Table S4: Class-Distinctive Sites Defined by Series of Mutual Information Calculations

Classes Included in MI Calculation at a Given Site¹ G(io) & G(io) & G(io) & G(q) & G(q) & G(s) & G(12)G(12)G(12)G(q)G(s)G(s)Invariant² 0.0 0.0 0.0 0.0 0.0 0.0 G(io)-D³ >0.0 >0.0 >0.0 0.0 0.0 0.0 $G(q)-D^3$ >0.0 0.0 0.0 >0.0 >0.0 0.0 Class **Distinctive** $G(s)-D^3$ 0.0 >0.0 0.0 >0.0 0.0 >0.0 Site

>0.0

0.0

>0.0

>0.0

0.0

 $G(12)-D^3$

0.0

 $^{^{1}}$ Six independent MI calculations were carried out, each MI calculation involving sequences from only 2 of the 4 G α classes.

²A site was defined as "Invariant" when the MI score was 0.0 for all 6 MI calculations at that site.

 $^{^{3}}$ A site was defined as "Distinctive" for a given G α class when the six MI scores at that site fit the criteria established for that class.