BEAGLE

Science Highlight

Determining controllability of sepsis using genetic algorithms on a proxy agent-based model of systemic inflammation

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ABSTRACT

Sepsis, the body's response to severe infection or injury, kills more people each year in the US than AIDS, breast cancer and prostate cancer combined. After nearly 50 years of investigation not a single drug is currently available to treat sepsis; therefore the question as to whether sepsis can be controlled is an open question. We approach this by viewing the systemic inflammatory response as a random dynamical system that can be represented with an agent-based model, the Innate Immune Response ABM (IIRABM) as an abstracted proxy model for human sepsis. We then deploy a genetic algorithm (GA) on Beagle to identify control strategies to guide sepsis back to a state of health. System behavior is generated primarily by a set of five external parameters (microbial invasiveness, microbial toxigenesis, host resilience, environmental toxicity, and initial injury size). The GA is trained on a single parameter set with multiple stochastic replicates. For the parameter set used to train the GA, an eight-stage intervention, with 12 cytokine synthesis pathways either inhibited or augmented at each state, was discovered which lowered the mortality rate from 82% to 16%. This intervention was generalizable to other parameter sets located near to the training set in parameter space; for two alternate but close parameter sets, the mortality rate was lowered from 79% to 10% and 99% to 27%. The derived intervention did not perform as well on parameter sets that were less similar to the training set, suggesting that individualized interventions are desirable.

INTRODUCTION

Approximately 1 million people will be diagnosed with sepsis, a condition with a mortality rate ranging from 28%-50%, each year. Attempts to discover biologically-targeted therapies for sepsis have thus far been focused on manipulating a single mediator/cytokine, generally administered with either a single dose or over a very short course (less than 72 hours). Unfortunately, all these attempts, likely due to both the nonlinear nature of the human inflammatory signaling network and the paucity of clinical time-course data to place network relationships in context, have been unsuccessful. It is well known in biology that the systemic response to identical perturbations in genetically identical individuals (i.e., mice) is governed according to some probability distribution. In a chaotic system, this small stochastic variability in response can ultimately lead to a radically different final state. It logically follows then, that a single time point/single cytokine intervention is unlikely to be successful on a broad range of patients with a broad range of conditions that have lead to the state of sepsis. The challenge, however, is that the range of possible interventions, which is a function of the number of potential molecular targets, the extent to which they are modified, the time at which such modification can occur and the combinations thereof, is staggering, and cannot be tractably investigated given the logistical and practical limitations of both experimental and clinical research. We propose to address this challenge by the use of evolutionary computing (in the form of genetic algorithms) applied to a sufficiently complex, albeit abstracted, proxy computational model of sepsis. We have previously proposed that dynamic computational modeling, and specifically agent based modeling, can be used to represent mechanistic biological knowledge in a way that reproduces the non-linear dynamics of the real world system. Specifically, was have previously developed an agent-based model (ABM) of systemic inflammation, the Innate Immune Response agent-based model (IIRABM). The IIRABM is a two-dimensional abstract representation of the human endothelial-blood interface. This abstraction is designed to model the endothelial-blood interface for a traumatic (in the medical sense) injury, and does so by representing this interface as the unwrapped internal vascular surface of an azimuthally averaged 2D projection of the terminus for a branch of the arterial vascular network. We have previously utilized Beagle to demonstrate that the IIRABM casts the immune response as a random dynamical system with chaotic elements (see Fig. 1). We propose to use the existing IIRABM as a proxy system for the investigation of potential control strategies for sepsis. Discovery of an effective or optimal intervention can then be viewed as a nonlinear optimization/optimal control problem. Given a sufficiently validated model GA's can be utilized to develop complex treatment strategies by solving the optimal control problem on a biological ABM.

RESULTS

We have selected a set of cytokines and associated targets (Platelet-activating factor (PAF), Tumor necrosis factor alpha (TNFα), Soluble tumor necrosis factor receptors (sTNFr), Interleukin-1 (IL1), soluble interleukin-1 receptors (sIL1r), Interleukin-1 receptor antagonist (IL1ra), Interferon-gamma IFNγ, Interleukin-4 (IL4), Interleukin-8 (IL8), Interleukin-10 (IL10), Interleukin-12 (IL12), and Granulocyte colony-stimulating factor (GCSF)), which are the principal drivers of the inflammatory/immune dynamics expressed by the model. In order to search for an optimal intervention strategy, we allow production of each of these targets to be augmented or inhibited alone or as a group. The best solution (that which minimized the probability of death for both the specific patient case and the general case) was found by using 8 sequential interventions. For the specific patient upon which the GA was trained, the probability of death was reduced from 68% to 12% through application in the intervention shown in Fig 2; for the general case, the probability of death with this intervention was reduced from 82% to 16%. This intervention is represented as a three-dimensional bar graph in Figure 2. The height of the bars along the z-axis represents the log2 of the intervention multiplier; the x-axis enumerates the interventions; the y-axis shows which cytokine has its protein synthesis augmented or inhibited according to its associated bar. This solution was also tested against two additional parameter sets with similar aggregate mortality rates. The first test cause used a medium sized injury on a weak host with a microbial infection of low virulence; in this case, the probability of death was reduced from 79% to 10%. The second test case used the same parameter set as the first, but with a larger initial injury; in this case, the probability of death was reduced from 99% to 27%. While GA is quite successful at healing at IIRABM under a wide range of conditions, it has a few drawbacks which preclude it from being the ideal solution: 1) more extreme conditions (either very large injuries or extremely virulent bacteria) require either a finer degree of control than is computationally tractable using GA, as each sequential intervention multiplies the size of the search space by a factor of 912 (approximately 5 billion), or more aggressive interventions; intervention multipliers were limited to a small set of values we considered clinically tractable – removing this constraint would lead to an unconstrained search, increasing computational cost and potentially generating implausible interventions; 2) adjusting the temporal density of interventions requires a new run of the GA, which can be computationally expensive; 3) the GA does not have the ability to react to non-responders and adjust the intervention accordingly – rather, it finds the single sequence of interventions which (locally) maximizes the survival probability for a given patient population.

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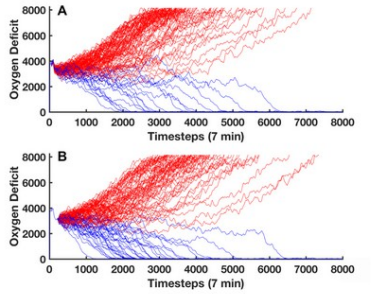

Figure 1. Panel A displays 100 stochastic trajectories generated by the IIRABM for a specific parameter set (Invasiveness=2; Host Resilience=0.1; Toxigenesis=5; Environmental Toxicity=2) with an injury with a radius of 33 cells. The total systemic oxygen deficit, an inverse measure of the in silico patient's health (y-axis) is presented as a function of time (x-axis). 82% of the simulated patients (red) end in death, while 18% heal completely (blue). The trajectories shown in panel B use the same parameter set as in panel A, however the run is started with a specific random number generator seed; the random number generator is re-seeded at 1 day post injury. At 1-day post injury, this specific patient has a 68% chance of death.

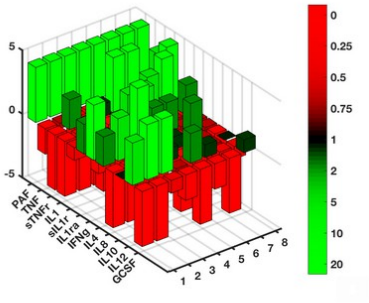

Figure 2. A 3d bar graph representing the series of 8 sequential interventions to which the genetic algorithm (GA) converged. The sequential order is displayed on the x-axis; the cytokines operated on are displayed on the y-axis; the base-2 logarithm of the augmentation or inhibition strength is displayed on the z-axis. This sequence of interventions lowered the probability of death from 68% to 12% for the patient upon which the GA was trained; the probability of death was lowered form 82% to 16% for the general population using an identical parameter set.

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https://doi.org/10.1016/j.devcel.2016.01.009

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