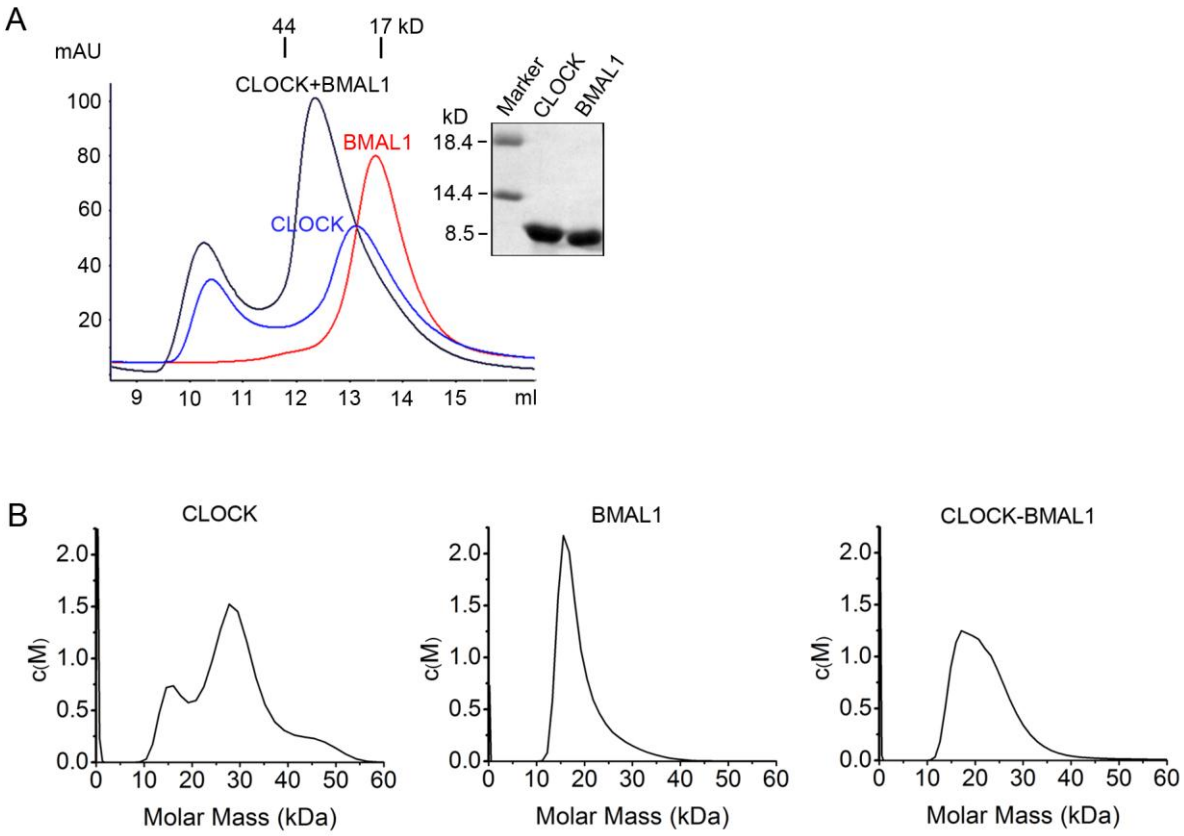

Figure S2. (**A**) Gel filtration results showed that, individual BMAL1 bHLH appeared to be only homodimer whereas individual CLOCK bHLH existed as equilibrium between homodimer and homotetramer in solution. SDS-PAGE gel showed both CLOCK and BMAL1 bHLH domains were approximately 8.5 kDa. The peak location of the bHLH complex protein corresponds to a tetramer form. (**B**) Ultracentrifugation analysis of CLOCK, BMAL1 and CLOCK-BMAL1 bHLH domains. Individual CLOCK bHLH domain exists as mainly homodimer and homotetramer, whereas individual BMAL1 bHLH domain exists as homodimer. The CLOCK-BMAL1 bHLH domain complex exists as equilibrium between heterodimer and tetramer. We have examined the crystal packing. Two types of crystallographic bHLH tetramers were observed, one mediated by two adjacent CLOCK molecules and the other by two adjacent BMAL1 molecules. The CLOCK-mediated heterotetramer is likely to be the main bHLH tetramer form in solution based on that individual CLOCK bHLH domain can form homotetramer by ultracentrifugation, and that strong van der Waals interactions are formed around the CLOCK-mediated but not BMAL1-mediated bHLH heterotetramer interface (an area of 528 $Å^2$). However, the bHLH heterotetramer observed in solution and in crystals might be a result of using the fragment of the protein in analysis.