

RESPONSE TO REFEREE #1
The chaotic, dynamical behavior of cellular blood flow in a model microvessel
Bryngelson, Guéniat, Freund

We are grateful for the referee's efforts in improving the quality of this paper. We quote the comments of the referee and discuss changes made to the paper in response to these comments in the following.

Referee #1:

The paper deals with the problem of modeling the flow of red blood cells within cylindrical vessels. The authors start out using a physically-motivated model from which they are able to perform long simulations. Then they set off to characterize the produced time series. Using Fourier analysis they find no dominant frequency and conclude that there is no evidence of recurrent structures. In the sequel they assert finding traces of sensitivity to initial conditions, then conclude that the flow is chaotic. Then they try to estimate the dimension of a potential attractor and conclude that the dimension is very high ($D > 10$ in the Conclusions). The natural way forward, and in fact the one pursued by the authors, is to tackle the flow as stochastic. Having asserted that the flow is not nonstationary based on the mean and variance (hence it is considered wide sense stationary) they propose a Markov chain model and using eigenanalysis they argue that the statistics of such a model is consistent to that of the physically-motivated one.

The paper is clearly written and the methodology has been carefully conceived and worked out. Most of my remarks are minor, but I do have a rather major concern that should be addressed by the authors.

1. My single major concern is the classification of the flow as being chaotic. In essence I would point out two difficulties. First, topological transitivity (recurrence) is a feature of chaotic dynamics. The authors have clearly stated, after performing Fourier analysis, that they did not find any recurrences. Of course, it can always be alleged that such recurrences have not been found due to the high dimensionality of the possible underlying “attractor”. Second, it seems that the conclusion in favor of chaos was based exclusively on a very-close-to-zero largest Lyapunov exponent. As for the calculation of this exponent, you seem to take small perturbations of the initial conditions at $t = 0$. This should have been done over the entire space, right? After all, Lyapunov exponents are local averages taken throughout time and space. On top of that no measure of uncertainty has been provided. The authors estimate $\lambda = 0.06$, what is the standard deviation of this estimate? What is the probability, based on this estimate, that the true largest Lyapunov exponent be indeed positive?

The first point raised by the referee is excellent. We failed to emphasize (or even explicitly acknowledge) the inherent recurrence of the confined, streamwise-periodic flow. Indeed these recurrences were explicitly utilized by our Markov chain model. The point we were trying to make in our recurrence discussion was that they are not associated with any distinct frequency. We have revised the abstract to qualify recurrent with “classifiable” and main text to make these points clear. We also now explicitly point out this inherent recurrence in section IV A 3.

We also agree with the referee's second point: strongly concluding that the flow is chaotic based upon a single near-zero Lyapunov exponent is questionable. (We were more explicit in our previous work [10] that our perturbations are over the entire space of amplifying trajectories.) We have revised our manuscript to include both the variance associated with the largest Lyapunov exponent and with the qualification that this serves as only one indication that the flow is chaotic. However, as was mentioned within multiple comments below (e.g., 1 (b)), this is ultimately only of secondary importance once the high-dimensionality of the flow dynamics is considered and a reduced-order model is formulated; the manuscript has been amended to make this point clear as well.

- (a) Although the flow might be chaotic, your evidences are very slim and, at the moment, they are not convincing. Hence, I would certainly remove the word chaotic from the title, and would deal with this as an hypothesis instead of a fact.

We agree in full, especially given the additional context we have provided regarding point 1. We have updated the title to the more appropriate "The irregular dynamics of cellular blood flow in a model microvessel."

- (b) Apart from the title, your paper and results nowhere require that the flow be chaotic. As a matter of fact, your own final approach — which is clear and convincing — is that we better deal with the flow as a stochastic process. So, in fact, there is no need to try to sell the hypothesis of chaos as a fact.

An excellent point. In addition to the title, we softened this claim as suggested throughout.

Minor comments follow:

1. "Chaotic dynamics are well understood to have a fractal character and extreme sensitivity to initial conditions, quickly devolving from ordered to disordered behaviors." Chaos is always ordered. Please rewrite.

Thanks. We have removed this erroneous claim about order.

2. As for Fig. 2, I have two remarks. After the seminal paper by David Ruelle: "The Claude Bernard Lecture, 1989 - Deterministic chaos: the science and the fiction", the field has been a lot more careful in stating very large attractor dimensions from somewhat limited data. I wonder if the authors from [48] have taken this into account in order to state that $D > 780$. To play safe and not to propagate "fiction" (to use Ruelle's terminology), I would just state that the time series in (b) is very high dimensional and perhaps chaotic. As for plot (c), this is most likely to be a heart-rate signal (a tachogram) and NOT an ECG. ECG signals are known to have a very strong deterministic component (e.g. the QRS complex etc.). On the other hand, the tachogram, which shows how heart rate varies with time (and which is estimated from the R-R peaks of the ECG) is known to be strongly stochastic. So, I would consider changing "ECG recording" to "Heart-rate signal".

We are grateful for this input. We agree that stating an exact dimension in this case can be misleading, and have revised the manuscript to adopt $D \gg 1$ instead. The in-text references are now parenthetical and include a reminder (with reference to Ruelle) that estimation of such large dimensionality is difficult. In addition, the referee is correct that the stochastic signal is indeed a tachogram as suggested. We regret this mistake and have updated the manuscript accordingly.

3. “stochastic electrocardiogram (ECG) signal of figure 2(c)” this sounds incorrect.

We have updated this sentence to reflect the comment and response above regarding tachograms.

4. “Stochastic systems have some degree of randomness yet no underlying strange attractor.” I suggest rewriting this phrase as, in general in the field of nonlinear dynamics, stochasticity IS randomness and therefore has no underlying attractor.

We agree and have gladly updated this sentence to clarify this point.

5. “intrinsically nonlinear models, such as Markov...” what do you mean by “intrinsically non-linear”? Stochastic? Please rewrite or define terminology.

We regret the ambiguity of this statement. We have updated the text to more precise (Markov, Langevin, and Levy processes) and in line with current literature.

6. “After the $t \leq 300U/r_o$ transient...” I suggest replacing with “After the transient period $t < t_o = 300U/r_o$...”

We agree. The suggested wording is more clear and we have adopted it.

7. I had some difficulty with symbols in some equations. For instance, in (6) I don’t find ω_n , R_o , U or T , all of which are mentioned in the next line. For the sake of the reader, I suggest using the same symbols and providing the definitions in loco whenever other symbols are used.

We regret mislabeling r_o as R_o in (6) and not defining the final time T ; these have been corrected. The frequency ω_n is defined following (6) and U is the mean streamwise velocity, as defined in Sec. 3 and used throughout.

8. The first phrase in Sec. B.1 is “We next confirm that the flow is chaotic” which seems to reveal a methodological bias. You really want to show the flow is chaotic, but... (see my comments above about this).

We agree that this sentence is premature and, ultimately, not entirely substantiated. Further, we did not intend to signal any methodological biases. We have gladly recast this sentence.

9. In Sec. B.2 I got somewhat lost about your estimates of dimension. Fortunately you clearly stated in the Conclusions that $D > 10$ (although it is not clear to me where did you get this value from). I suggest this conclusion be made more clear in this section.

We have updated the manuscript to make these values more clear and precise.

10. Figure 8. I see no scaling region. I don’t think there is any scaling, which is, in fact, consistent with the conclusion that the dimension is very large.

The region for ℓ just larger than the “knee” location we label “scaling region” has been used to estimate the correlation dimension [75,87]. However, we agree with the referee that this evidence is tentative and have updated the figure and corresponding text to reflect this. We also augment our computations of the correlation dimension with an additional disclaimer that it is possible no robust scaling region exists, though this is also consistent with our conclusions (as you point out in the next comment).

11. Coming back to Ruelle’s paper, he argued that in order to correctly estimate the dimension D , its relation with the data length N should be $D \ll \log_{10}(N)$. Of course this “result” assumes that sampling is consistent with embedding theory, that is, the delay time is neither too long nor too short. In practice the delay time is much larger than the integration step. Well, I tried to find the data length and sampling time to see if, minimally, $D \ll \log_{10}(N)$ was being satisfied, but I failed to find that information. I would strongly encourage the authors not only to provide such information in this section too (assuming it is somewhere else in the paper — I couldn’t find it) and also to comment on the recommendation put forward by Ruelle. In any case, the results in this section are consistent with the main message of your paper: the dimensionality of the flow is very large and a stochastic model is probably the best choice of a compact model.

We agree that this discussion should have been included. We have added our values for this parameter to the text of this section and connected this result to our main point: the dimensionality is large and a stochastic model is more appropriate.

12. Figure 12. You divided your space in 20 possible states, but your Markov model shows 10. You say that “neighboring states are coalesced” but this is not totally clear to me. So, say, node 9, actually represents states 17 and 18. How are these connected. In short, I am unable to figure out, from Figure 12, what your full Markov model looks like.

Our presentation caused this confusion. The intention was that Figure 12 only serves as a visualization of state transitions. Neighboring states are also close in space, so coalescing them does not eliminate substantial information and, we believe, makes visualization clearer. We have updated this figure to indicate that each node in the network represents two neighboring Markov states, and have rephrased the caption to make these points more clear.

13. “For the Markov process (19), the left eigenvectors \mathbf{S} are statistically invariant distributions that can indicate recurring flow processes not identified via Fourier analysis.” It would be nice to have a reference here.

We have updated this sentence to include references, as suggested.

RESPONSE TO REFEREE #2
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Bryngelson, Guéniat, Freund

We are grateful for the referee's efforts in improving the quality of this paper. We quote the comments of the referee and discuss changes made to the paper in response to these comments in the following.

Referee #2:

The authors are considering the flow of red blood cells within cylindrical vessels using simulations. Their intention is to obtain its reduced order model by analyzing its time series data. Their approach is interesting, the reduced model they finally reached reproduced the statistics of the original high-dimensional system. Thus, I basically would like to support its publication after a revision on my following major concerns.

1. I could not find strong reasons on why we should use a stochastic model for reducing the underlying dynamics. For example, in Fig. 8, the scaling region of the correlation integral is not clear. I am feeling that this result should be associated with the fact that the underlying dynamics cannot be low-dimensional, rather than its stochasticity. The authors' main logic to reach a stochastic model seems to depend only on Refs. [14, 35]. Thus, it would be more desirable if the authors discuss why we should model the underlying dynamics with a stochastic model with more depth.

We appreciate this comment, which has led to better positioning of this whole issue in the revised paper. The difficulty in distinguishing a clear scaling region in Fig. 8, which we have updated the manuscript to discuss, also suggests a high-dimensional dynamic behavior, and section IV B 3 seeks to quantify this point directly. For these high-dimensional dynamics, stochastic models have been widely successful in the past. We have bolstered our references and discussion at the beginning of sections IV B 3 and IV C to reflect this.

2. As far as I have learned so far, modeling the underlying dynamics with a transition matrix is something similar to modeling the dynamics by a piecewise linear model, and mostly ignores its nonlinearity. Thus, it would be great if the authors could discuss the limits for the applicability for the proposed reduced model.

We are glad the the referee raised the point, and we have revised the paper to address it. Markov chain models intrinsically account for data nonlinearity via a training procedure (Eq. 18). This said, model improvements are likely possible. We have revised the manuscript to discuss these possibilities and limits at the end of section V.

3. How can the discretized model be used for its applications? If the authors generated a continuous model, I could imagine how they want to use the reduced model. Some discussions will help readers understand how, or in which applications the obtained reduced model will be used in the future.

Similarly, we are glad to address this in the paper. The discrete model generally follows from the discrete nature of our simulations and we did not attempt to formulate an interpolative (e.g., machine learned) model here. More discrete Markov states will correspond to a more accurate model and less required interpolation, though the exact number required is of course application dependent. We focused on the $N_p = 20$ parameterization in our manuscript since it was relatively small while still accurately reproducing the actual moments of the flow statistics and allowing for a useful physical interpretation of the model. We have appended the manuscript with additional discussion of these points.

4. P.20, line 7, “the cell kinetics we indistinguishable” seems to be “the cell kinetics were indistinguishable”.

This has been corrected.