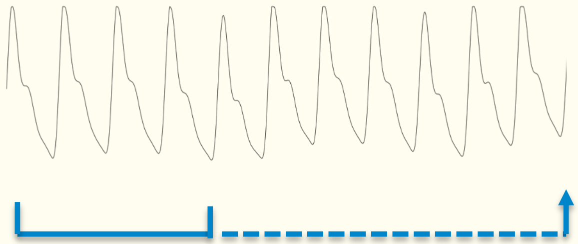
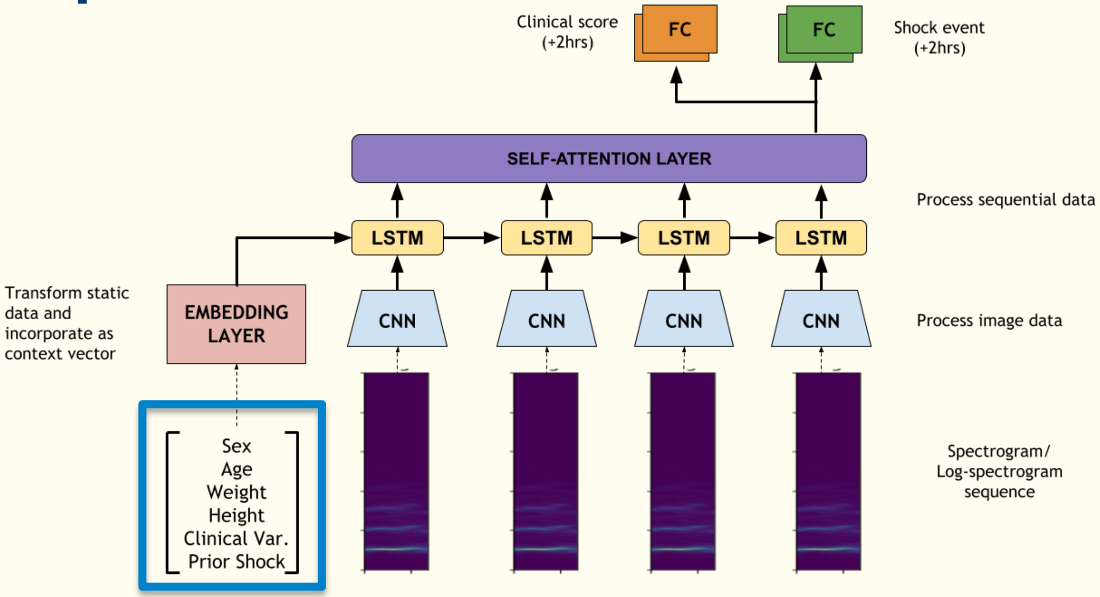
Multi-modal approach to prediction





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Beyond patient related factors

- Synthesis of seasonal, epidemiological, population level data as a proxy of strain virulence etc…

- Dengue prediction and seasonality factors

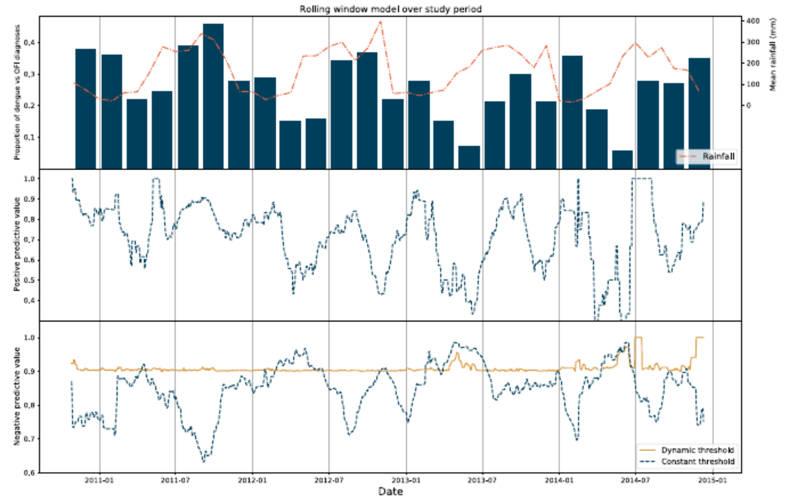

FIGURE 2 | Results of rolling window model. Top: Proportion of dengue diagnoses grouped in 2-month bins plotted against mean rainfall in Vietnam for the entire study period. Middle: Positive predictive value of the rolling window model for the constant threshold model only, with each point on the graph representing the upper range of the 30-day window used as the test set. Bottom: Negative predictive value of the rolling window model for the constant and dynamic model, with the NPV of the latter model fixed to > 90%.

Conclusion

- Time series dependencies are important and a move away from static scores applied at one timepoint could bring benefits to clinical care

- Leveraging such modalities relies on availability of data
  - Connectivity and electronic healthcare records
  - Role of signal acquisition such as through wearable devices

- Complex diverse datasets need synthesis to provide relevant classifications/predictions