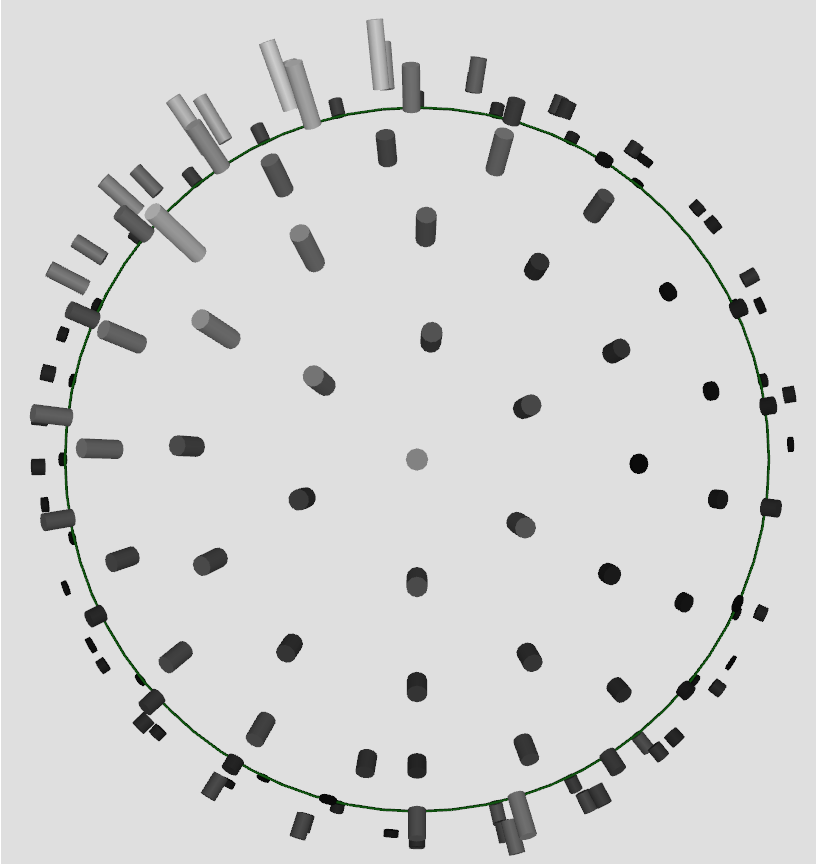S4 Fig