Supporting Information: Free-Energy Surface Prediction by Flying Gaussian Method: Multisystem Representation

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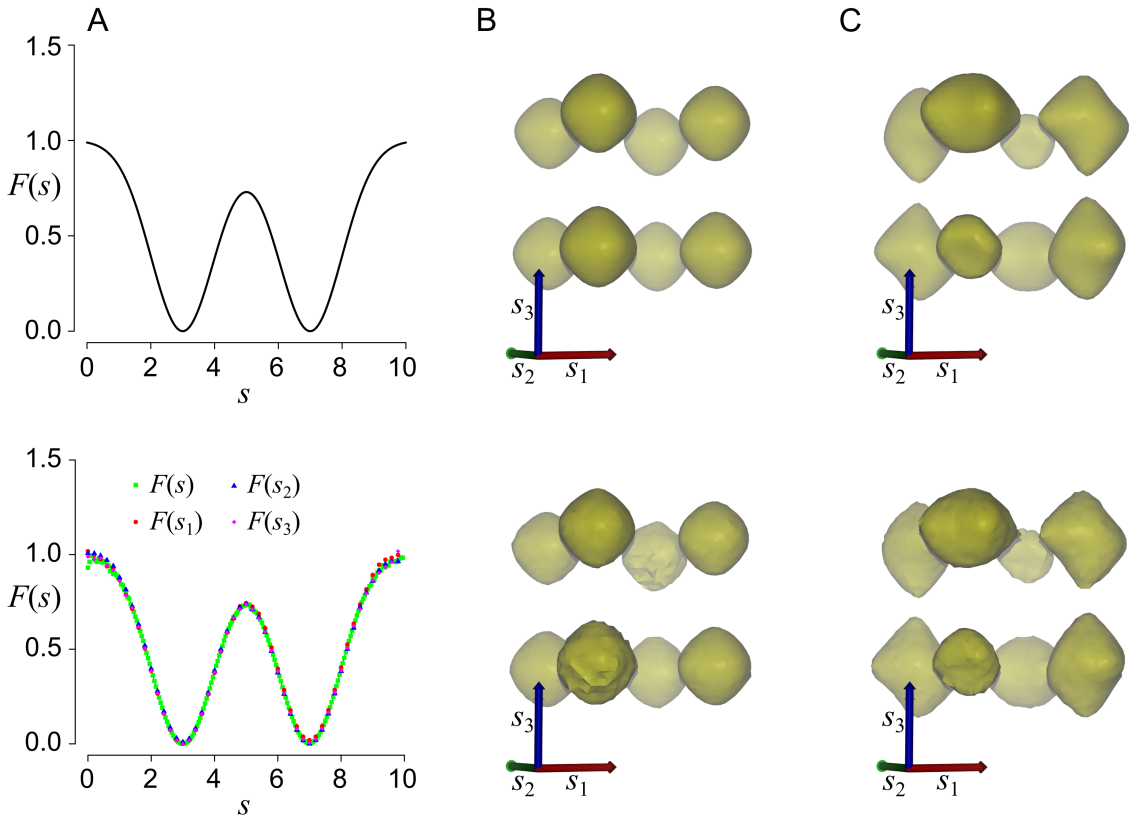

Figure S1: Reconstruction of a free energy surface by flying Gaussian method demonstrated on a model energy profile ($F(s) = -\exp(-(s-3.0)^2/2) - \exp(-(s-7.0)^2/2) + C$), three walkers and $V_{bias,i}(\mathbf{s}) = 0.2\exp(-\sum_{j=1;j\neq i}^{3}(s_i(t) - s_j(t))^2)$. A. One-dimensional model energy profile, B. Three-dimensional multi-system energy surface, C. Biased three-dimensional multi-system energy surface, top - ideal energy surfaces, bottom - sampling and reweighing. Free energy surfaces are depicted as isosurfaces at $F = 0.5$.

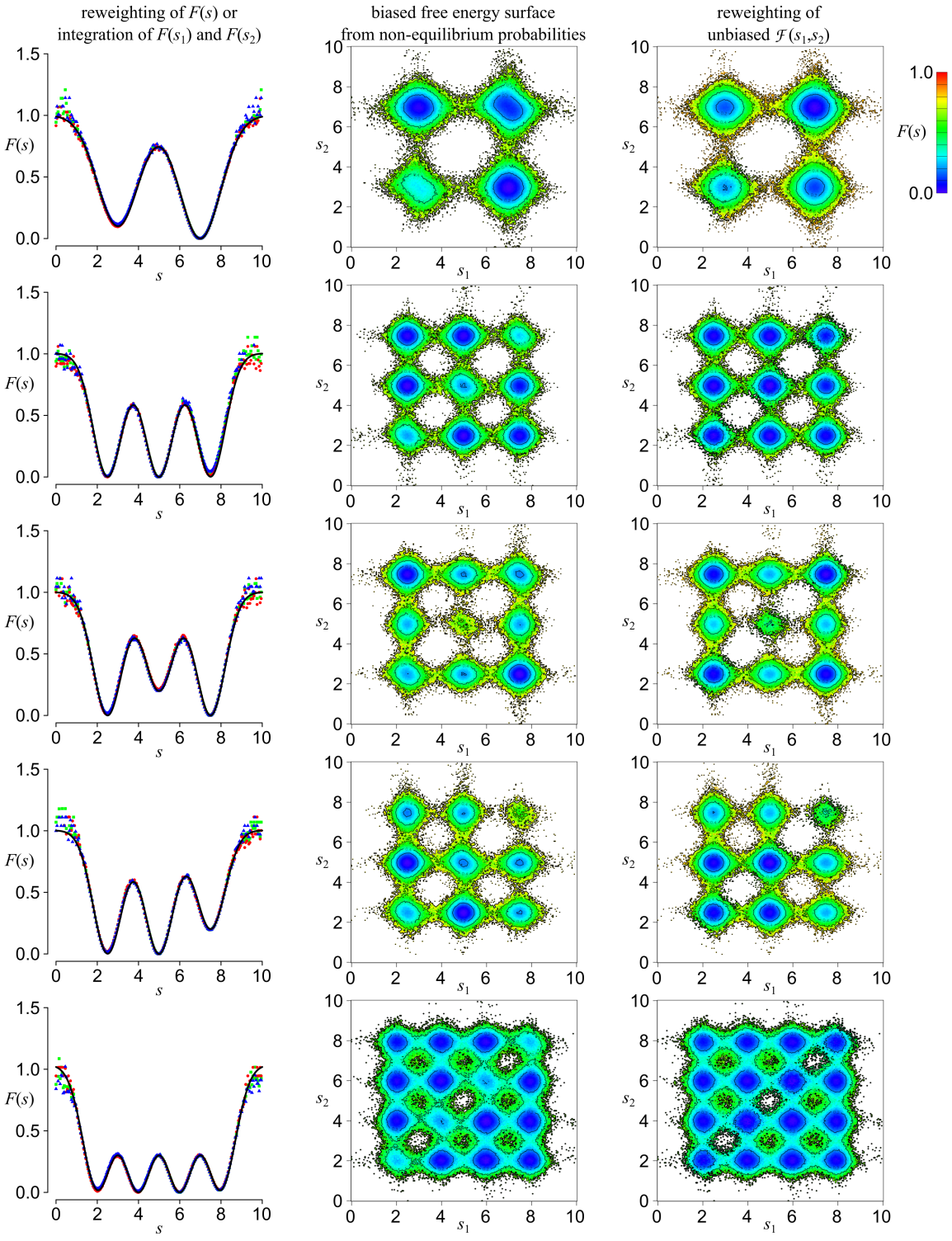

Figure S2: Reconstruction of a free energy surface by flying Gaussian method demonstrated on model energy profiles with 2-4 symmetric or asymmetric minima and two walkers. All parameters except the model energy surfaces were same as in Figure 1.

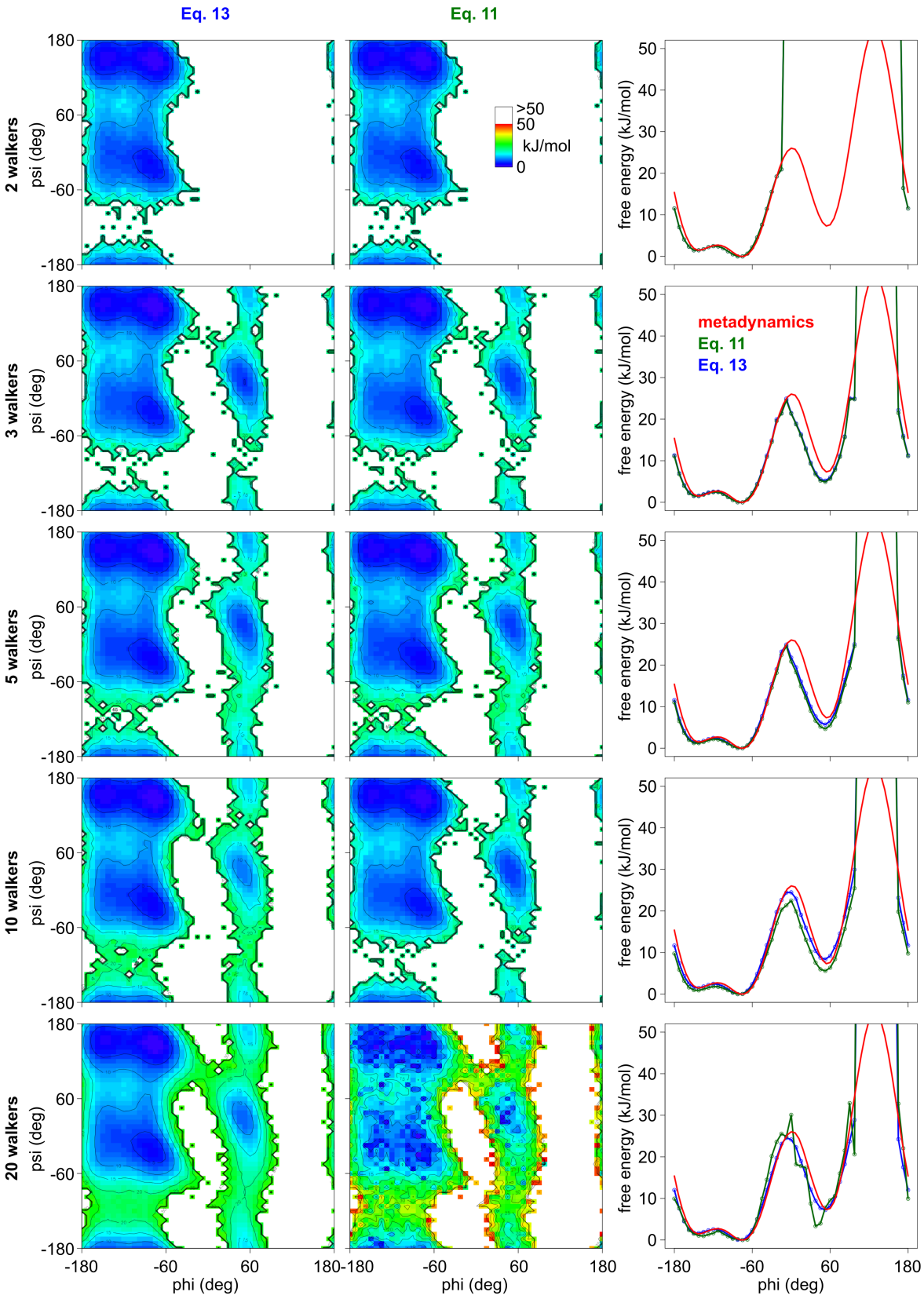
Eq. 13
Eq. 11
2 walkers
3 walkers
5 walkers
10 walkers
20 walkers
psi (deg)
phi (deg)
free energy (kJ/mol)
>50
50
kJ/mol
0
metadynamics
Eq. 11
Eq. 13
180
60
-60
-180
50
40
30
20
10
0

Figure S3: (previous page) FES of alanine dipeptide in water calculated flying Gaussian method with 2, 3, 5, 10 and 20 walkers (10 ns). Equation 13 (left) and 11 (middle) were used to reconstruct the free energy surface. In principle, findings of the manuscript should apply to flying Gaussian method with low (i.e. insufficient) number of walkers. We would expect the method to sample only a part of the CV space, yet provide accurate free energy surface of this region. An extreme case of one walker corresponds to unbiased simulation. This was the case of flying Gaussian method with 2 walkers where only C5/C7eq/αR regions were sampled. The issue that must be kept in mind is that there must be a sufficient number of energy barrier crossing during the simulation. If not, we would obtain a pair (or multiple) accurate free energy surfaces for separated parts of the CV space, but inaccurate free energy differences between them. This was the case of flying Gaussian method with 3 walkers. One walker visited αL/C7ax, but there was only two barrier crossings so the relative free energy difference is inaccurate. Finally, free energy surfaces calculated with 5, 10 and 20 walkers provide accurate free energy surfaces.

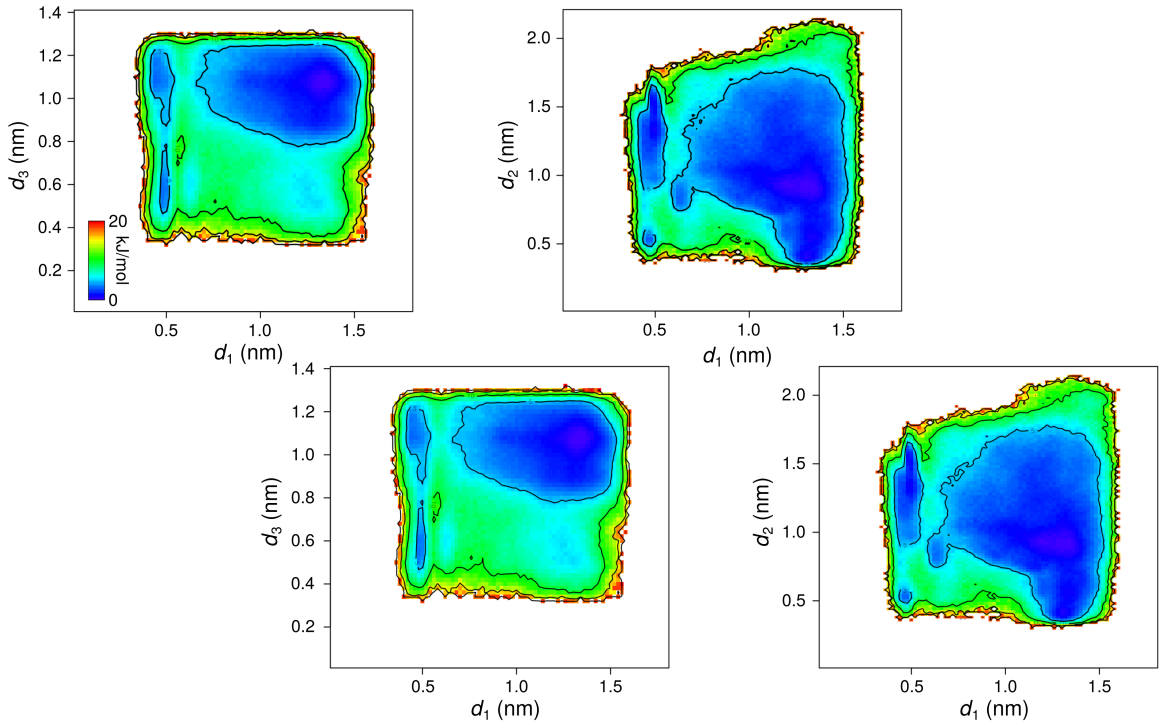

Figure S4: Comparison of free energy surfaces of Met-enkephalin calculated by Equation 13 (top) and Equation 11 (bottom). Free energy surfaces calculated by Equation 13 (top) were taken from the article introducing the flying Gaussian method [*J. Chem. Theory. Comput.* **2016**, *12*, 4644-4650, ACS Author Choice]. Free energy surfaces calculated by Equation 11 (bottom) were calculated from CV and bias potential records. There is excellent agreement between these two methods.