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A three-dimensional mathematical and computational model of necrotizing enterocolitis

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HIGHLIGHTS

- We present the first 3D PDE model of issues related to necrotizing enterocolitis.
- The model produces realistic simulations of necrotizing enterocolitis (NEC).
- The model considers how injury severity and extent and breast feeding affect NEC.
- The model shows that spatial inhomogeneities can significantly alter NEC outcomes.

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ABSTRACT

Necrotizing enterocolitis (NEC) is a severe disease that affects the gastrointestinal (GI) tract of premature infants. Different areas of NEC research have often been isolated from one another and progress on the role of the inflammatory response in NEC, on the dynamics of epithelial layer healing, and on the positive effects of breast feeding have not been synthesized to produce a more integrated understanding of the pathogenesis of NEC. We seek to synthesize these areas of research by creating a mathematical model that incorporates the current knowledge on these aspects. Unlike previous models that are based on ordinary differential equations, our mathematical model takes into account not only transient effects but also spatial effects. A system of nonlinear transient partial differential equations is solved numerically using cell-centered finite differences and an explicit Euler method. The model is used to track the evolution of a prescribed initial injured area in the intestinal wall. It is able to produce pathophysiologically realistic results; decreasing the initial severity of the injury in the system and introducing breast feeding to the system both lead to healthier overall simulations, and only a small fraction of epithelial injuries lead to full-blown NEC. In addition, in the model, changing the initial shape of the injured area can significantly alter the overall outcome of a simulation. This finding suggests that taking into account spatial effects may be important in assessing the outcome for a given NEC patient. This model can provide a platform with which to test competing hypotheses regarding pathological mechanisms of inflammation in NEC, suggest experimental approaches by which to clarify pathogenic drivers of NEC, and may be used to derive potential intervention strategies.

1. Introduction

Necrotizing enterocolitis (NEC) is a disease affecting 7–10% of very low birth weight (501–1500 g) premature neonates (Fanaroff et al., 2007; Guner et al., 2009) that involves necrosis of the epithelial layer of the gut. NEC is one of the leading causes of surgical emergencies in neonatal intensive care units (NICUs) among premature babies (Ade-Ajayi et al., 1996; Henry and Moss, 2005). Survivors of NEC often experience sepsis or multisystem organ failure and prolonged NICU stay, leading to increased resource utilization (Bisquera et al., 2002). Long-term consequences include short bowel syndrome, surgical obstructions due to intestinal strictures, and developmental delays

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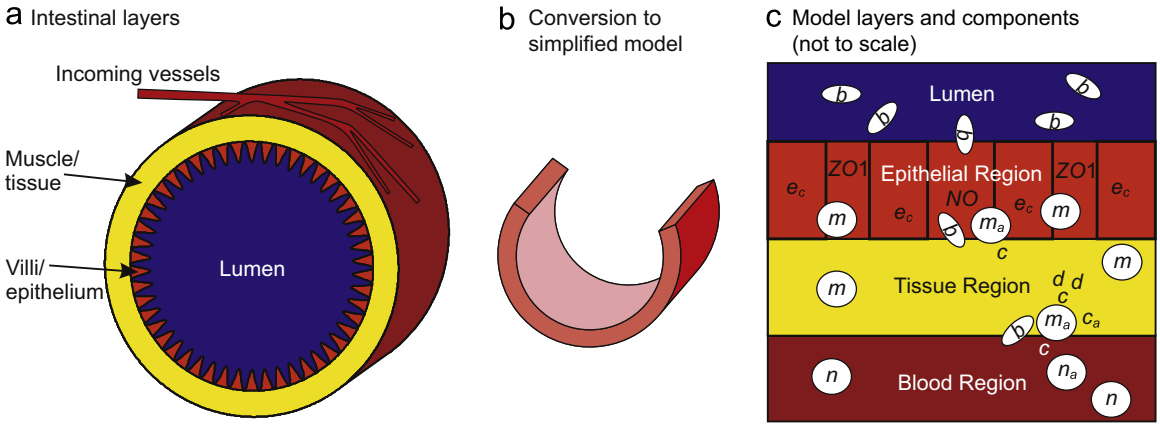

Fig. 1. (Color online) Physical system and model derivation. (a) Schematic illustrating the general physiological structure of the intestine, (b) to arrive at the simplified computational model, a portion of the intestine is sliced longitudinally and laid out as seen in Fig. 3. (c) Illustration of the layers used in the simplified model and the model components that typically reside in those layers (see Section 2.1).

due to poor nutritional status (Lin et al., 2008). Intestinal immaturity, bacterial invasion of the epithelium, low tissue oxygenation, and an exaggerated inflammatory response are known contributing factors to NEC (Morgan et al., 2011; Lin and Stoll, 2006). Since the relative roles these factors play in the development and course of NEC remain unclear, treatments for NEC are limited to antibiotics and surgery for severe disease and bowel perforation. None of these remedies are specifically targeted at reversing pathogenic drivers except antimicrobials (Neu and Walker, 2011). Yet, there are clear indications that local inflammation, immune vulnerability, and epithelial integrity are all important pathogenic mechanisms in NEC.

Over the past decade, mechanistic computational modeling has been used to gain insights into acute inflammation and associated tissue damage processes in the settings of sepsis and trauma, and has provided initial insights into NEC (Daun et al., 2008; Vodovotz et al., 2004, 2006; Vodovotz, 2006; Upperman et al., 2007; Vodovotz et al., 2008, 2009). We therefore reasoned that a detailed, model-based synthesis of NEC might create an opportunity for improved understanding of the interplay among the mechanisms involved in NEC, suggest an experimental program to test model predictions, and potentially lead to specific, biologically based interventions in neonates with NEC.

Here we present a model developed for performing such a synthesis. In contrast to another computational model of NEC based on ordinary differential equations (Arciero et al., 2010), this model is a partial differential equation model and takes into account both temporal and spatial effects. Previous agent-based models have also considered spatial and temporal effects (Kim et al., 2012), but those studies were predominantly focused on the events that initiate NEC, while we have focused on the inflammatory and healing responses that affect the progression of NEC. The three major goals of the paper are to present this original model, show that the model is capable of reproducing physiologically realistic results, and investigate the potential importance of spatial effects such as shape of the injured/inflamed area on the outcome of NEC.

Necrotizing enterocolitis involves a complex interplay between pathogens (e.g. bacteria), the intestinal lining, and the inflammatory response. When the intestinal lining (epithelial layer) is weak, the pathogens in the intestinal lumen can translocate into surrounding regions and instigate an inflammatory response. While the inflammatory response eliminates the pathogens, at the same time it also causes collateral damage to the surrounding tissues. Whether or not full-blown NEC develops depends on multiple factors including the ability of the epithelial layer to heal itself, the speed with which the inflammatory response can eliminate the pathogens, and the severity of the damage caused while the inflammatory response works. Our current model, like most models, is limited in its scope. We consider only the major events that occur during pathogen translocation after an epithelial layer breakdown has occurred and before more severe events such as thrombosis or full thickness necrosis occur. The model can be easily extended to consider factors that may cause the initial epithelial layer breakdown or dynamics that occur after severe NEC has set in (see Section 3.4).

2. NEC model

The model we have developed consists of a set of partial differential equations that are solved numerically using finite differences. The equations track concentrations of inflammatory cells, bacteria, and other proteins and molecules involved in the inflammation process. These equations allow us to simulate the dynamics of NEC.

2.1. Intestinal structure and NEC dynamics

The general layered structure of the intestine is shown in Fig. 1(a). The bacterial density in the lumen of the intestine is typically very high (10^3-10^{12} bacteria/cm^3 Leser and Molbak, 2009) and can consist of both commensal and pathogenic bacteria. The epithelial layer that lines the intestine provides a barrier that prevents luminal bacteria from invading the underlying intestinal tissue. If, however, the epithelial layer breaks down and loses integrity, as can occur in NEC, the bacteria can invade the surrounding tissue and instigate an inflammatory response. Our model focuses on the dynamics surrounding bacterial invasion following an epithelial layer breakdown.

The events occurring during a bacterial invasion are shown in Fig. 1(c). Bacteria penetrate the epithelial layer through a region of low epithelial integrity and activate resident resting macrophages. Activated macrophages start killing bacteria and produce cytokines and nitric oxide. Pro-inflammatory cytokines activate neutrophils and more macrophages and act on the surrounding tissue to produce tissue damage. Activated neutrophils produce more cytokines and kill bacteria while damaged tissue releases proteins that further activate inflammatory cells. Nitric oxide impairs the appropriate localization of tight junction proteins, thereby inhibiting the ability of the epithelial cells to form a tight barrier. Anti-inflammatory cytokines, produced at a slower rate than the pro-inflammatory cytokines, eventually slow down the inflammatory response. The rate at which the bacteria invade the surrounding tissue, the rate at which the immune system is able to respond, and the effectiveness of the inflammatory response depend on the properties of the inflammatory cells and bacteria, the properties of the layers, and the ability of the