CHAPTER 2

Integral Sliding Mode Control of Immune Response for Kidney Transplantation

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1. INTRODUCTION

Acute kidney injury (AKI) is a prevalent secondary disease for patients who are in the treatment process inside hospitals. Even those who passed the recovery period of AKI are still at the risk of other complications, such as chronic kidney diseases (CKD) [1]. According to the annual report of the United States Renal Data System in 2018, people with estimated Glomerular Filtration Rates (eGFR) less than 60 mL/min/1.73 m^2 are at the risk of kidney diseases. CKD has five stages characterized by eGFR magnitude: stage 1 with eGFR $>$ 90 mL/min/1.73 m^2 is the least dangerous stage, while people in stage 5 with eGFR $<$ 15 mL/min/1.73 m^2 are suffering from the end-stage renal disease (ESRD) that is mortal in the absence of dialysis or renal transplantation [2, 3]. eGFR that shows kidney performance is calculated by the CKD-EPI creatinine equation, based on the serum creatinine concentration in blood (a breakdown product resulting from the activity of muscles), race, sex and age [4].

In developing countries such as India and Pakistan, which together are home to one-sixth of the world's human population, the annual incidence of ESRD is estimated at around 100 per million people. This means 100,000 and 15,000 patients are at the risk of ESRD in 1-billion and 150-million populations of India and Pakistan, respectively. When dialysis equipment is not satisfactory, kidney transplantation is the best way of treatment [5]. In developed countries such as the United States, the number of people with kidney failure (in the ESRD stage) is continually growing and has the highest increase rate in the world. Research studies have shown that 75% of children in the United States with ESRD got renal transplants, which implies the significance of this treatment [2]. In renal transplantation, there is a possibility of kidney rejection in the absence of standard health care. Pharmacological immuno-suppression is currently the most effective way to reduce the chance of this rejection. However, using this therapy, patients' bodies will be exposed to several viral loads and bacterial pathogens [6].

Human herpesvirus five or Human Cytomegalovirus (HCMV) is the most common and significant pathogen among renal transplant recipients. Primary HCMV infection is usually without any specific symptom, but the uncontrolled case will lead to a life-long infection in patients' bodies. Moreover, HCMV disease can be caused by the reactivation of HCMV latent infectious viral load [7].

In recent years, a wide range of investigations and experiments have been conducted regarding the HCMV infection, its dynamics, diagnosis, risk factors and international guidelines on its management [8–12]. Emery et al. [8] opposed the popular belief that Cytomegalovirus (CMV) replicates slowly, which had been an accepted theory due to time-consuming in vitro experiments for showing up the cytopathic effects. Taking three different cases into account, they proved that CMV in vivo replication has tremendous dynamics (variation). Serological tests, standard tube cell culture technique, antigenemia assay, polymerase chain reaction (PCR), immunohistochemistry, nucleic acid sequence-based amplification (NASBA) and hybrid capture assay are recognized methods of CMV detection that each has some merits and demerits [9]. Bataille et al. [11] investigated modern immunosuppression and its risk factors on 300 people having the same trial therapy, and the case D+/R− (CMV-seropositive donor/CMV-seronegative recipient) had the highest risk factor. Also, based on their observations, it was mentioned that a patient with impaired early kidney function becomes a candidate at risk.

Mathematical modeling or analysis is a vital tool for investigating the dynamic behaviour of biological systems and making decisions about treatment methods

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