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Towards Predictive Control of African Infant Infections

By Steven Schiff and Tim Sauer

At the 2019 SIAM Conference on Applications of Dynamical Systems, which took place in Snowbird, Utah, we reported preliminary findings from our research, which seeks to characterize the dynamics of African infant infections. It serves as a case study of ways in which the principles of dynamical systems can accelerate understanding and suggest appropriate care in medical and clinical settings.

Severe systemic bacterial infection in the neonatal period—known as neonatal sepsis— accounts for an estimated 680,000-750,000 neonatal deaths per year worldwide; this is more than the total childhood deaths from malaria and HIV combined. The most common brain disorder in childhood is hydrocephalus, and the most frequent instance of hydrocephalus in the world is sequelae of neonatal sepsis, which accounts for an estimated 160,000 cases of postinfectious hydrocephalus in infancy each year [3]. The microbial agents responsible for this enormous loss of human life have been poorly characterized, so we have been applying next-generation molecular methods to improve the identification of causal agents in Africa and Southeast Asia. Both neonatal sepsis and postinfectious hydrocephalus occur disproportionately in the developing world, and most hydrocephalic patients die in childhood without adequate treatment [5]. This substantially compounds neonatal sepsis' effective mortality and tremendous burdens on societies.

We have completed a five-year project on infants with neonatal sepsis, which involves teams of scientists across Africa, Europe, and the U.S. Thanks to support from the National Institutes of Health (NIH), we employed advanced genomic techniques to uncover some of the major bacterial and viral underpinnings of infections from eastern Uganda [6].

When examining the brains of African infants, we discovered a new, highly virulent strain of bacteria—a Paenibacillus—upon a background of cytomegalovirus. Our pan-genomic approach to pathogen discovery in syndromic infectious disease has the power to reveal microbial causalities in millions of cases of neonatal sepsis and postinfectious hydrocephalus annually. The impact of these findings could save hundreds of thousands of lives each year. But such genomic methods of organism discovery are too expensive and slow to help individual infants.

We are developing predictive mathematical models that will enable the utilization of detailed surveillance of more than a thousand of these infants. When combined with environmental variables from satellite rainfall measurements, these methods will predict optimal point-of-care (POC) treatment (see Figure 1).

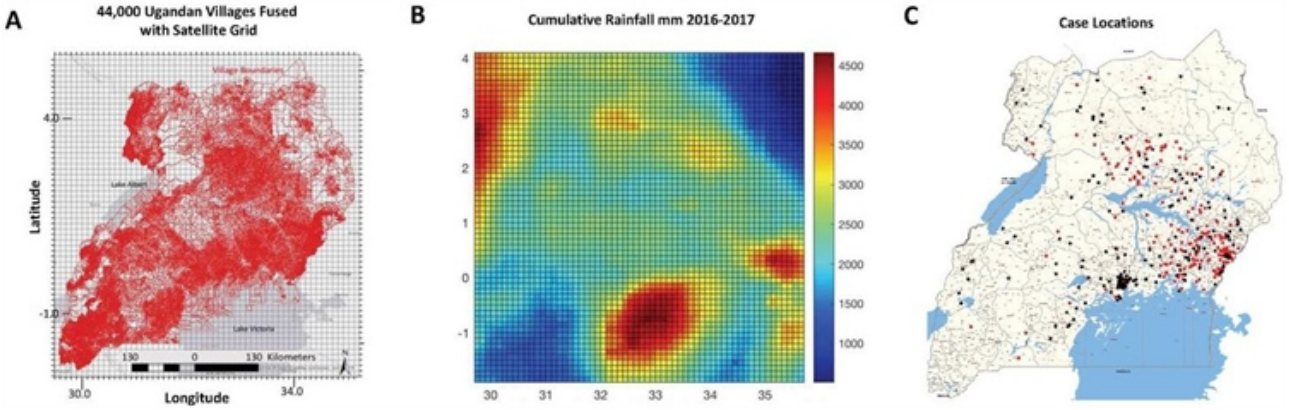

Figure 1. Environmental and microbial surveillance. **1a.** Ugandan village boundaries fused with the satellite rainfall grid. **1b.** Cumulative rainfall during case collection. **1c.** Locations of infected (red) and non-infected (black) postinfectious hydrocephalus cases. Figure 1a and 1b reproduced from [9], 1c adapted and based on the UN Office for the Coordination of Humanitarian Affairs/ReliefWeb and used with permission.

We call this paradigm predictive personalized public health (P3H), which is a novel means of controlling infectious disease. The concept is new and untested, so it falls under the NIH director's High-Risk, High-Reward Research Program. Our project requires a close fusion of mathematicians, statistical scientists, and control engineers; genomic and medical investigators handle the biology and treatment of the diseases.

The key issue is that we must dissociate the painstaking and slow microbial surveillance for unknown organisms from urgent POC decision-making. Infants with serious infections constitute a medical emergency at any medical system in the world. In industrialized countries, physicians are familiar with the organisms that typically cause such infections in the first few weeks of life. But when it comes to the developing world, scientists are unfamiliar with the majority of organisms. We call this the microbial dark matter problem [8]. Predictive modeling between large-scale microbial surveillance and POC treatment serves as a bridge between the two.

For much of the last century, infectious disease modeling has utilized the ordinary differential equation system called SIR: susceptible, infected, recovered [4]. We recently adapted this model to examine neonatal infection by adding hydrocephalus as a possible sequela following recovery; this yielded the SIRH model [2]. Another situation that is common with any disease is that patients present for care as if they were produced by a random process with an underlying Poisson generator. We have been developing the formal fusion of Poisson dynamics with linear and nonlinear Kalman filtering [2]. We have also employed such Poisson Kalman filtering as an ensemble filter [7].

With the advent of the novel coronavirus pandemic, we recognized that many aspects of our project could be helpful to the public health community that is struggling to track and control this new viral threat. The situation is very different from infant infections in the developing world in one important way — we have a single viral agent that is causing the vast majority of COVID-19 cases, and we know what that agent is. In contrast, the large number of asymptomatic coronavirus

patients creates unique challenges in efforts to perform accurate state estimation of the number of cases and estimate the degree of infectiousness.

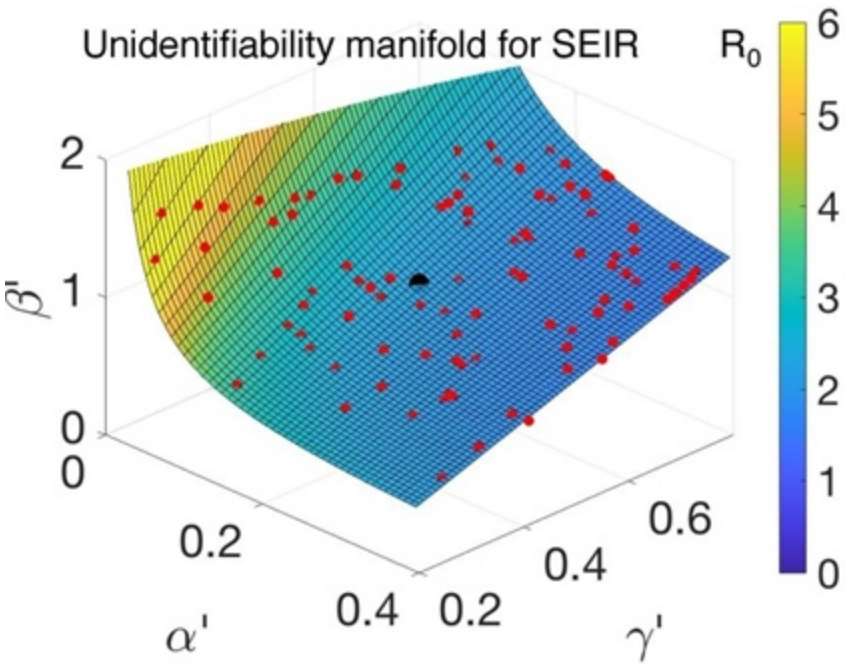

Figure 2. The unidentifiability manifold. The red plotted points are the optimal parameter values (α, β, γ) that minimize errors from a stochastic nonlinear epidemic model; they are in remarkable agreement with the quadric surface generated by the deterministic equation solutions that form an infinity of values, all of which are consistent with the same time series of observed infectious cases. The true parameter triplet is shown as a black point. The color represented on the surface corresponds to the computed reproductive number, R_0. Figure courtesy of Tim Sauer and adapted from [7].

We are focusing on improving aspects of the mathematics pertaining to the data assimilation strategies currently in use. In addition to developing the infrastructure for optimal incorporation of Poisson dynamics with Kalman filtering, we have explored the difficulty of estimating a virus' infectivity at the onset of an epidemic [7]. We find that the concept of dynamical compensation—discussed in existing classical work [1]—is relevant to parameter estimation of infectious disease compartmental models. In the case of the SEIR model (susceptible, exposed, infected, recovered/removed), Figure 2 shows an "unidentifiability manifold" of alternative parameter sets in R^3 that are consistent with a single measured time series $I(t)$ of the infected population early in the epidemic. The existence of this manifold is an obstruction to inference of important invariants, such as the reproduction number R_0, and may be crucial to uncertainty quantification of parameter estimates and forecasting.

When the pandemic eases and we can return to our work with newborn infant infections in Africa and Asia, we will incorporate all of the aforementioned mathematical efforts into our research. And of course, the coronavirus will now be part of the list of worrisome pathogens that we need to add to our predictive models as we seek to improve the care and survival of neonates with serious infections in the developing world.

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