Mathematical Modeling of Myocardial Infarction

Benito Chen-Charpentier
Department of Mathematics
University of Texas at Arlington

Abstract

Coronary artery disease is the leading cause of death worldwide. It occurs when the buildup of plaque within the walls of the arteries obstructs the flow of blood. This condition is called atherosclerosis. The flow of blood to the heart tissues will be restricted, a condition called ischemia, and it can cause the heart cells to receive insufficient amounts of oxygen, If untreated, coronary artery disease can lead to Myocardial Infarction (MI), commonly known as a heart attack, when a lack of blood flow (ischemia) and oxygen (hypoxia) to a region of the heart results in the death of cardiac muscle cells. A Myocardial Infarction can also occur when a portion of an unstable atherosclerotic plaque travels through the coronary arterial system and lodges in one of the smaller vessels.

The complex loco-regional myocardial healing process can be schematically divided into four distinct phases:
1. Necrotic phase: acute cell death secondary to necrosis and apoptosis (immediately after MI).
2. Acute inflammatory phase: inflammatory response in order to absorb necrotic tissue (1-7 days).
3. Sub-acute granulation phase: granulation tissue formation consisting of proliferating myofibroblasts, which increase the myocardial tensile strength and promote blood vessel proliferation thereby improving tissue perfusion and cell survival (1-3 weeks).
4. Chronic scar phase: fibroblasts formation and micro-vessel regression generating the final collagen-rich scar tissue (1month).

In this presentation we are concerned with the first two phases. That is, with the death of cardiomyocytes, and on the effects of the immune system in cleaning the heart of death cells. The immune cells recruited after MI are neutrophils, monocytes and macrophages, both M1 and M2. There is a wide variety of molecular mediators can be cytokines, chemokines and growth factors. Some are pro-inflammatory like $IL_1 - \beta$, tumor necrosis factor *(TNF)*, IL_{12}, IL_{18} and IL_{23}. And others are anti-inflammatory like IL_{10}, $TGF\text{-}\beta$, $TNF\text{-}\alpha$.

We construct two mathematical models. The first one deals with the second phase: cardiomyocytes have died and the immune system is cleaning the death cells. In the second model we add the death process of the cardiomyocytes. We assume the following hypotheses: Communication between cells is done through a series of chemical factors and we assume that the amount of each factor is proportional to the number of cells that produce it. We consider a small part of the heart tissue where the distribution of the involved cells is homogeneous. Neutrophils are involved in the initiation of pro-inflammatory response following myocardial infarction. They phagocytosize the dead cardiomyocytes. Following neutrophil infiltration, circulating monocytes migrate from blood to the site of the lesion, where they differentiate into macrophages, gradually replacing neutrophils. M1 macrophages continue eliminating dead

cardiomyocytes and also dead neutrophils. The rate of conversion of monocytes to M1 macrophages depends on the number of dead dells. Macrophage conversion from a pro-inflammatory (M1) to an anti-inflammatory (M2) phenotype is a central process. Several molecular and cellular processes are involved in macrophage phenotype transition. Macrophage phagocytosis is one of the mechanisms leading to M1/M2 conversion. M2 macrophages inhibit M1 macrophages.

The first mathematical models consists of six ordinary nonlinear differential equations in the unknowns death cardiomyocytes, neutrophils, death neutrophils, monocytes, macrophages M1 and macrophages M2. The analysis of the model shows it has only one biologically realistic fixed point, when the number of all cells is zero. This solution is stable. The model involves sixteen parameters. Measurements of the parameters are few and they have large variations. The decay rates are the best known. The second model adds an equation for live cardiomyocytes which will die due to lack of oxygen.

Parameter estimation is a difficult issue since there are large variations and uncertainties associated with them. Therefore it is important to determine how sensitive the model output is to variations in the parameter values. A local sensitivity analysis determines the model sensitivity to parameter variations over a localised region around the used parameter values.
A global sensitivity analysis (GSA) investigates the sensitivity over the entire parameter space. Since there is sensitivity index for each type of cell with respect to each parameter, and they are functions of time, there is a large amount of information. We investigate ways of reducing it by looking only at the steady solutions, and by just considering them at a few selected times, and by taking time averages over the simulation time. We also investigate the effects on only considering the indices for one relevant variable such as the number of death cardiomyocytes, and by looking at the average, maximum and minimum values of the indices with respect to the unknown variables.

We also compare the results of using localized indices that can be calculated inexpensively calculated using an augmented system of ordinary differential equations, with the results of several global sensitivity analysis indices.

We present numerical simulations simulations and the results of several sensitivity analysis. We end the presentation by stating conclusions.