REPLY TO GRAHAM ET AL.:

In silico atomistic coordinates and molecular dynamics simulation trajectories of the glucocerebrosidase–saposin C complex

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To our knowledge, there are no established policies among journals on the submission of atomistic coordinates of in silico models or molecular dynamics simulation trajectories. Atomistic coordinates are customarily made available on request. However, microsecond-long molecular dynamics trajectories can range from several hundred gigabytes to terabytes in size. Our multiple simulations are no different (1), and it is therefore difficult, if not impossible, to host them on a server. All published datasets will be shared upon request. In response to the request by Graham et al. (2), we now provide a file (3) containing atomistic coordinates of the model (as we have done in response to other requests). We fully support unfettered transparency and the unencumbered sharing of all data (e.g., refs. 4 and 5).

Graham et al. (2) further raise two important technical issues. The first relates to the orientation of the enzyme glucocerebrosidase (GCase) and the facilitator protein saposin C (SAPC) at the membrane. Our study instead reports the interaction of GCase with SAPC as well as the structural mechanism that links protein–protein interactions with binding site loop dynamics. It also highlights the mechanism through which two of the most common mutations, N370S and L444P, disrupt GCase–SAPC interactions in Gaucher disease. Unfortunately, in view of the extensive (and comprehensive) dataset that we provide (1), notwithstanding figure S2 of ref. 1, we chose not to report the interaction of the GCase–SAPC complex with the membrane in this manuscript. For those interested in this important process of membrane association, please refer to the publicly available PhD thesis of Romero (6). Figure 2.7 and table 3.4 of ref. 6 show the orientation and specific membrane-interacting residues, respectively.

The second issue relates to the conformation of SAPC used when in complex with GCase, and specifically its stability. Graham et al. (2) refer to their previous elegant work, wherein they report the apo structures of SAPC (i.e., in the absence of GCase) and state the inability of SAPC to interact with the membrane in the closed conformation (7). However, we describe interactions between SAPC and GCase as a complex, and our data are supported by experimental evidence (8). Notably, during the course of the simulation of the GCase–SAPC complex, we observe conformational changes in SAPC, but no unfolding of the stable SAPC helices (1). Testifying to the stability of SAPC are figures 3.7 and 3.8 of ref. 6. In figure 3.8 of ref. 6, the rms fluctuation values for the helices are less than 2 Å, indicating that the helices are stable. Finally, as noted by Graham et al., we have previously made comparisons between GCase–SAPC and GalCase–SAPA complexes, as shown in figure 2.8 of ref. 6 (9).

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The authors declare no conflict of interest.

Data deposition: Atomistic coordinates have been deposited in FigShare, https://doi.org/10.6084/m9.figshare.8161877.v1.

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