Inferring viral dynamics in chronically HCV infected patients from the spatial distribution of infected hepatocytes

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Chronic liver infection by hepatitis C virus (HCV) is a major public health concern. Despite partly successful treatment options, several aspects of intrahepatic HCV infection dynamics are still poorly understood, including the preferred mode of viral propagation, as well as the proportion of infected hepatocytes. Answers to these questions have important implications for the development of therapeutic interventions.

In this study we present a mathematical method to determine and characterize clusters of infected hepatocytes after sampling individual hepatocytes by single cell laser microdissection from liver biopsy samples of patients chronically infected with HCV. The mathematical method, which is based on methods from spatial statistics, determines the internal structure of the clusters of infected cells. We found that individual clusters range in size from 2-50 infected hepatocytes. In addition, the HCV RNA content in a cluster decreases approximately exponentially from the cell at the cluster center that presumably founded the cluster to its periphery. These observations suggest that HCV preferentially spreads locally.

Assuming that the amount of intracellular HCV RNA indicates the age of infection, and using mathematical models to describe intracellular viral replication and accumulation of viral RNA with homogeneous dynamics among infected cells, we estimate that the cells in the clusters have been infected for fewer than 10 days. This finding seems to indicate a high-turnover of infected hepatocytes in chronic HCV infection, or that infected hepatocytes vary substantially in their viral replication dynamics, e.g. due to local innate and adaptive immune responses. Our method represents a novel approach to form inferences about infection dynamics in solid tissues from static spatial data.