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Stabilization of 3D scroll waves and suppression of spatio-temporal chaos by heterogeneities

Florian Spreckelsen,[1,2] Daniel Hornung,[1] Oliver Steinbock,[3] Ulrich Parlitz,[1,4,5] and Stefan Luther[1,4,5]

[1]*Max Planck Institute for Dynamics and Self-Organization Am Faßberg 17, 37077 Göttingen, Germany*
[2]*Institute for Theoretical Physics, Georg-August-Universität Göttingen, Friedrich-Hund-Platz 1, 37077 Göttingen, Germany*
[3]*Department of Chemistry and Biochemistry, Florida State University, Tallahassee, FL 32306-4390, United States*
[4]*Institute for Nonlinear Dynamics, Georg-August-Universität Göttingen, Am Faßberg 17, 37077 Göttingen, Germany*
[5]*German Centre for Cardiovascular Research, partner site Göttingen, 37077 Göttingen, Germany*

Scroll waves in a three-dimensional medium with negative filament tension may break up and display spatio-temporal chaos. The presence of heterogeneities can influence the evolution of the medium, in particular scroll waves may pin to such heterogeneities. We show that as a result the medium may be stabilized by heterogeneities of a suitably chosen geometry. Thin rod-like heterogeneities suppress otherwise developing spatio-temporal chaos and additionally clear out already existing chaotic excitation patterns.

I. INTRODUCTION

The emergence of nonlinear spatio-temporal patterns in excitable media has been extensively described for chemical [1–4] and biomedical systems [5, 6]. In the latter case, the view of the heart as an excitable medium offers an explanation for the propagation of electrical activation waves. Valuable insight can be gained already by considering the heart as a two-dimensional medium [7, 8]. For potentially fatal conditions such as ventricular fibrillation, however, it is necessary to take into account the full three-dimensional dynamics including the formation of scroll waves.

Often, the evolution of phase singularities is sufficient to describe the characteristic dynamics of excitable media. In three-dimensional systems, these phase singularities form *filaments*, the center lines of rotating scroll waves. The stability of the filament length, i.e. whether small perturbations from a straight line will shrink or grow, is determined by the filament tension (see [9]). The sign of the filament tension determines the qualitative dynamics: perturbations shrink for positive and grow for negative filament tension. This growth may eventually lead to turbulent behavior of the medium and to breakup of the filament at system boundaries.

In this article we investigate the dynamics of scroll waves in a medium with heterogeneities. These heterogeneities introduce additional no-flux boundaries into the otherwise homogeneous medium. Examples for such heterogeneities in the cardiac muscle are blood vessels or damaged tissue. The impact of the cardiac vasculature on the response of tissue to external stimulation as required by low-energy defibrillation methods has been shown previously [10]. Tissue damage may occur due to the local lack of oxygen during traumatic events such as infarction. Subsequently the lesion undergoes a complex remodeling process but always results in a region of reduced conductivity and contractility. We show that the presence of cylindrical heterogeneities in an excitable medium can lead to a stabilization even in the case of negative filament tension. As an example Fig. 1 shows a scroll wave that is already partly pinned to a cylindrical heterogeneity. Similarly to spiral waves in two dimensions [11], a pinned scroll wave can synchronize the full medium due to its higher rotation frequency. This extends previous findings by Jiménez and Steinbock [12] on the self-wrapping of filaments with positive tension around continuous cylindrical heterogeneities.

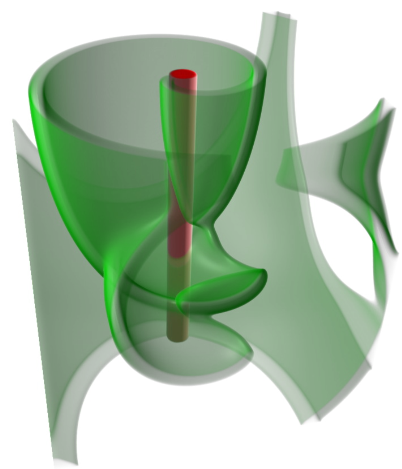


FIG. 1. (Color online) Scroll wave which is partly pinned to a heterogeneity (vertical cylinder). The simulation was started with initial conditions as described in Sec. V A. An intermediate state is shown where the scroll wave is only attached to the upper part of the heterogeneity, the rest of the medium is not synchronized yet.

II. METHODS

In the following, we use the Barkley model [13, 14] as a model for excitable media. It describes two variables u and v, whose dynamics are governed by a set of reactiondiffusion equations

$$\frac{\partial u}{\partial t} = \frac{1}{\varepsilon}u(1-u)\left(u - \frac{v+b}{a}\right) + \nabla^2 u \quad (1)$$

$$\frac{\partial v}{\partial t} = u - v \quad (2)$$

with parameters a, b and ε. ε is chosen to be small and determines the relative time scale of the dynamics of u. For all simulations, $\varepsilon = 0.02$ is used. The parameters a and b determine the dynamics of the excitation of the medium. In two-dimensional media spiral waves and in three-dimensional scroll waves typically emerge.

The Laplace operator in Eq. (1) is approximated using a 9-point (2D) or 27-point (3D) discretization on a square lattice. The local dynamics in the Eqs. (1) and (2) are solved using explicit forward Euler steps. In all simulations, no-flux boundary conditions between inside and outside are used at the boundaries of the simulation lattice and of the heterogeneities. The latter are implemented using the phase-field method described in [15]. The phase-field method represents the geometry of a simulated medium by a phase field with values between 0 (outside) and 1 (inside) and implements obstacle boundaries as interfaces of finite width.

The Barkley model parameters a, b are chosen such that the negative filament tension is maximized: We simulated the growth of a slightly perturbed, straight filament (as described in Sec. IV A) in the three-dimensional Barkley model for $0.5 \leq a \leq 0.9$ and $0.01 \leq b \leq 0.1$. To exclude parameter pairs (a, b) which allow no spiral and scroll waves, we added the condition $b \leq \frac{a}{6} - \frac{1}{30}$ (see [14], Fig. 4). As a result from these simulations, we choose $a = 0.54$ and $b = 0.055$, because this set of parameters yields the most negative filament tension, i.e. a filament of a free scroll wave with these parameters grows the fastest.

III. SPIRAL WAVE PERIODS IN THE TWO-DIMENSIONAL MEDIUM

A. Setup

In order to choose a favorable heterogeneity size, we perform two-dimensional simulations with a circular heterogeneity of varying size.

The integration of the Eqs. (1) and (2) is carried out on a 100×100 lattice covering a two-dimensional domain of size 20×20 with spatial discretization $\Delta x = 0.2$. Unless noted otherwise, further sizes in this text are given in system units, not lattice points. For the used parameters, the side length 20 of the simulated medium is roughly one spiral wave length. The time step for the Euler integration is $\Delta t = 0.0005$.

As the periods of spiral waves pinned to a circular obstacle are to be examined, a circular heterogeneity with radius r is placed in the middle of the medium. The radius of this heterogeneity is varied from 0 to 4 in steps of 0.2, corresponding to the chosen Δx. Results obtained from radii up to about 0.6 are expected to suffer from the finite interface width of the heterogeneity boundary introduced by the phase-field method. The pinning of a freely rotating spiral wave to a heterogeneity strongly depends on the size of the obstacle and on the distance between spiral wave tip and obstacle [16]. For sizes of the heterogeneity which allow pinning we want to examine pinned spirals. Therefore, we construct the initial conditions as follows: we take the u, v values of a freely rotating spiral and translate it so that its tip would lie inside the heterogeneity (for $r > 0$).

For each radius, the spiral periods are measured by averaging the time differences between two consecutive maxima of u at a fixed point, distant to both the obstacle and the boundary. To exclude influences from transients after initialization, the measuring of the periods starts at $t = 25$, i.e. after roughly four free spiral periods for the chosen parameters. The overall simulation time is 100.

B. Results

The period T of a pinned spiral wave as a function of the heterogeneity's radius r is shown in Fig. 2. For unpinned spirals (radii smaller than 1.5), the variance between measurements and deviations from a constant value are caused by spiral meandering. Since the period is recorded at a fixed point on the lattice, meandering influences the duration between two maxima of u and thus the measured period.

For $r \leq 1.4$ the periods of spirals in presence of a heterogeneity are nearly the same as the period of a free spiral wave i.e. a spiral wave in a homogeneous medium ($r = 0$) which is $T_f = 7.04$. For these radii, the heterogeneities are too small for the spirals to pin permanently (see e.g. [16]).

The spiral waves stay permanently pinned to heterogeneities with $r \geq 1.6$, a radius which is large enough such that boundary effects from the phase-field method do not dominate. The measured periods increase nearly linearly with larger radii as predicted earlier [17–19]. For the smallest heterogeneities to which the spiral can pin – those with radius $1.6 \leq r \leq 2.4$ – the periods of the pinned spirals are shorter than that of a free one. In this range, the smallest period is $T = 4.98$ at $r = 1.6$, which is about 25.6% smaller than the period of a free spiral.

IV. SCROLL WAVE STABILIZATION IN THE THREE-DIMENSIONAL MEDIUM

In the preceding section we showed that spiral waves pinned to small heterogeneities can have a reduced period compared to that of a free spiral. In this section we will explore this effect for scroll waves in the presence of heterogeneities in a three-dimensional medium.

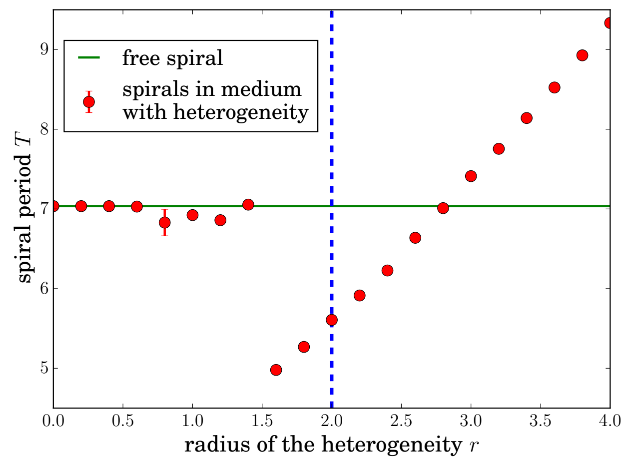


FIG. 2. (Color online) Periods T of spiral waves in the two-dimensional Barkley model pinned to circular heterogeneities with radii $0 \leq r \leq 4$. The vertical dashed blue line denotes the radius used for further simulations, the horizontal solid green line is the spiral period of a freely rotating spiral. For comparison with longer periods, additional simulations (Fig. 6) are performed for $r = 3.6$. The error bars denote ten standard deviations between subsequent periods. The standard deviation is nonzero for the unpinned spirals due to spiral wave meandering. The system size is 20×20. Model parameters are $a = 0.54$, $b = 0.055$ and $\varepsilon = 0.02$.

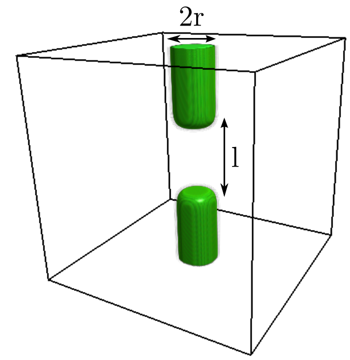


FIG. 3. (Color online) Example of a cylindrical heterogeneity with a gap. The system size is $20 \times 20 \times 20$, the cylinder radius $r = 2$ and the length of the gap $l = 6$. The cylinder caps appear rounded due to the phase-field method.

It is known (e.g. [11]) that in an excitable medium with two or more excitation sources, the fastest source dominates the overall dynamics. Since a spiral wave pinned to a small heterogeneity can rotate faster than an unpinned one, we expect that a system with a scroll wave which is at least partially pinned to a cylindrical heterogeneity of a similarly small radius will be governed by the frequency of the pinned scroll wave and the geometry of the heterogeneity. As a result, for system dynamics with negative filament tension, the part pinned to the heterogeneity could prevent the filament from growing and thus prevent the scroll wave from eventually breaking up.

To verify this hypothesis, we investigate a scroll wave with negative filament tension pinned at both ends to heterogeneities; that is, to a cylindrical obstacle of radius r with a gap of length l in its middle as shown in Fig. 3. As can be seen in Fig. 3, the edges of the cylinders are smoothened by the phase-field method.

To characterize filament stabilization, we first apply the skeletonization algorithm [20, 21] of the image processing software Fiji [22, 23] to the detected filament locations and subsequently measure the length of the skeletonized filament by adding the distances between the filament pixels. The breakup of a filament is typically preceded by a growth of this measured filament length. We consider a simulated medium stabilized if it does not break up until the end of the simulation. The volume rendering engine Voreen [24] (version 3.0.1) is used for visualization.

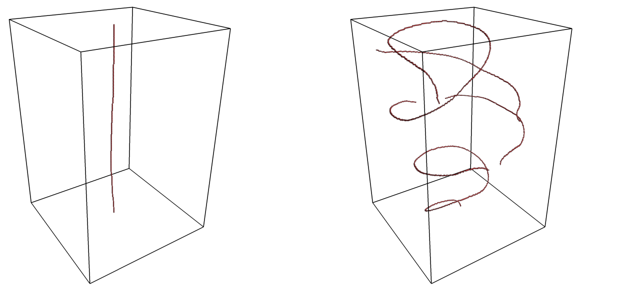
A. Setup

We want to statistically analyze the filament stability depending on gap size and simulation time and therefore vary the gap sizes and use randomized initial conditions. Using the same spatial resolution as in two dimensions, the three-dimensional simulations are carried out on a system of size $40 \times 40 \times 60$ (x, y, z). At this size we expect no noticeable effects of the boundaries on the dynamics while the computational effort is kept at a tolerable level.

Again, the time step for the Euler algorithm is $\Delta t = 0.0005$; the total simulation time for each simulation is 500 time units or roughly 100 periods of the corresponding pinned 2D-spiral. As an additional stopping condition, the simulation stops if the filament breaks up i.e. if more than one filament is detected in the medium. The gap size l in the cylinder of length 60 which is oriented in z direction and centered in the xy plane, is varied in steps of 2 ranging from 0 to 60, i.e. the results include one continuous cylinder ($l = 0$) and a medium without heterogeneities ($l = 60$).

Our aim is to investigate the behavior of a scroll wave with a nearly straight filament which connects the two obstacle ends. Since filament tension has no effect on a perfectly straight filament, we used slightly perturbed initial conditions: We construct 13 distinct initial filaments from a linear combination of six sinusoidal modes with random amplitudes, each with a different random number generator initialization. The maximal perturbation amplitude, i.e. the maximum distance from the axis of the heterogeneity is limited to 1. For each initial filament realized that way, simulations are carried out for all gap lengths.

A radius $r = 2$ is used for the cylindrical heterogeneities to investigate the predicted stabilizing effect of the shortened spiral wave period. Since we are only interested in the qualitative effects of the shortened period, it should not matter which exact radius is chosen as long



(a) $t = 0$ (b) $t = 68.75$

FIG. 4. (Color online) Initial (a) and final (b) filament of a free scroll wave in the Barkley model described by Eq. (1) and (2) with parameters $a = 0.54$ and $b = 0.055$. During a simulation from $t = 0$ to $t = 68.75$, the filament grows strongly and finally breaks up.

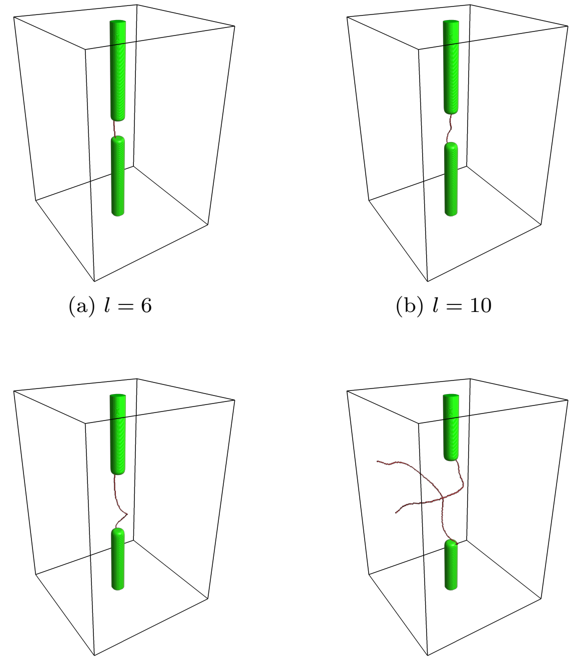
as it fulfills $T < T_f$. Not choosing the smallest radius $r = 1.6$ (see Fig. 2) reduces numerical artifacts resulting from the phase-field method[1]. For comparison we also carry out simulations with $r = 3.6$ (i.e. $T > T_f$) to be able to distinguish effects of a shortened period from general effects of a discontinuous heterogeneity.

For each simulation, we evaluate the stability of the scroll wave by measuring the filament length. If the filament does not break up until the end of the simulation, we consider the system to be stabilized by the heterogeneity with the tested gap length.

B. Results

The evolution of the filament of a free scroll wave in a homogeneous medium is shown in Fig. 4, at $t = 0$ and $t = 68.75$. Due to negative filament tension, the filament has grown significantly and has finally broken up into three parts.

The simulations described above are carried out for 13 different realizations of the initial filament. In general, these simulations show that there are three types of systems characterized by gap length: In systems with large gaps, the filament grows rapidly and breaks up during the simulation time in all simulated cases. Similarly, systems with small gaps lead to stabilization of the filament in all 13 realizations. However there are also systems with intermediate gap lengths, where the growth and the breaking up of the filament depend on the initial conditions.



(a) $l = 6$ (b) $l = 10$ (c) $l = 18$ (d) $l = 26$

FIG. 5. (Color online) Filaments of scroll waves pinned to discontinuous heterogeneities of radius $r = 2$ with different gap lengths $l = 6, 10, 18, 26$ either at $t = 500$ (end of the simulated period) or for $l = 26$ at $t = 278.75$. For all obstacles with $l \leq 20$, the waves remain pinned and the filament is stabilized in this realization; for the heterogeneities with larger l, the wave unpins and breaks up.

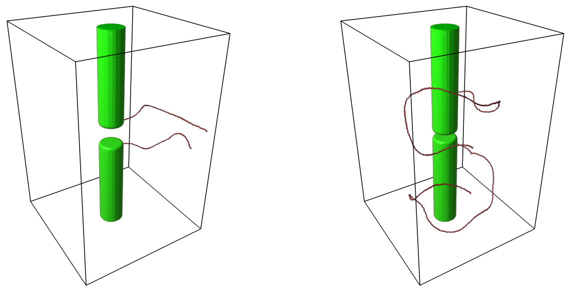
For scroll waves pinned at both ends to discontinuous heterogeneities of different gap lengths l, the situation at the end of the simulation period is depicted in Figs. 5(a) to 5(d). For the shown simulations, at small gap sizes $l \leq 20$ the filament did not break up, the structure remains almost linear despite the negative filament tension; the filament is stabilized between the two parts of the heterogeneity. Other simulations showed comparable results in that smaller gaps tended to stabilize the system.

For gap sizes $l > 20$ the filament tends to grow in our simulations; the scroll wave unpins and eventually breaks up like the free filament does, although the growth is generally slower and the breaking up is delayed compared to the free scroll wave after the same simulation time.

Figures 6(a) and 6(b) show simulations with the same initial conditions as Fig. 5 at $t = 50$. Here the heterogeneities have a larger radius $r = 3.6$, which leads to $T > T_f$. Obviously the filaments are not stabilized; they unpin and break up even for the smallest simulated gap length. The result is the same for all other simulated gap lengths l.

For the smaller radius $r = 2$, the evolution of filament lengths of systems with different gap sizes is shown in Fig. 7. Here the filament lengths, relative to the box

[1] At this radius the interface width of the phase field becomes essential. In pilot simulations, the filament unpinned for $\xi = 1$ (interface width about 0.8) and remained pinned for $\xi = 0.75$ (interface width around 0.6), here the parameter ξ from [15] governs the interface width.



(a) $l = 6$ (b) $l = 2$

FIG. 6. (Color online) Filaments and obstacles with $r = 3.6$ (i.e. $T > T_f$) at $t = 68.75$ (a) and $t = 88.75$ (b). The initially pinned scroll waves break up and unpin; even for relatively small gap lengths $l = 6$ and $l = 2$.

length, averaged over the 13 realizations for gap sizes 20, 24, 26, 28, and 32 are shown over simulation time. The shaded regions denote the standard deviation among the corresponding filament lengths[2]. Each white dot corresponds to the termination of one realization due to filament breakup. The curves end prematurely if all the scroll waves in all realizations have broken up before reaching the simulation time limit at $t = 500$. If at least one realization survives over the whole simulation time, the survival rate is shown. The survival rates are again shown in Fig. 8 as functions of time.

In all systems with gap size $l \geq 28$, the filaments in all realizations grow rapidly leading to their breaking up significantly before reaching the simulation time limit. Only $l = 28$ and $l = 32$ are depicted in Fig. 7, however the overall picture is the same for all larger l. For smaller gap sizes, the stabilizing effect of the heterogeneities increases, leading to no breaking up in the simulations for $l = 20$. Except for minor oscillations the average filament length stays constant at about 1.2 times the box length. For even smaller gap lengths, breaking up of filaments only occurs rarely. For example, for gap length $l = 18$ this happened 1 out of 13 times.

The two examples of an intermediate gap length, $l = 24$ and $l = 26$, show the breaking up with some — in the case of $l = 26$ all but one — initial conditions after a certain simulation time. In contrast, other initial conditions do not show an extreme growth of the filament during the simulation; the filaments survive over the whole simulation period. The survival of the filament thus is highly sensitive to the initial filament, since different realizations only differ in the random deviation of the filament from the axis of the heterogeneity. The evolution of the surviving filaments at intermediate gap lengths shows no different behavior compared to the evolution of filaments in small gap systems over longer times. Even those filaments which break up at a later point in simulation time may at first show a similar evolution as the surviving ones. We were not able to identify a sharp boundary between intermediate and small gap lengths, where no initial condition would lead to filament breakup. The evolution of the average filament lengths in Fig. 7 looks similar for all l for short simulation times up to $t \approx 100$. Thus, it seems to be impossible to decide whether a scroll wave will break up based on the transient during the first 15 to 20 rotational periods only.

[2] If a filament breaks up before reaching the simulation time limit at $t = 500$, we included its final length before breakup into the calculation of the standard deviation.

V. OTHER INITIAL CONDITIONS

In the previous section we have shown that for one very special kind of initial conditions heterogeneities of adequate size stabilize scroll waves that would break up without the presence of these heterogeneities. The scroll waves we presented in this article so far were initiated with an almost straight filament and thus, were almost cylindrically symmetric. In the following we will test whether stabilization can be observed for other scroll waves. The radius of all heterogeneities is kept at $r = 2$. Because the stabilization effect was observed for all investigated system sizes, we limit ourselves to a system size of $20 \times 20 \times 20$ in order to reduce computation time.

A. Toroidal scroll wave

The initial conditions shown in Fig. 9(a) correspond to those in the simulations presented in [12]. A quarter of a toroidal scroll wave connected to one heterogeneity is used as initial conditions. In contrast to the previously described initial conditions, the corresponding filament does not connect both heterogeneities (see Fig. 9(a)). During simulation the filament grows due to the negative filament tension and eventually reaches both heterogeneities. For small gap sizes $l \leq 14$, the filament is stabilized at $t = 100$ as shown in Fig. 9(b).

B. Initially broken up scroll wave

As the previous initial conditions have shown, the effect of stabilization occurs at least for some favorable initial conditions: there is only one filament which already connects initially to at least one of the two heterogeneities. We now use an already broken up scroll wave as initial condition. Figures 10(a) and 10(b) show initial and final (at $t = 200$) state of the simulation for a gap length $l = 6$. As one can see, again, the filament is stabilized. In further simulations, other similarly broken up scroll waves are used as initial conditions. These simulations yield essentially the same results, although the time needed for stabilization to occur varied.

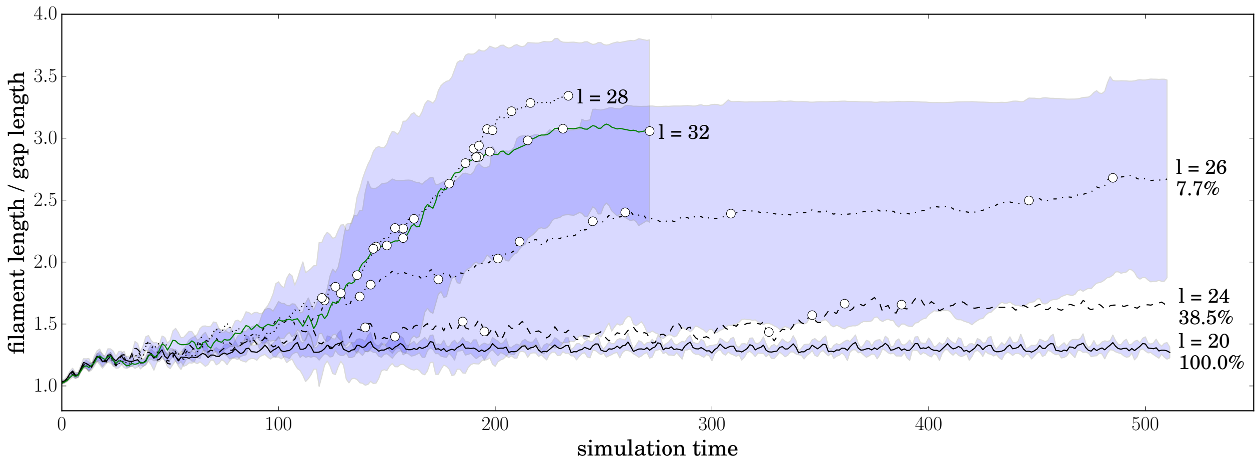


FIG. 7. (Color online) Averaged relative filament length for different gap sizes l. The standard deviations between realizations for gap lengths 20, 26 and 32 are shown as shaded regions. White dots denote times when the filament in one of the 13 realizations breaks up. Survival rates are shown for those simulation ensembles where the time limit was reached before all simulations broke up.

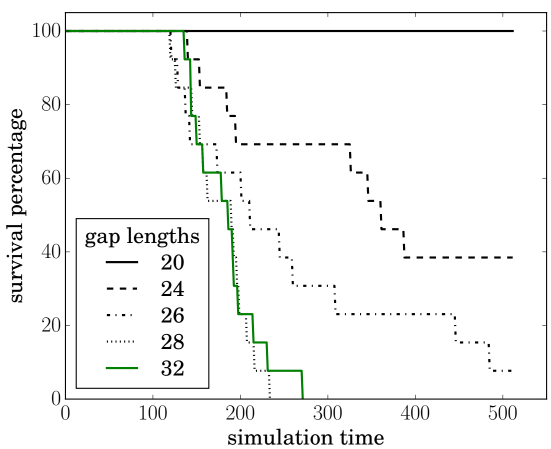
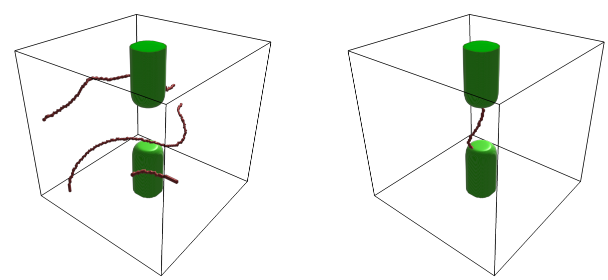
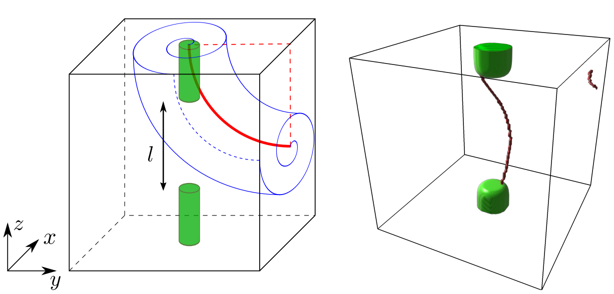


FIG. 8. (Color online) Kaplan-Meyer plot (filament survival rates without breakup) for different gap lengths.



(a) $t = 0$ (b) $t = 200$

FIG. 10. (Color online) Initial filament (a) and filament at $t = 200$ (b); gap length $l = 6$. Even this example of a broken up scroll wave is stabilized by the two heterogeneities with gap length $l = 6$.



(a) (b) $t = 100$

FIG. 9. (Color online) Sketch of the initial filament and scroll wave (a) and filament at $t = 100$ (b); gap length $l = 14$. The small remaining second filament in the background will be driven out of the system a few simulation steps later.

VI. DISCUSSION

We have seen that in the two-dimensional Barkley model spiral waves pinned to small circular obstacles rotate faster than a freely rotating spiral or a wave pinned to a larger heterogeneity.

Varying obstacle size and system geometry provides insight into stabilization mechanisms of three-dimensional scroll waves. The pinned parts of the scroll waves rotate faster if the heterogeneities have a sufficiently small radius r. In this case stabilization occurs with a mechanism corresponding to [11], since the higher frequency around the heterogeneity governs the whole medium.

In the demonstrated cases, the free part of the filament is located in between the two heterogeneities and its growth is limited despite its negative filament tension, given that the gap length l is small enough.

At this point the question arises if this stabilization is an effect of the shorter period of a spiral wave at the chosen r or if it is a more general property of a scroll wave pinned to a heterogeneity with gap length l. This question can be answered by looking at simulations with a larger radius (see Fig. 6), which show no stabilization at all. Because the simulation setup is exactly the same except for the increased radius of the heterogeneities, we can conclude that the shortened period of the pinned wave is the reason for the observed stabilization in three-dimensional simulations.

This dependency on the radius and thus on the spiral periods of the pinned filaments is also in accordance with the observation of [12], where it is shown that filaments with positive tension self-wrap faster around cylindrical heterogeneities with smaller radii (and do not stabilize at all for too large radii).

We have shown that stabilization depends mainly on the geometry of the heterogeneities, i.e. the radius r and gap length l. Especially for intermediate gap sizes, the time until breakup varied strongly, with smaller gaps tending to longer times. To obtain significantly better statistics for small gap lengths l, much longer simulations are required.

Except for the cases in which a too large r or l makes stabilization impossible at all, a necessary condition for stabilization is that at some point during the evolution of the system, one of the initially growing filaments is attached to both parts of the heterogeneity. The pinned wave then drives away other activity patterns over time. We have shown that this type of stabilization can happen even when the simulated medium is initially in a turbulent state (see Fig. 10).

VII. CONCLUSION

The presence of adequately shaped heterogeneities can not only prevent turbulence in excitable media but even terminate initially induced turbulence and stabilize the medium. Thus the dynamics of the medium with obstacles can be less complex than the dynamics of a homogeneous medium. This extends previous studies [25–27] which used external stimulation, either directly through pacing or by changing the medium's excitability, to suppress spatio-temporal chaos in three-dimensional media. In contrast, the method presented here only depends on a local change of the geometry.

Further studies should investigate other, more complex shapes of heterogeneities, e.g. curved ones as well as the behavior for even longer simulation time. Finally, our findings may be of relevance for systems with turbulent activity in heterogeneous excitable media, such as fibrillation in cardiac muscle.

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[1] A. N. Zaikin and A. M. Zhabotinsky, Nature **225** (1970), 10.1038/225535b0.
[2] B. J. Welsh, J. Gomatam, and A. E. Burgess, Nature **308** (1983), 10.1038/304611a0.
[3] T. Bánsági and O. Steinbock, Chaos **18**, 026102 (2008).
[4] S. Jakubith, H. H. Rotermund, W. Engel, A. von Oertzen, and G. Ertl, Phys. Rev. Lett. **65**, 3013 (1990).
[5] C. J. Wiggers, Am. Heart J. **20**, 399 (1940).
[6] A. Karma, Annu. Rev. Condens. **4**, 313 (2013).
[7] J. Jalife, R. A. Gray, G. E. Morley, and J. M. Davidenko, Chaos **8**, 79 (1998).
[8] K. H. Ten Tusscher, R. Hren, and A. V. Panfilov, Circ. Res. **100**, e87 (2007).
[9] V. N. Biktashev, A. V. Holden, and H. Zhang, Phil. Trans. R. Soc. A **347**, 611 (1994).
[10] S. Luther, F. H. Fenton, B. G. Kornreich, A. Squires, P. Bittihn, D. Hornung, M. Zabel, J. Flanders, A. Gladuli, L. Campoy, E. M. Cherry, G. Luther, G. Hasenfuss, V. I. Krinsky, A. Pumir, R. F. Gilmour, and E. Bodenschatz, Nature **475**, 235 (2011).
[11] V. Krinsky and K. Agladze, Physica D **8**, 50 (1983).
[12] Z. A. Jiménez and O. Steinbock, Phys. Rev. E **86**, 036205 (2012).
[13] D. Barkley, Physica D **49**, 61 (1991).
[14] D. Barkley, Scholarpedia **3**, 1877 (2008).
[15] F. H. Fenton, E. M. Cherry, A. Karma, and W.-J. Rappel, Chaos **15**, 013502 (2005).
[16] D. Pazó, L. Kramer, A. Pumir, S. Kanani, I. Efimov, and V. Krinsky, Phys. Rev. Lett. **93**, 168303 (2004).
[17] J. J. Tyson and J. P. Keener, Physica D **32**, 327 (1988).
[18] C. Cherubini, S. Filippi, and A. Gizzi, Phys. Rev. E **85**, 031915 (2012).
[19] Y.-Q. Fu, H. Zhang, Z. Cao, B. Zheng, and G. Hu, Phys. Rev. E **72**, 046206 (2005).
[20] I. Arganda-Carreras, R. Fernández-González, A. Muñoz-Barrutia, and C. Ortiz-De-Solorzano, Microscopy Research and Technique **73**, 1019 (2010).
[21] T. C. Lee, R. L. Kashyap, and C. N. Chu, CVGIP: Graphical Models and Image Processing **56**, 462 (1994).
[22] C. A. Schneider, W. S. Rasband, and K. W. Eliceiri, Nature Methods **9**, 671 (2012).
[23] J. Schindelin, I. Arganda-Carreras, E. Frise, V. Kaynig, M. Longair, T. Pietzsch, S. Preibisch, C. Rueden, S. Saalfeld, B. Schmid, J.-Y. Tinevez, D. J. White, V. Hartenstein, K. Eliceiri, P. Tomancak, and A. Cardona, Nature Methods **9**, 676 (2012).
[24] J. Meyer-Spradow, T. Ropinski, J. Mensmann, and K. Hinrichs, IEEE Computer Graphics and Applications **29**, 6 (2009).
[25] S. Alonso, F. Sagués, and A. S. Mikhailov, Science **299**,

1722 (2003).
[26] H. Zhang, Z. Cao, N.-J. Wu, H.-P. Ying, and G. Hu, Phys. Rev. Lett. **94**, 188301 (2005).
[27] S. W. Morgan, I. V. Biktasheva, and V. N. Biktashev, Phys. Rev. E **78**, 046207 (2008).