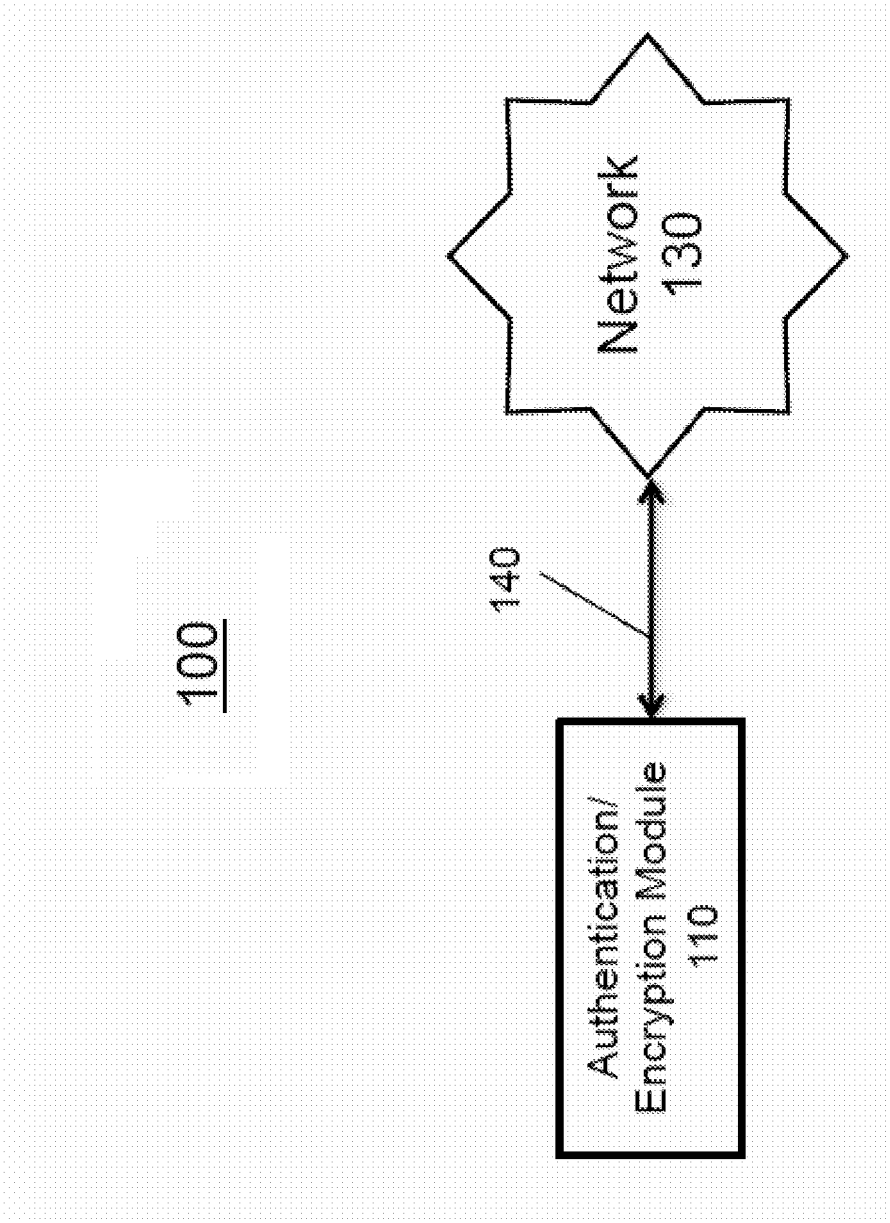Fig. 1A