Analysis of Critical Transitions in a Model of Human Endotoxemia

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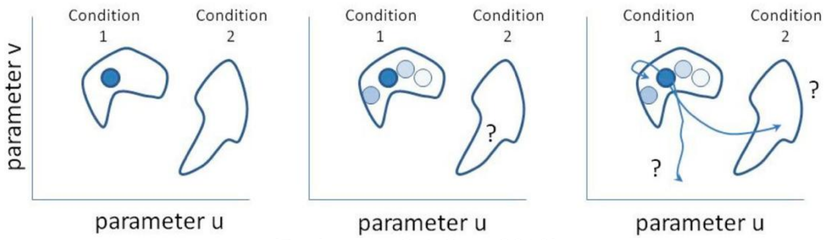
Transitions in Physiological State Space



(Buchman, *Crit Care*, 2010)

We don't need an exact measurement of a patient's state. We want to identify what cluster a patient lies in, and if they are likely to transition to another cluster or remain stable.

If transitions could be predicted ahead of time, clinicians could respond earlier to deteriorating health. However, measuring levels of individual biomarkers tends not to be predictive in complex disorders like sepsis.

Hypothesis: The dynamics of the inflammatory response can be used as a warning signal before state variables visibly change. This can be practical if the following goals are met:

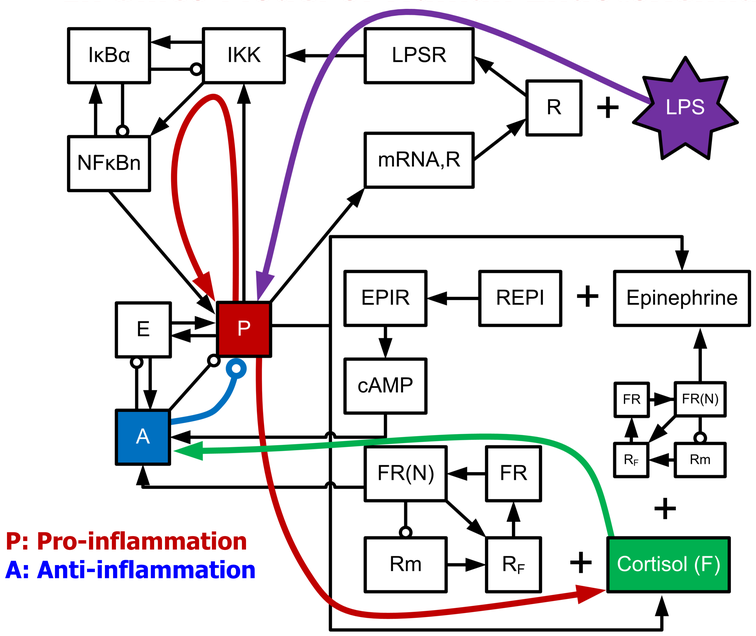
- Do not require a perfect model based on perfect knowledge.
- Do not require data that cannot be feasibly measured.
- Use data as it streams in, making an evolving prediction in real time.

We propose to accomplish this through analysis of the stability of a surrogate model of inflammation.

Human endotoxemia is am experimental model of systemic inflammation that evokes physiological responses similar to those of critical illness.

We use a relatively large mathematical model of human endotoxemia under conditions of gradually increasing LPS levels to generate *in silico* data to use for predicting warning signals of an impending transition.

In Silico Model of Human Endotoxemia



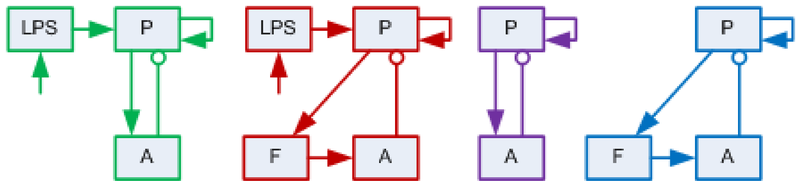
P: Pro-inflammation
A: Anti-inflammation

Generalized Modeling: Methods and Results

How can stability be feasibly estimated?

Problem: The detailed model contains much uncertainty, both in parameter values and in equation structure. Furthermore, data for all variables is not generally available. This limits practical applications.

Approach: Build "generalized models" that account for some high-level network structure linking measureable variables. From this, estimate the Jacobian matrix and its eigenvalues λ. When eigenvalues increase above 0, the steady state is unstable. This can happen before model variables visibly begin to move to the new steady state.



$$LPS' = f_1(\mu) - f_2(LPS)$$
$$P' = f_3(LPS, A, P) - f_4(P)$$
$$A' = f_5(F) - f_6(A)$$
$$F' = f_7(P) - f_8(F)$$

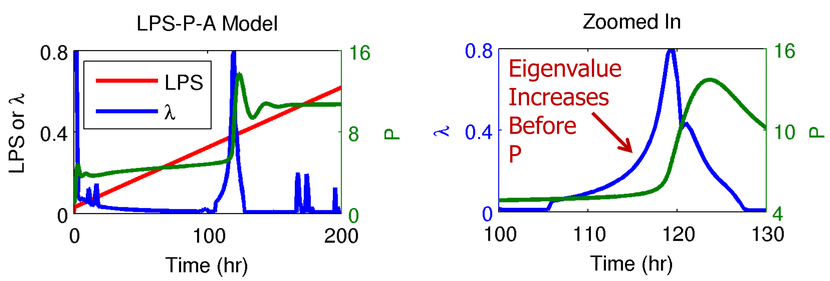
Each f_i represents a generalized production or degradation rate. These terms are never explicitly defined, they are just numerically estimated from data. To calculate the Jacobian for this system, the partial derivatives of each f_i must be estimated relative to each variable it depends on.

Assume we have data for how each state variable is changing over time. That is still not enough information to directly estimate all partial derivatives.

One solution is to assume that enough of the partial derivatives are known (*e.g.* assuming degradation is linear with a known rate) so that all the others can be calculated (Lade, *PLoS Comput Biol*, 2012).

But in general, *nothing* is known about the partial derivatives. So, we estimate all of them using linear regression over a 10 hour time window.

Are good estimates of partial derivatives required to make an estimate of stability that serves as a warning signal?



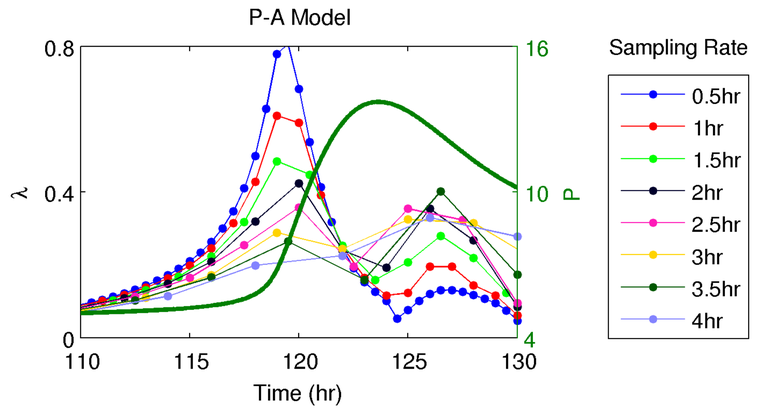
Eigenvalues estimated from the generalized models begin to clearly increase well *before* the state variables. The estimated eigenvalues are warning signals of forthcoming transitions.

Generalized models have similar dynamics to the detailed model in regards to stability, despite their simplified network structures and limited input data.

Even relatively poor estimates of partial derivatives can lead to informative predictions in the context of a network structure.

How much data is needed?

We assume measurements of all of the variables in the generalized models are available. But at what sampling frequency?



Performance improves with higher resolution data, but even at low sampling frequencies, the maximum eigenvalue visibly increases before the state variables.

Discussion

In general, model-free data analysis does not take advantage of all domain knowledge. By combining information about network structure and directionality with data analysis, we can make better predictions.

Tradeoff: Include too much detail, and partial derivatives can't be estimated with sufficient accuracy. Include too little detail, and the generalized model might be too trivial or inaccurate to estimate stability.

The dynamics of the system can be captured in a generalized model that does not include the initial inflammatory instigator, which is important given that in a real system this may not be a known or measurable quantity.

References

Foteinou PT, Calvano SE, Lowry SF, Androulakis IP. Multiscale model for the assessment of autonomic dysfunction in human endotoxemia. *Physiol Genomics* 2010, 42(1):5-19.

Lade SJ, Gross T. Early warning signals for critical transitions: a generalized modeling approach. *PLoS Comput Biol* 2012, 8(2):e1002360.

Acknowledgements: JDS and SEC: NIH GM34695. IPA: NIH GM082974.

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