Transportation systems are the lifelines of economies and societies, and their loss in a disaster of significance results in “ripple effects” on directly and indirectly related industries. Therefore, the foundation of a complete assessment of the economic impact of a disaster includes evaluating economic losses in transportation systems. The objective of this study is to propose a framework in which transportation network modeling tools are incorporated for estimating the direct and indirect economic impacts of a disaster on intermodal transportation systems. Highway and railroad systems are two major concerns in this framework. The computational methods used to assess the economic damage sustained by these two systems are presented. This framework can be directly utilized or easily further expanded as a decision-making tool for state Departments of Transportation (DOTs) and Metropolitan Planning Organizations (MPOs) to prioritize their recovery plans and resilience enhancement projects after a disaster. A case study was conducted using the effects of Hurricane Katrina in the Gulf Coast Region of Mississippi, U.S.A. Under the proposed framework, indirect economic loss of intermodal transportation systems disruptions amounted to over $1 million per day after one week Katrina ravaged and totaled $473 million. The results also indicate that cost of rerouting and congestion delays was the major factor of indirect economic loss in highway systems while the rent cost of right-of-way was the chief component of that in railroad systems. The estimated total economic loss of intermodal transportation systems disruptions due to Katrina in Mississippi was around $1.5 billion.