Re: EY10205 From Baseline to Epileptiform Activity: A Path to Synchronized Rhythmicity in Large-Scale Neural Networks by Vladimir Shusterman and William C. Troy

July 26, 2007

Dear Dr. Foster,

We are re-submitting the revised manuscript referenced above, which incorporates modifications and clarifications suggested by the Reviewers. Every effort has been made to answer all the questions and criticisms raised by the Reviewers, as detailed in our point-by-point answers below.

Per your request, we have also clarified the extent of overlap of this paper with those cited in references 15 and 19 in previous version (in our answer to Reviewer’s #1 question 2).

Sincerely,

Vladimir Shusterman, MD, PhD
Cardiovascular Institute
University of Pittsburgh Medical Center
200 Lothrop Street, Room B535
Pittsburgh, PA, 15213
shustermanv@upmc.edu
412-647-6272
PROBLEMS WITH FIGURES:

In reviewing the figures of your paper, we note that the following changes would be needed in order for your figures to conform to the style of the Physical Review. Please check all figures for the following problems and make appropriate changes in the text of the paper itself wherever needed for consistency.

* Please supply us with separate PostScript figure files (in addition to your PDF/MSWord/PostScript manuscript file containing the figures).

* Captions to color PostScript figures should begin with "(Color online)", unless they are to be published in color in print, in which case they should begin "(Color)".

* Please ensure that captions and text references to the figures are appropriate for both online color and print grayscale versions, and that the figures will be sufficiently clear in both versions, since the same file is used for both versions. Please note that many standard colors have similar grayscale values and therefore may be indistinguishable in the print version (see http://forms.aps.org/author/h24coloronline.pdf for more information).

* The corresponding author of a submitted manuscript can check the PDF file of the latest version of their manuscript via logging into our submissions server (http://authors.aps.org/esubs/). New users can register at any time. All papers should be available via this service regardless of how they were submitted; hardcopy submissions are currently scanned. It may be to your advantage to view the version of the paper available to referees (if applicable) and editors. Any problems with figures and text should thus be identifiable.

Margaret Foster
Senior Assistant Editor
Physical Review E
The paper by Shusterman and Troy has been improved in the resubmission, and the relation to other papers have been clarified. Some work remains to be done in my opinion for publication in PRE. A basic problem remains the justification of the bold biological interpretations (epilepsy, remote synchronization), which require that the model be matched to the biology at least in the essentials.

1. "The authors must supply numerical values for *all* parameters used in their actual simulations, so that their results can be independently confirmed. In particular, epsilon, tau, R, theta_1, theta_2, and perhaps hidden parameters (see next point). This could be done in a table or one-by-one when the parameters are being introduced."

We have provided numerical values for all parameters (epsilon, tau, theta_1, theta_2), as suggested by the Reviewer, in the text that follows formula (1). The initial value of variable R(x,y,0)=0 is given in equation (3).

2. "The connectivities are represented by normed exponentially decaying Gaussians, see comment below Eq. (4). These Gaussians are presumably origin centered and isotropic? What then are the standard deviation (sigma) of these Gaussians actually used in the simulations? Are all these sigmas identical? *If so, how does that match with purely excitatory long-range connections in the real brain?*"

We apologize for the confusion. These Gaussians are indeed origin centered and isotropic. But these functions don’t include any noise/stochastic effects, and hence, the sigma values are not defined. To avoid ambiguity, we have provided the exact mathematical definition of this function on Page 6, Para 1 (\( \omega_{ij} \geq 0 \) denotes connectivity from population \( i \) to population \( j \) and has the typical connectivity form of \( \omega_{ij} = A e^{-\sqrt{x^2+y^2}} \) (in our computations in equation (4) we set \( \omega_{EE} = 2.1 e^{-\sqrt{x^2+y^2}} \)).

"It is not sufficient to refer to previous publications. First, the authors' work is not presented well, if one has to dig through references in order to guess at the precise maths used. Second, the authors claim to present novel findings on the synchronization of *remote* sites in the brain. Thus they *must* discuss the appropriateness of their modeling of long-range propagation. If they do have unphysiological long-range inhibition, and their results do not survive appropriate adjustment (e.g., setting the sigmas for the inhibitory connections differently), then not all may be lost: these results may then still be relevant for *short range* entrainment of neural masses in the cortex (with an exponential decay in the mm range!)."

As explained earlier, we have clarified the manuscript to explain that our model does not include stochastic effects and hence, does not have “sigma” values (see our answer to question #2 above).

We have also clarified the manuscript to explain that our model does not have non-physiological long-range inhibition, although it might be reproduced if necessary (Page 6, Para 1):
“In each equation the integral term with a negative sign in front represents the contribution from the population of inhibitory neurons. Hence, the excitatory and inhibitory functions representing non-local influences are always positive and clearly separated. The advantage of such a separation is in its flexibility to model various combinations of the two processes, which might exist in different experimental and clinical settings (at a cost of adding an additional equation to the system). Recently, Kang et al. have successfully used the flexibility of this approach to investigate the interactions between the spatial range of inhibition, its time constant, and the resulting electrophysiological pattern (REF).”

3. "In their experiment setting D1 and D2 to the *same* beta and *stimulating* D1 into self-sustained oscillation (SSO) all that is happening is that the activity waves travel to D2 and stimulate it into SSO as well. This is however not really "synchronization", it's more "activation spreading". If one blocked the activity waves from D1 and instead stimulated D2 separately, one would see exactly the same thing: due to the same beta, both D1 and D2 would be oscillating at the same frequency. So D1 and D2 did not synchronize with each other, rather D1 simply activated D2 here, and they happen to have the same "natural" oscillation frequency. To show proper *frequency locking*, the authors should set D1 at beta_1 leading to omega_1 frequency SSO, and D2 at a slightly *different* beta_2 leading to omega_2 frequency SSO. And then upon activating both (or one and letting it activate the other), they should find oscillations in the disks at frequencies Omega_1 = Omega_2 and the capital Omega do not have to be identical with the omega. In that case D1 and D2 have actually synchronized their frequencies by their interaction, usually by detuning somewhat from their "natural" frequency to the shared one. It would be interesting to see whether the system supports such proper frequency locking, and what difference in beta are possible before the disks synchronize to their own "natural" frequency (or the faster oscillation eats the slower one, if they are close)."

"I do not see what the current experiment with the same beta in D1 and D2 shows, other than that the "activity waves" are strong enough to trigger D2 into SSO."

We agree with the Reviewer that the part, describing the experiment with D1 and D2 having the same beta, did not provide substantial information and have deleted this part. To avoid ambiguity, we have also removed all references to the “synchronization of the two regions” from the Abstract and throughout the text of the manuscript.

3. “Is the integral part of the stimulus added at T1 an integral over omega_EI, see Eq. (2) and Table 1, or over omega_IE, see Appendix?”

Thank you for pointing our attention to this mishap. We have corrected this to read “omega_IE” in equation (2) and Table 1.

4. “The authors claim that stimulus input Psi plays a role only in the excitatory part, in spite of (now) being added to the inhibitory part as well. Does that statement include the strong shock at T2?”

Following the Reviewer’s comment, we have clarified this point in the manuscript. Specifically, we have explained that a combination of the activation factor Eta and...
stimulus \( \Psi \) in the equation describing the inhibitory activity \( I \) is sufficiently general to allow one to obtain a rich variety of dynamical patterns. When \( \eta \) is small and \( \Psi \) is absent (or small), the inhibitory activity \( I \) will remain relatively unchanged, leaving the dynamics of the model unchanged as well. On the other hand, when \( \eta \) becomes large enough, it can counterbalance \( \omega_{II} \) by itself (or in combination with \( \Psi \)). In the Appendix, for mathematical simplicity, we let \( \eta \) itself be large enough to negate the \( \omega_{II} \) term and to cause \( I \) to quickly and uniformly exceed the threshold. Then the presence of \( \Psi > 0 \) causes \( I \) to exceed the threshold even faster but does not change the dynamics of the system qualitatively. Thus, when \( \eta \) is sufficiently large, the presence of \( \Psi \) in the equation for the inhibitory activity \( I \) does not play a significant role in the dynamics of \( I \) whether or not there is a strong shock at \( T_2 \). We have modified the text of the manuscript as follows (Page 8, Para 1):

“A combination of the activation factor \( \eta \) and stimulus \( \Psi(x,y,t) \) in the equation describing the inhibitory activity \( I \) is sufficiently general to allow one to obtain a rich variety of dynamical patterns. When \( \eta \) is small and \( \Psi(x,y,t) \) is absent (or small), the inhibitory activity \( I \) will remain relatively unchanged, leaving the dynamics of the model unchanged as well. On the other hand, when \( \eta \) becomes large enough, it can counterbalance \( \omega_{II} \) by itself (or in combination with \( \Psi(x,y,t) \)). In the Appendix, for mathematical simplicity, we let \( \eta \) itself be large enough to negate the \( \omega_{II} \) term and to cause \( I \) to quickly and uniformly exceed the threshold. Then the presence of \( \Psi(x,y,t)>0 \) causes \( I \) to exceed the threshold even faster but does not change the dynamics of the system qualitatively. Thus, when \( \eta \) is large, the stimulus \( \Psi(x,y,t) \) plays a significant role in the dynamics of the system only in the excitatory part.”

5. “It is unclear to me what the precise state of the "time-varying (physiologically relevant) baseline" (Table 1, entry IV) actually is, which is then shocked into epilepsy. If this is a truly "natural" state as in for example Bojak & Liley PRE 71 (2005) 041902, i.e., \( 1/f+alpha \) with reasonable firing rates, then that should be mentioned and perhaps shown with a power spectrum. If it is not, then it should be motivated why this is not so important here, e.g., by pointing out different goals the Bojak & Liley paper may have had.”

The Reviewer is correct: the goals of our study were different from those in the study of Bojak & Liley PRE 71 (2005) 041902. We did not attempt to reproduce a realistic power spectrum (\( 1/f+alpha \) with reasonable firing rates) which represents a complex combination of a number of electrophysiological processes. Theoretically, it is possible to extend our approach in this direction (by adding more appropriately chosen components to the stimulus function \( \Psi \)), but it would divert the paper from the main subject of our study. Our goal was to describe general properties (principles) of the system dynamics/transformations from mathematical rest to a more realistic (time-varying) state, referred to as the “time-varying or physiologically relevant” baseline (Table 1), and finally to a state of SSO. This description is intended as a first step towards development of future models that might include more complex, multi-component stimuli \( \Psi \) for specific physiological settings. We have clarified the text accordingly (Page …, Para …):

“Previously, Bojak and Liley have reproduced a realistic spectrum of electrophysiological activity in a mean-field model (REF). In this study, we did not attempt to reproduce a realistic power spectrum which represents a combination of a number of electrophysiological processes. Theoretically, it is possible to extend our approach in this direction by adding more appropriately chosen components to the stimulus function \( \Psi(x,y,t) \). However, our goal was to describe general properties (principles) of the system dynamics and transformations from mathematical rest to a more realistic (time-varying) state, here referred to as the time-varying baseline, and finally to a state of SSO.”
6. "Table 2 does not illustrate the claim that "delta-t gives a 5% error of the numerically computed solutions". It should. I suggest to show: beta, delta-t, T, c, delta-t/T*c (i.e., the prediction), and RATE (i.e., the numerical result). Note also that the table has a capital "C" whereas the text has a "c"."

Thank you. We have replaced “C” with “c” in Table 2, and added a comparison between predicted and computed values, as suggested by the Reviewer. We have also corrected the estimate of error presented in the previous version of the manuscript (that estimate was inaccurate) and provided detailed description of the numerical experiments and the error estimation for each value of beta. Because the error accumulates as the number of oscillatory cycles increases, we have also provided the estimates for the error per oscillatory cycle, as well as the accumulated error over all oscillatory cycles required for the leading edge of the region of SSO to reach x=100.

7. “Panel 2 B bottom shows data from which delta-t and T could be estimated. Thus at least one could compute the ratio RATE/c to see whether the model predicts that epilepsy spreads faster or slower than normal brain activity. If one were given the data from a second electrode at some distance, one should be able to estimate RATE and/or c as well, thereby really constraining Eq. (8).”

We thank the Reviewer for this interesting suggestion and have included the following paragraph in the text of the manuscript (Page…, Para…):

“Comparison of the theoretically predicted and experimental RATE in a human case study. To compare the RATE predicted by formula (8) with experimental data obtained by Towle et al., by placing an array of recording electrodes on the cortical surface of a human subject experiencing epileptic seizures, we estimated the period T and the length $\Delta t$ of the concave segment in each oscillatory waveform of the human corticographic recording in Figure 2, Panel C. Using this estimation, we found that the values of T and $\Delta t$ in each cycle lie in the ranges

$$0.21 \text{ s} \leq T \leq 0.22 \text{ s} \quad \text{and} \quad 0.03 \text{ s} \leq \Delta t \leq 0.05 \text{ s}.$$ 

From these bounds we obtained the range $0.136 \leq \frac{\Delta t}{T} \leq 0.238$. Substituting these bounds into formula (8), and using experimentally measured wave speed $c$ in the human visual cortex (22.4 mm/s$^2$), we obtain the range of theoretically predicted RATE

$$3.046 \text{ mm/s} \leq RATE_{\text{THEOR}} \leq 5.331 \text{ mm/s}.$$ 

(9)

Next, we estimated the rate of migration of the leading edge of synchronized oscillatory activity from the simultaneous multi-electrode “maps” of cortical activity constructed by Towle et al., which gave an experimentally measured RATE $\approx 4$ mm/s. Note the experimentally measured RATE is within the range of the theoretically predicted values, despite the approximate values used in these computations. Summarizing, the ratio RATE/c predicts that the leading edge of the region of synchronous seizure activity migrates approximately 4-7 times slower than normal brain wave activity, which is not in disagreement with the results of human case study of epileptic seizure reported by Towle et al. These preliminary data also suggest that further research into the accuracy and generalizability of formula (8) for different populations and types of epileptiform activity is warranted.”

8. "The citation of the Robinson et al. model for "alpha by a wave equation" is entirely misplaced. It is well-known that the Robinson et al. model does *not* produce proper alpha without their thalamocortical feedback loop, which they added at some stage to their model (basically, the alpha rhythm results from the time to complete the loop). The authors would be better off addressing the Bojak & Liley PRE
paper in this way, for there at least alpha is generated dynamically only between coupled cortical populations. This is more comparable to what is done in this paper. But they should realize that the Liley group itself claims that it is local inhibitory-inhibitory feedback, rather than long-range "wave dynamics", which yields their alpha.

The authors are strangely enthusiastic about "not having a wave equation", given that such wave equations quite generally arise "effectively" as a result of the same sort of connectivity they assume as well. See the seminal Jirsa and Haken Phys Rev Lett 77 (1996) 960, Eqns. (11), (14) and (15), and Liley, Cadusch, Dafilis, Network: Comput Neural Syst 13 (2002) 67-113, Appendix B, for two dimensions. Other mean field models simply separate out their impulse conduction, and when that is approximated with a PDE, "wave equations" result.”

We have removed the citation to Robinson and added the citation to the Bojak & Liley PRE study, as suggested by the Reviewer. See our answer to the question 5 above. We have removed the statement in question about not having a wave equation in our model to avoid confusion.

“I also note that cortical synchronization already has been seen in other mean field models, e.g., Bojak & Liley Neurocomputing 70 (2007) 2085-2090.”

We have added the information that cortical synchronization already has been seen in other mean field models and included the citations to several previous studies suggested by Reviewer #2 and to the study of Bojak & Liley published in Neurocomputing 70 (2007) 2085-2090 suggested by Reviewer #1 (Page..., Para...):

“"Our work further extends a large body of work on pattern formation, including global oscillations (i.e. cortical synchronization) and more complicated behavior, that have been well documented in neural field models (REF). Similar field models with non-local coupling have been described by Ermentrout (REF), Gerstner and Kistler,43 Coombes.44 and Bojak and Liley (REF).”

9. "On page 7, there's a reference "(1.1)", which presumably should be "(1)". There seems to be a hard to see black curve in the right top panel of Fig. 1, presumably a sub-threshold curve which can't be discerned (or is absent) in the left panel? The presentation thereof should be improved, or removed."

The reference in question and the Figure have been corrected as suggested by the Reviewer.
Second Report of the Second Referee -- EY10205/Shusterman

Overall, I find the resubmitted manuscript a more focused and clearer study. The authors have, for the most part, given satisfactory rebuttals to my previous remarks. I only have one major point as well as a few minor ones.

1. "In response to my criticism of their work fitting in to a large body of work on pattern formation in neural fields the authors state: "However, previous studies (in particular, those described in the review article by Ermentrout cited by the reviewer) are devoted to WC field models without non-local, spatial terms. The novelty of our study is in the analysis of oscillations and dynamical patterns in a WC field model that does include non-local, spatial terms, which make the model more relevant in representing the spatially averaged effects of long-range connections."

I disagree on this point. The Ermentrout review has a clear section on field models with spatial -- "non-local" coupling (sections 6 and 7 of the review). In addition the textbook by Gerstner and Kistler -- Spiking Neuron Models (2002), as well as the review by Steve Coombes (S Coombes 2005 Waves, bumps, and patterns in neural field theories, Biological Cybernetics, Vol 93, 91-108) all treat spatially distributed field models. The submitted paper, as originally written, had the feel to it as if the authors were proposing this approach for the first time -- which is certainly not the case. However, this is not to say the authors do not present new results. In particular, the refractory variable $R$ is new as well as the specific forcing function chosen. In the new manuscript the authors cite a few more background studies, however, citations to a few reviews on spatial field models (those above for instance), as well as admitting that there is a vast literature already, is in order. This will help orient the readers to identifying what is new in the paper, compared to replication of older work."

We have removed the statement in question from the discussion and added the following information as suggested by both Reviewers (Page..., Para...):

“Our work further extends a large body of work on pattern formation, including global oscillations (i.e. cortical synchronization) and more complicated behavior, that have been well documented in neural field models (REF). Similar field models with non-local coupling have been described by Ermentrout (REF), Gerstner and Kistler, Coombes, and Bojak and Liley (REF). Our work further extends these studies and provides new results with respect to the refractory variable $R$ as well as the specific forcing (the activation factors $\gamma$ and $\eta$, and stimulus function $\Psi(x,y,t)$) that effectively force the system to undergo a series of transformations from mathematical rest to the baseline state and, ultimately, to self-sustained oscillatory activity.”

2. "Rather than refer to single cell activity as "voltage", use "membrane potential" to be more specific."

Thank you. The word "voltage" has been replaced by "membrane potential" as suggested by the Reviewer.

3. "On page 6. the authors refer to $f(u)$ as a "probability-based" sigmoid function."
The function $f(u)$ is not really based on any stochastic treatment yet is "inspired" by the smooth $f-u$ curves observed in stochastic models. Since $f(u)$ ends up being a Heaviside function remove the connection to probability since it may be confusing.”

The text has been modified as suggested by the Reviewer. Thank you.

4. Table 1. Fourth row -- 2nd column. Replace "blocks" with "counterbalances"

Thank you. The table has been modified as suggested by the Reviewer.

5. Figure 1 -- third and fourth row really does not show any bistability. Please show stable fixed point attractor and time series to indicate the bistability.

The figure has been modified as recommended by the Reviewer. To clarify the two trajectories, we have marked them by different colors and, in addition, showed the two trajectories, associated with bi-stability (at beta=12.61), in two separate panels (rows 2 and 3). The 2nd row shows self-sustained oscillations (caused by a stronger stimulus $\zeta(x,y,t)$) and the 3rd row shows the trajectory (caused by a weaker stimulus) decaying to the stable rest state.

======================================================================

IMPORTANT: We cannot publish your manuscript without the following information:

We have yet to receive a valid copyright form for this manuscript.

Copyright can be transferred via a simple web interface as part of the electronic (re)submission process (http://authors.aps.org/ESUB). Alternatively, the Copyright Transfer form is available for download at:


Please see the following forms:

  Copyright notice to author
  Copyright Transfer form - Physical Review (Copy included)
The following transfer agreement must be signed and returned to the APS Editorial Office, 1 Research Road, Ridge, NY 11961-2701 before the manuscript can be published). For further information about APS policies and practices regarding copyright, see http://forms.aps.org/author/copyfaq.html.

Article Title: From baseline to epileptiform activity: A path to synchronized rhythmicity in large-scale neural networks

Names of All Authors: Vladimir Shusterman, William C. Troy

TRANSFER OF COPYRIGHT AGREEMENT

Copyright to the above-listed unpublished and original article submitted by the above author(s), the abstract forming part thereof, and any subsequent errata (collectively, the `Article') is hereby transferred to the American Physical Society (APS) for the full term thereof throughout the world, subject to the Author Rights (as hereinafter defined) and to acceptance of the Article for publication in a journal of APS. This transfer of copyright includes all material to be published as part of the Article (in any medium), including but not limited to tables, figures, graphs, movies, and other multimedia files. APS shall have the right to register copyright to the Article in its name as claimant, whether separately or as part of the journal issue or other medium in which the Article is included.

The author(s), and in the case of a Work Made For Hire, as defined in the U.S. Copyright Act, 17 U.S.C. S 101, the employer named below, shall have the following rights (the `Author Rights'):

(1) All proprietary rights other than copyright, such as patent rights.
(2) The nonexclusive right, after publication by APS, to give permission to third parties to republish print versions of the Article or a translation thereof, or excerpts therefrom, without obtaining permission from APS, provided the APS-prepared version is not used for this purpose, the Article is not published in another journal, and the third party does not charge a fee. If the APS version is used, or the third party republishes in a publication or product charging a fee for use, permission from APS must be obtained.
(3) The right to use all or part of the Article, including the APS-prepared version without revision or modification, on the author(s)' web home page or employer's website and to make copies of all or part of the Article for the author(s)' and/or the employer's use for lecture or classroom
purposes. If a fee is charged for any use, APS permission must be obtained.
(4) The right to post and update the Article on free-access e-print servers
as long as files prepared and/or formatted by APS or its vendors are not used
for that purpose. Any such posting made or updated after acceptance of
the Article for publication shall include a link to the online abstract
in the APS journal or to the entry page of the journal. If the author wishes
the APS-prepared version to be used for an online posting other than on the
author(s)' or employer's website, APS permission is required; if permission is
granted, APS will provide the Article as it was published in the journal, and
use will be subject to APS terms and conditions.
(5) If the Article was prepared under a U.S. Government contract, the
government shall have the rights under the copyright to the extent
required by the contract.

All copies of part or all of the Article made under any of the Author Rights
shall include the appropriate bibliographic citation and notice of the APS
copyright.

By signing this Agreement, the author(s), and in the case of a Work Made
For Hire, the employer, jointly and severally represent and warrant that
the Article is original with the author(s) and does not infringe any
copyright or violate any other right of any third parties, and that the
Article has not been published elsewhere, and is not being considered
for publication elsewhere in any form, except as provided herein. If
each author's signature does not appear below, the signing author(s)
represent that they sign this Agreement as authorized agents for and on
behalf of all the authors, and that this Agreement and authorization is
made on behalf of all the authors. The signing author(s) (and, in the
case of a Work Made For Hire, the signing employer) also represent and
warrant that they have the full power to enter into this Agreement and
to make the grants contained herein.

_____________________________  ______________________________
Author's Signature                                            Date

__________________________________________________________________________
Name(s) (print)

If the Article has been prepared as a Work Made For Hire, the transfer
should be signed by both the employee (above) and the employer (below):

_____________________________
Employer

_____________________________  ______________________________
Authorized Signature(s) Name(s) (print)          Title          Date

U.S. GOVERNMENT EMPLOYEES

A work prepared by a U.S. Government officer or employee* as part of his or
her official duties is not eligible for U.S. copyright. If at least one of
the authors is not in this category, that author should sign the transfer
Agreement above. If all the authors are in this category, one of the authors
should sign below, and indicate his or her affiliation.
* Employees of national laboratories, e.g., Brookhaven National Laboratory, are not U.S. Government employees.

---