Referee Report 1: A. R. Honerkamp-Smith, P. Cicuta, M. Collins, S. L. Veatch, M. den Nijs, M. Schick, and S. L. Keller. Line tensions, Correlation Lengths, and Critical Exponents in Lipid Membranes Near Critical Points. *Biophysical Journal*, 95:236-46, 2008. doi: 10.1529/biophysj.107.128421

This paper investigates the critical behaviour of bilayer membranes composed of a ternary mixture of lipids: a high chain-melting temperature lipid, a low chain-melting temperature lipid and cholesterol. Previous papers have reported a phase transition in the lipid bilayer following a change in temperature, during which a uniform mixture of lipids separates into two liquid phases. In this paper, the universality class of this phase transition has been identified by measuring the critical exponents ν and β. These exponents have been derived from the temperature dependency of line tension, correlation length and pixel intensity distribution, which were obtained from quantifying the fluctuations in domain boundaries and lipid compositions. Fluorescence microscopy and image processing have been utilised for this purpose. Since the critical exponents and the temperature dependencies are in accordance with the predictions of the Ising model, the authors suggest that the critical behaviour of the lipid bilayer is identical to that of a two dimensional Ising model.

The paper has three major issues:

- Since the two dimensional Ising model is a well-known statistical model which has been solved analytically, the interesting finding of this paper may be biologically significant, providing better insight into the behaviour and properties of bilayer membranes. However, this biological aspect of the finding is not clear in the paper and needs further investigation. In particular, it should be explored whether any of the characteristics of lipid bilayers could be related to the properties of 2D Ising model at body temperature.

- The method used to obtain the line tension and its time dependency, as well as the method utilised for calculating the critical exponent β seem accurate and reasonable. In calculating β in particular, measurements were fit to a function that could describe not only the Ising model, but also any critical statistical system. Thus, the consistency between the obtained value of β and the prediction of the Ising model provides a promising evidence for the conclusion of this paper. However, there is a major issue with another evidence, i.e. consistency between the obtained ν and the Ising model prediction, which led to the conclusion that the lipid bilayers fall into the universality class of the 2D Ising model. To be more specific, ν was obtained from the temperature dependency of the line tension and correlation length. In order to derive the correlation length, the structure factor S(k) was measured for different wave numbers (k) in eight temperatures. Then the correlation length ξ for each temperature was chosen such that structure factors fit the Ising model curve of $S(k) \times k^{7/4}$ versus $k\xi$. This means that in obtaining the correlation length, and thus ν, it has been assumed that the behaviour of lipid bilayers is similar to a 2D Ising model. It is wrong to make this assumption when the main goal is to investigate the existence of this similarity. Hence, another approach should be taken to calculate the correlation length. For example, instead of fitting the structure factor, ξ could be obtained by fitting the measured values for the correlation function G(r) to the curve of relation $G(r) \simeq e^{-r/\xi}$ [1], which applies to any critical statistical system.

- To confirm the conclusion, further investigation should be performed to show that other models (e.g. mean field theory) could not provide better fits to the measurements. It can be inferred from the figure captions that some studies have been done. However, the results of these studies have not been presented in the paper. It would be helpful if these results were explicitly included.

To conclude, the paper provides a novel approach to the critical behaviour of lipid bilayers by quantitatively measuring the critical exponents. Since such measurements were not done in previous studies, I believe that this study should be appropriate for publication following revision.

[1] Guiseppe Mussardo. *Statistical Field Theory: An Introduction to Exactly Solved Models in Statistical Physics*. Oxford University Press, 2010.

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Referee Report 2: A. Altinok, D. Gonze, F. Levi, and A. Goldbeter. An Automaton Model for the Cell Cycle, *Interface Focus*, 1:36-47, 2011. doi: 10.1098/rsfs.2010.0009

The existing kinetic models for describing the mammalian cell cycle, which is driven by a regulatory network of Cdks, incorporate a large number of variables and thus, have a high degree of complexity and are hard to interpret. To overcome this problem, a novel automaton model has been successfully developed in this paper, which simulates the progression of mammalian cells through the cell cycle. This automaton is composed of four phases, i.e. G1, S, G2, M. Phase durations are assigned to the cell at the beginning of the cell cycle and the cell proceeds to the next phase when the duration of a given phase has passed. The authors have thoroughly studied the effects of different factors on the dynamics of the automaton model. They have also studied the effect of entrainment of the automaton by the circadian clock.

One remarkable feature of this model, which is not included in the kinetic models, is that it reflects the stochastic nature of the phase transitions by randomly choosing the phase durations from a distribution of durations. Another interesting feature of this model is that it can correctly predict the steady state distribution of cells. The authors have verified the accuracy of these predictions by showing that similar results could be obtained from a deterministic model. This feature is one of the strengths of the automaton model, extending its application to a wide range of problems, notably cancer chronotherapy and drug administration, where the distribution of cells between different phases plays a more important role than the biochemical details.

There are two minor points which could be improved:

- In order to allow for homeostasis, some cells are marked to die at the end of each time step. It is assumed that these cells can only exit the cell cycle at the nearest G1/S or G2/M transition. The authors have discussed that this assumption displays the role of checkpoints in eukaryotic cell cycles. However, not all cell types require checkpoints to maintain their size. The automaton model does not require the user to choose the cell type. The only place where the cell type is defined is in choosing the mean duration of the four phases, which according to the paper, only affects the steady state proportion of cells in different phases. Thus, it is expected that the dynamics of the automaton should be the same for different cell types. Even if this is not the case, it should be noted that the values used in this paper are typical to those of mammalian cells. Therefore, it can be concluded that the automaton is modelling the cell cycle for mammalian cells, if not for any cell type. However, experimental results (e.g. Conlon and Raff, 2003[2]) suggest that the presence of checkpoints is unnecessary for many mammalian cells, because they display a size-independent linear growth. Hence, removing cells from the cell cycle at two specific points cannot be interpreted as presence of checkpoints. In fact, it is more likely that this assumption reflects a common feature between the cell cycles of different cells, rather that a feature which is specific to a certain group of cells. It is suggested that the authors re-consider their interpretation of this assumption. It would also be helpful to run the automaton with another set of mean durations, which are typical of yeast (or other cells with a size-dependent growth) to investigate whether the automaton displays different dynamics for different cell types.
- It has been found that the steady state distribution of cells between different phases is independent of the initial conditions, only depending on the mean duration of each phase. Figure 7 of the paper clearly shows that the final distribution is independent of the initial proportion of cells in each phase. However, it does not demonstrate that the final distribution would be different for a different set of mean phase durations. Thus, it is suggested that authors provide the results obtained for a different set of phase durations (similar to figure 8).

All in all, I recommend this paper for publication after minor revisions.

[2]Ian Conlon and Martin Raff. Differences in the Way a Mammalian Cell and Yeast Cells Coordinate Cell Growth and Cell-Cycle Progression. *Journal of Biology*, 2(1), 2003. doi: 10.1186/1475-4924-2-7

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