Application 1:
Dengue infection is one of the most significant arthropod-borne viral diseases of the modern era, with more than 2 billion people at risk of infection (Guha-Sapir and Schimmer, 2005). Infection can result in a range of response, ranging from no response to a mild fever to abdominal pain, liver enlargement and mucosal bleeding, to severe plasma leakage and organ failure (Hadinegoro 2012).

The Centers for Disease Control and Prevention (CDC) reports that one manner of categorizing these clinical presentations is into Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF), and Dengue Shock Syndrome (DSS). DF presents as a 2-7 day period of often biphasic fever, occasionally accompanied by some epithelial hemorrhage. DHF's first phase is similar to DF, but is followed by plasma leaking into pleural and abdominal cavities and a subsequent reabsorption phase. DSS has extensive plasma leakage which leads the patient to develop shock. The progression of DF is largely benign, however DHF / DSS can be life-threatening and needs proper clinical care. It is for this reason that early clinical recognition of DHF / DSS can alter treatment and save lives. However, methods for differentiating these syndromes remains a challenge for clinicians.

The proposed meta-analysis platform was applied on a set of genome-wide microarray expression profiles to determine a set of genes to distinguish these syndromes. After they were developed, IPCA was used to confirm their effectiveness at this discrimination. Devignot et al. 2010 was used for this purpose. In this study, whole blood genome-wide expression profiles of Cambodian children infected with dengue virus were collected. IPCA was then performed with respect to the meta-analysis genes discovered previously (Figure 1). The clustering reflects the "debate as to whether DHF/DSS represents a separate pathophysiological process or is merely the opposite end of a continuum of the same illness" (CDC), since the DHF and DSS clusters are not as defined with respect to each other, while DF is better defined as a separate entity.

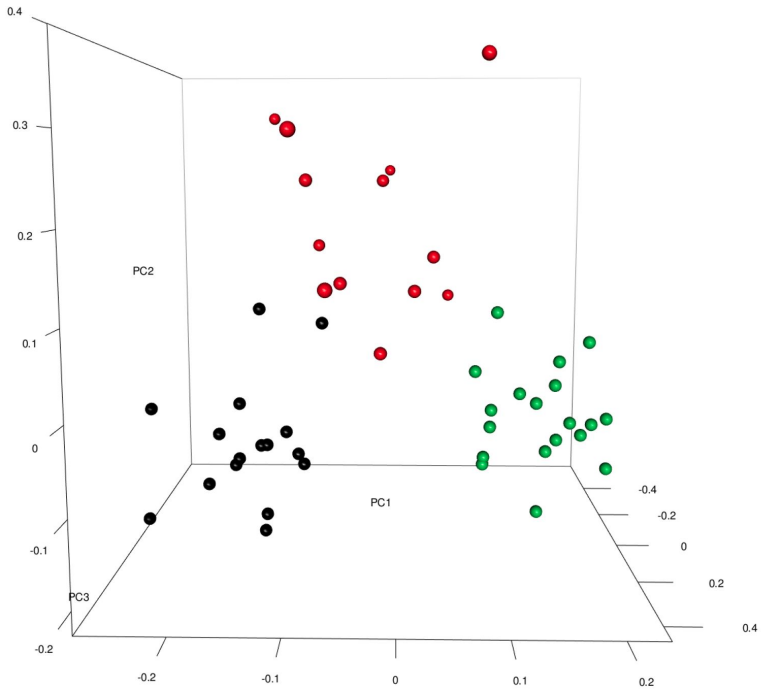

Figure 1: IPCA plot of Devignot et al. dataset, with DF cases in black, DHF cases in red, and DSS cases in green.

Works Cited:

Centers for Disease Control and Prevention. (2014). Clinical / Laboratory Guidance. Retrieved from http://www.cdc.gov/dengue/clinicalLab/clinical.html

Koren, Y., & Carmel, L. (2003). Visualization of Labeled Data Using Linear Transformations. In *Proceedings of the Ninth Annual IEEE Conference on Information Visualization* (pp. 121–128). Washington, DC, USA: IEEE Computer Society. Retrieved from http://dl.acm.org/citation.cfm?id=1947368.1947392

Application 2:
Systemic Sclerosis (SSc) is a rare connective tissue disease characterized by immune dysfunction. Its cause is a complex interplay between a genetic predisposition to autoimmune infection and environmental triggers (Katsumoto et al. 2011). Because of its clinical heterogeneity in presentation and its relative rarity, accurate diagnosis remains difficult; patients often mistakenly diagnosed with other more common autoimmune inflammatory diseases (Katsumoto et al. 2011). Although environmental risk factors like exposure to silica and organic solvents are likely to play a role in the development of the disease (Dospinescu 2013), SSc is also partially heritable: the population attributable risk associated with SSc is 8%, and first-degree relatives of SSc patients have a statistically significant increase in risk for developing the condition (Frech et al. 2010).

Furthermore, large amounts of clinical and genetic heterogeneity exist within the condition. There are three major classes of specific autoantibodies involved in different variants of SSc: (1) anticentrometere antibodies, (2) anti-topoisomerase I antibodies, and (3) anti-RNA polymerase III antibodies, each of which has its own clinical associations (Katsumoto et al. 2011). Furthermore, microarray studies have shown more subsets of SSc than were previously appreciated, and hint at a variety of largely mutually exclusive pathways in the development of the condition (Katsumoto et al. 2011). Therefore, it is clinically important to determine a set of genes that can distinguish SSc patients from control ones by capturing the various pathways that define the genetic components of the condition.

As with Dengue, the meta-analysis platform was applied on a set of genome-wide microarray expression profiles (GSE 19617, GSE 22356, and GSE 33463) to determine a set of 19 genes to distinguish these syndromes.

These genes were then validated on Hinchcliff et al. This study includes 83 samples of RNA expression profiling by microarray, with 20 coming from control patients and 63 coming from SSc patients. As can be seen in figure 2, these genes do indeed ‘capture’ the heterogeneity of the disease. The cases (the patients with SSc) are those that are clustered together, while the controls are not clustered all. These results prove encouraging that these genes capture the most important immunologic pathways involved in the development of SSc and suggest a radial kernel for any SVM that needs to be trained on such data.

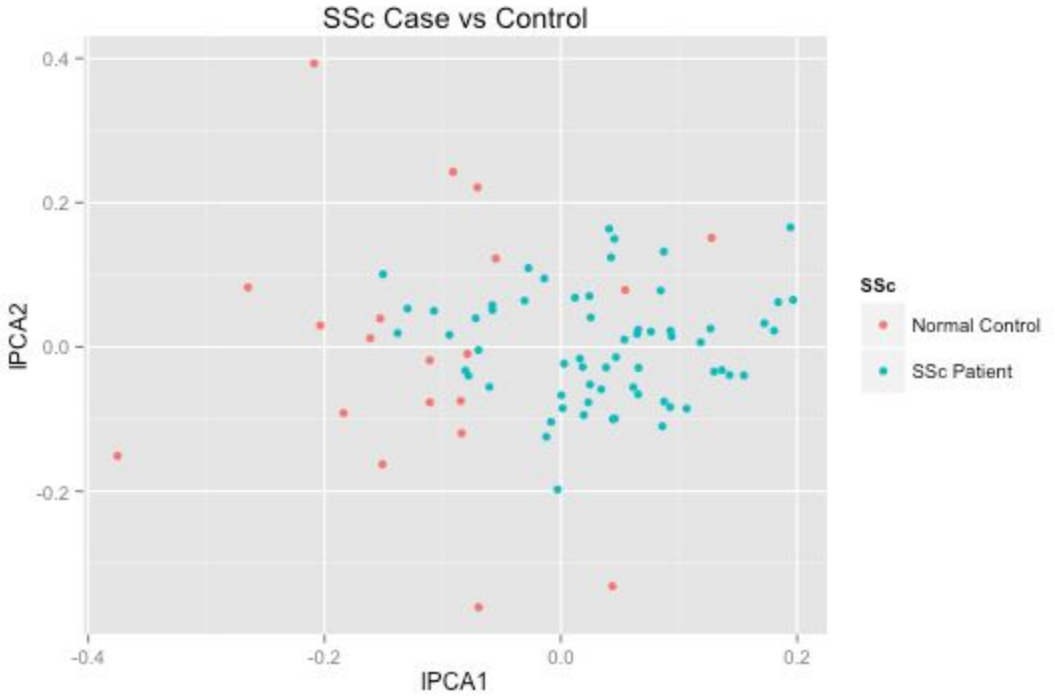

Figure 2: Labelled PCA plot of the Hinchcliff et al. dataset (GSE45485).

Application 3:

Plot and abstract present in the following:

Sweeney, T. E., Shidham, A., Wong, H. R., & Khatri, P. A comprehensive time-course–based multicohort analysis of sepsis and sterile inflammation reveals a robust diagnostic gene set. Science Translational Medicine, 7(287), 287ra71–287ra71.