Report on the manuscript titled "Two-Dimensional Vesicle Hydrodynamics from Hydrophobic Attraction Potential" by *Fu et al.*

Summary:

The authors are introducing a novel numerical approach to study vesicles under flow conditions in two dimensions. The vesicle is modelled as a collection of amphiphilic Janus particles (JP) interacting with each other through a hydrophobic attraction potential (HAP) and a short-range repulsion force to avoid the overlap between particles. Both the mobility of the particles and the HAP are recast in the form of an integral equation of the second kind and solved numerically. The authors presented some results on the deformation and dynamic of a single vesicle and a pair of vesicles in different type of external flows.

Suitability:

The originality of this work stems from coupling the HAP and Stokes equations through a boundary integral formulation which I personally find quite interesting. However, numerical models for vesicles and other class of soft particles in 2D and 3D are already well established in the literature. Disregarding the 2D nature of the model, I am not fully convinced on how this approach outperforms the existing models either in computational performance or in new applications. The authors should make an extra effort to highlight this. Another weakness of this model, if I understood correctly, is that the area of the vesicle is not conserved beyond the small deformation limit. To the best of my knowledge, a 2D vesicle should fulfill both constant area and perimeter constraints. This means that the range of application of the model is limited to the small deformation limits when used to mimic vesicles under flow. Finally, this paper lacks a thorough validation of the numerical results with the existing data in the literature and/or an original application/result describing a physical phenomenon not covered by the previous literature. This work is suitable for publication in this journal but a major revision is needed. Below additional minor comments to be addressed.

Additional minor suggestions:

1. The abbreviation HAP is not defined in the text. I guess it stands for hydrophobic attraction potential.
2. u is used for both the velocity and the solutions of the Laplace equation. Please use another variable for the scalar function u.
3. ρ used in the HAP is not the same as the one used in the mobility boundary integral equation. One is a decay length of the attraction potential, while the second is the Euclidean distance between two JPs.
4. ν is used on multiple instances, sometimes as a normal vector (see line 97 for example), and other times as some scalar function (see line 203).
5. What is the bending modulus here? I guess that it is not a direct input parameter in this model but rather a quantity that can be deduced from other input parameters. If I am right then, what are these parameters? And could you tune them if needed to simulate the effect of the membrane stiffness? This can be important in some applications such as rigidity-based microfluidic sorting devices.
6. To compare the results with the existing literature, I would suggest introducing the capillary number for vesicles as defined in https://doi.org/10.1016/j.crhy.2009.10.001.
7. For both examples with the linear shear flow and the Poiseuille flow, the area of the vesicle is not conserved and the relative error with respect to the stress-free area increases with the increase of the external stresses. It can reach roughly 7-8% for the higher shear rate in the shear flow example. This is quite significant. Do you have a way to reduce this error to below 1%? Note that in other numerical models for vesicles (e.g. https://doi.org/10.1016/j.jcp.2008.11.036), both constant area and perimeter constraints are fulfilled even when the vesicle is more deformed than the cases reported here.
8. In some interesting applications, the fluid encapsulated by the bilayer membrane has a viscosity which is different from the suspending fluid. How difficult it is to add this feature to your model?