Reaction-Diffusion Patterns and Waves: From Chemical Reactions to Cardiac Arrhythmias

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Abstract Reaction-diffusion processes are behind many instances of pattern formation in chemical reactions and biological systems. Continuum reaction-diffusion equations have proved useful models for a wide variety of pattern dynamics starting with seminal work by Turing on the chemical basis of morphogenesis and by Hodgkin and Huxley on the propagation of electrical impulses along neurons in 1952. This article reviews basic concepts for and applications of reaction-diffusion models with an emphasis on spiral and vortex dynamics, related instabilities like spiral and scroll wave breakup and their potential role in cardiac arrhythmias.

1 Patterns in Reaction-Diffusion Systems

Spontaneous pattern formation under natural and laboratory conditions is a trademark of systems far from thermodynamic equilibrium. These systems are typically subject to a constant through flow of matter and energy and can be classified as open and dissipative systems. In closed systems patterns that may emerge initially typically decay in the long run and the systems often approach a featureless, spatially homogeneous state - thermodynamic equilibrium. This is in line with the demands of the second law of thermodynamics: the entropy in a closed system increases until equilibrium is reached. Open systems, however, are not subject to the constraint of the second law - they can export entropy to their surroundings.

Theoretical research has initially focused on the question under which nonequilibrium conditions a system switches from a homogeneous state to a pattern. These transitions are known as instabilities or bifurcations and can be classified [1]. For example, one can distinguish between continuous (supercritical) and discontinuous

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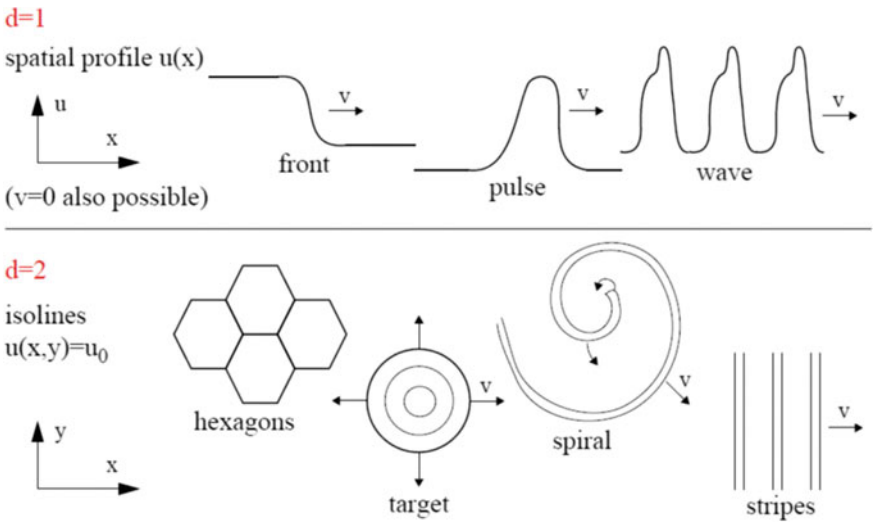

Fig. 1 Examples for simple reaction-diffusion patterns in one, two and three dimensions

(subcritical) instabilities. The emerging pattern may be stationary (Turing instability) or dynamic (Hopf instability) as well as of either periodic or localized nature. In one spatial dimension, periodic stationary patterns are typically stripes, while the range of dynamic patterns comprises traveling and standing periodic waves. In higher dimensions, periodic patterns display various symmetries, e.g. in two dimensions parallel stripes, hexagons and square patterns are known. Localized patterns include traveling and stationary fronts and pulses in one dimension. Some examples are given in Fig. 1.

A rotating spiral represents an interesting combination between a localized and a periodic pattern since it has a well defined pointlike center of rotation (core), from which periodic waves are emitted in all radial directions. In three dimensions, spiral cores in the plane are transformed into lines that are called filaments. If the filament forms a straight line, one speaks of a scroll wave.

2 A Short History of Reaction-Diffusion Systems

The most remarkable property of reaction-diffusion systems is doubtless the spontaneous formation of a great variety of patterns. These structures do not offer only aesthetical pleasure, but can also provide efficient means of communication and signal transmission. For the latter purpose, a reaction-diffusion medium has to be sensitive to small stimuli from the environment and must be able to propagate them in a reliable and fast fashion. Excitable media are particularly well suited for that purpose. They have a stable rest state and a threshold. Perturbations larger than the

threshold may cause a large response, while small perturbations and noise decay immediately. Superthreshold perturbations lead via diffusion to propagation of fast reaction-diffusion waves that transmit information in a reliable fashion. A second important application of reaction-diffusion systems is their ability to form stationary periodic patterns (Turing structures). Such structures a play an important role in morphogenesis and the development of structures in living organism.

The field of reaction-diffusion systems can to a large extent be traced back to two quite different landmark papers published in 1952. British mathematician Turing considered the "Chemical Basis of Morphogenesis" [2] and showed that the interplay of nonlinear reaction and diffusion transport may lead to sustained stationary concentration patterns, henceforth often called "Turing structures". The first example of an excitable medium derived from underlying physico-chemical processes has been provided in 1952 by British physiologists Hodgkin and Huxley. They derived a set of ordinary differential equations neglecting spatial variations from extensive measurements of ionic currents at the membrane of the squid giant axon [3]. Their nobelprizewinning effort is still considered the most successful model in physiology and the basis for many more detailed models of electrical excitation propagation in neurons or in cardiac tissue [4].

The resulting Hodkin–Huxley model accounts for the dynamics of action potentials in neurons. The equations describe the dynamics of the fast membrane potential dynamics and its dependency on the dynamics of slow gating variables for sodium channel activation and deactivation and for potassium channel activation, respectively. The concept of an excitable medium described by continuous variables has found many applications in pattern forming chemical and biological systems [5]. Since the Hodgkin–Huxley equations are coupled nonlinear ordinary differential equations, they have largely resisted analytical treatment and have been mostly studied numerically. A simplified version has been derived by FitzHugh and Nagumo in the early 60s. It is known as the FitzHugh–Nagumo model [6]. One version of it reads

$$\begin{aligned} \frac{du}{dt} &= u^3 + u - v = f(u, v), \\ \frac{dv}{dt} &= \varepsilon(u - rv + \beta) = \varepsilon g(u, v). \end{aligned} \tag{1}$$

Originally, the activator u is derived from the membrane voltage of the Hodgkin–Huxley equations, while the inhibitor v represents a slow gating variable. If one allows for a spatial variation of the variables one can simply add transport by diffusion and obtains a coupled set of nonlinear partial differential equations

$$\begin{aligned} \partial_t u &= f(u, v) + D_u \Delta u, \\ \partial_t v &= \varepsilon g(u, v) + D_v \Delta v. \end{aligned} \tag{2}$$

If one intends to use the FitzHugh–Nagumo model as a description for propagating action potentials, inhibitor diffusion has to be neglected, i. e. $D_v = 0$. The spatiotem-

poral dynamics of these equations is governed by control parameters including ε and the diffusion constants D_u and D_v. The variables are often specified as fast activator (u) and slow inhibitor (v) after Gierer and Meinhardt [7]. A nice feature of the FitzHugh–Nagumo model is that it contains both the Turing patterns and the excitable medium as special cases depending on the choice of the parameters. Requirements for excitation waves are fast activator dynamics ($\varepsilon \ll 1$) and diffusion ($D_u/D_v > 1$) and a suitable form of the functions f and g, whereas Turing pattern require long-range inhibitor diffusion ($D_u/D_v \ll 1$).

A computationally more efficient version of the FitzHugh–Nagumo model for the study of excitable media ($D_v = 0$) has been provided by Barkley [8] and modified by Bär and Eiswirth to study spatiotemporal chaos [9]. Its general form reads:

$$\begin{aligned} \partial_t u &= \tfrac{1}{\varepsilon} u(1-u)\Big(u - \tfrac{b+v}{a}\Big), \\ \partial_t v &= h(u) - v. \end{aligned} \tag{3}$$

Barkley's original version uses a linear inhibitor production $h(u) = u$. For excitable conditions, the medium then has a single homogeneous fixed point $(u, v) = (0, 0)$ like the original FitzHugh–Nagumo model (cf. **Generation of Spirals in Excitable Media**). The modification of Bär and Eiswirth introduces a nonlinear function $h(u)$ for the inhibitor production, that leads to additional unstable homogeneous fixed points. The simple change leads to interesting new nonlinear wave physics including appearance of spatiotemporal chaos via pulse backfiring in one and spiral breakup in two dimension.

Excitable media usually appear near oscillatory regimes. Bistable systems should exhibit fronts between the two stable states that typically travel with constant speed and shape. For excitable conditions, Eq. 3 typically possess one stable fixed point (the rest state) and, depending on the shape of the function $h(u)$ in Eq. 3, zero or two more additional unstable fixed points. For oscillatory conditions, the system of Eq. 3 typically contains only one unstable spatially homogeneous fixed point. Note, that spirals and vortices can occur for excitable as well as for oscillatory and bistable conditions. In the course of the 1960s, the interest for "dissipative structures" in chemical systems started to grow. As a simplification of Turing's model, Lefever, Nicolis and Prigogine suggested the following reaction scheme

$$\begin{aligned} A &\to U; & B + U &\to V + D; \\ 2U + V &\to 3U; & U &\to E. \end{aligned}$$

where the concentrations of A and B are used as control parameters and have constant values a and b, respectively. The chemical species U and V play similar roles as activator and inhibitor, respectively, in the FitzHugh–Nagumo and Barkley models. The corresponding reaction-diffusion model is widely known as the "Brusselator" and reads

$$\partial_t u = a - (b+1)u + u^2 v + D_u \Delta u,$$
$$\partial_t v = bu - u^2 v + D_v \Delta v, \tag{4}$$

where $u(x,t)$ and $v(x,t)$ denote the concentrations of U and V. All rate constants have been set to unity. The Brusselator allows for oscillations, if $a > a_C = b^2 + 1$ and $D_u > D_v$, and for a Turing instability, if $D_u \ll D_v$. It has been often used as a prototype model for pattern formation and may serve here as a simple example for a strategy widely used in the modeling of chemical and biological reaction-diffusion systems. First, identify the kinetic scheme for a particular system, second write down the corresponding set of differential equations, third add the relevant transport processes (diffusion) and last but not least look out for bistability as well as dynamic, oscillatory respectively. pattern forming instabilities. Since the arrival of the Brusselator, this strategy has been applied to many systems in homogeneously and heterogeneously catalyzed chemical reaction [10] as well as in biochemical and biological systems [11].

In parallel to the first studies of the Brusselator model, first experimental observations of reaction-diffusion waves in the form of target patterns [12] and spiral waves [13] have been reported in the Belousov–Zhabotinsky (BZ) reaction. The BZ reaction is the oxidation of malonic acid and involves more than 100 chemical species. Nevertheless, Field, Köros and Noyes extracted a core mechanism of the reaction that has become known as the Oregonator model [14]; it explicitly includes only three species and is often even reduced further to a typical two-variable activator-inhibitor form. Until the early 1990s, more and more details of spiral dynamics in the BZ reaction have been investigated [15]. However, many results until then have been limited due to the use of "closed" reaction vessels (see chapter **Chemical Oscillations and Spiral Waves**).

A major breakthrough has been the design and use of open reactors both in homogeneously and heterogeneously catalyzed reactions (see Fig. 2). They allow for steady supply of educts and removal of products, thus maintaining constant concentrations of key species and keeping the system far away from chemical equilibrium. Turing structures have been discovered in 1D and 2D set-ups of the Chlorid-Iodid-Malonic-Acid (CIMA) reaction [16, 17]. The second half of the 1990s has then seen the discovery of further structures under bistable conditions, namely labyrinthine patterns [18] and replicating spots [19]. A second exciting line of research in pattern-forming chemical systems originated from the study of reaction on catalytic surfaces [20–22] after 1990 (see chapter **Shedding Light on Chaos - Controlling Surface Reactions**). Catalytic reactions can be operated under a wide range of external conditions regarding pressure and temperature and they are truly two-dimensional (Fig. 2, right).

The use of open reactors also enabled a systematic study of transitions between stable spirals and spatiotemporal chaos in experiments [23–25], in the next section we will adress the theoretical understanding of these phenomena.

Another important field where reaction-diffusion processes play a prominent role are nonlinear waves and pattern formation in biological systems. Pioneering experiments in aggregating slime mold colonies revealed spiral waves of chemoattractant

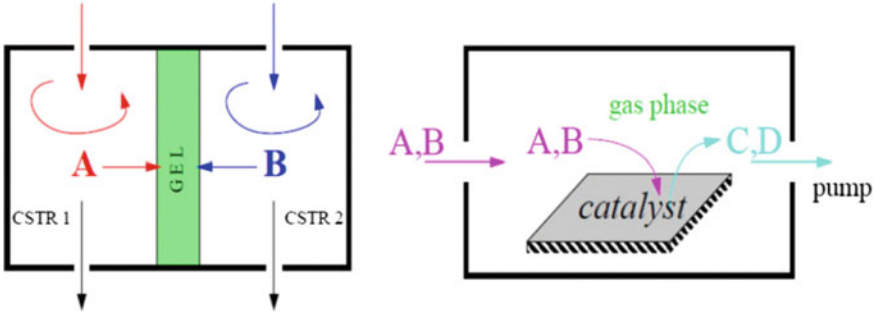

Fig. 2 Sketch of open reactor types used in homogeneous catalysis. Left: continuously fed unstirred reactor (CFUR) with two continuously stirred tank reactors (CSTR), right: in heterogeneous catalysis

in the early aggregation stage [26]. By now the whole cycle of aggregation and the spatial patterns associated with its stages have been thoroughly studied [27, 28] (see chapter **Spiral Waves of the Chemo-Attractant cAMP Organise Multicellular Development in the Social Amoebae**). Another frequently studied example of reaction-diffusion behavior in biology are intracellular calcium waves [29, 30] (see **Yet More Spirals**). Somewhat surprisingly, the simple activator-inhibitor picture as well as the concept of an excitable medium could be applied to many of these examples.

Since 2000, a dominating theme in biological reaction-diffusion systems have been the discovery and investigation of intracellular protein patterns, most prominently standing and traveling waves of the so-called Min proteins found in *in-vivo* experiments of *Escherichia Coli* bacteria [31] and *in-vitro* experiments of a reactive solutions of Min proteins at lipid monolayers [32]. Since the Min patterns are crucial in the regulation of cell division, many theorists have worked to obtain quantitative models for this system; for reviews see e.g. [33, 34]. In general, it seems that protein patterns can often be explained by models that assume a total conservation of one or more protein species [34] which clearly distinguishes these system from chemical reactions in open reactors subject to a constant throughflow of reactants and products. In chemical pattern formation a prominent direction after the year 2000 was control of patterns e.g. by tuning of diffusion coeffients in microemulsions [35] or by feedback strategies [36, 37]. Finally, the decade after 2000 also lead to detailed studies of scroll waves [38, 39] and Turing patterns in 3D [40] in BZ systems.

3 Instabilities of Spiral and Scroll Waves: From Chemical Reactions to Arrhythmias in the Heart

An important motivation for the study of excitable media has been the quest for the cause of irregular high-frequency electrical activity in cardiac muscle typically observed during ventricular and atrial fibrillation [41]. The reason for the onset

of ventricular fibrillation as well as possible treatments remain subjects of intense experimental and theoretical research. Rotors (or spirals) of electrical excitation are still in the focus of researchers addressing cardiac arrhythmias and dynamical diseases such as atrial and ventricular fibrillation, see [42] and the chapter **Spiral Waves in the Heart** in this book. Over the years many different aspects of cardiac dynamics have been linked with theory of reaction-diffusion systems and nonlinear dynamics; for recent reviews see e.g. [43–45].

Early experiments in thin sheets of heart tissue displayed only stable spirals in contrast with the irregular activity seen in experiments with whole hearts. In addition, hearts with small mass and, in particular, small wall thicknesses were found not to support irregular spiral turbulence-like electrical dynamics. Consequently, Winfree suggested that irregular activity in the heart might be a genuinely 3D phenomenon [46]. In parallel, the phenomenon of spiral breakup has emerged as a candidate mechanism for ventricular and atrial fibrillation and shall be briefly reviewed in this section. For a comprehensive discussion of spiral breakup in simple models and chemical reactions, compare [47].

3.1 Breakup of 2D Spirals

In excitable reaction-diffusion media, the mechanism of spiral breakup has been linked to radial instabilities that are observed frequently in cardiac models [43–45, 48], typically unstable modes in the radial direction cause spiral instability and possibly breakup. In what follows, we shall concentrate mostly on destabilization against modes in the radial direction, since these are the most relevant ones for cardiac dynamics exhibiting spiral breakup. Simple equations like Eq. 4 have been found to contain transitions directly from stable rotation to spatiotemporal chaos via spiral breakup. These examples have been also at the focus of a number of papers employing numerical stability analysis (see [9, 49]). As a result it is now firmly established that spiral breakup results from a linear instability of the stable rotating spiral.

It is crucial to note that in all examples of radial spiral breakup in reaction-diffusion models and related experiments two different scenarios are observed: spirals may break first close to their core or alternatively far away from the core, see Fig. 3. The core breakup in Fig. 3a is accompanied by a meander instability, which introduces a Doppler effect into the waves emitted from the spiral core. Breakup near the core is found in simulations in excitable media [9, 47] and in experiments with a chemical reaction [24], whereas breakup far away from the core as in Fig. 3b is typically seen under oscillatory conditions both in chemical experiments [23, 25] and in simulations of the complex Ginzburg-Landau equation (CGLE) [50] and of oscillatory reaction-diffusion systems [47].

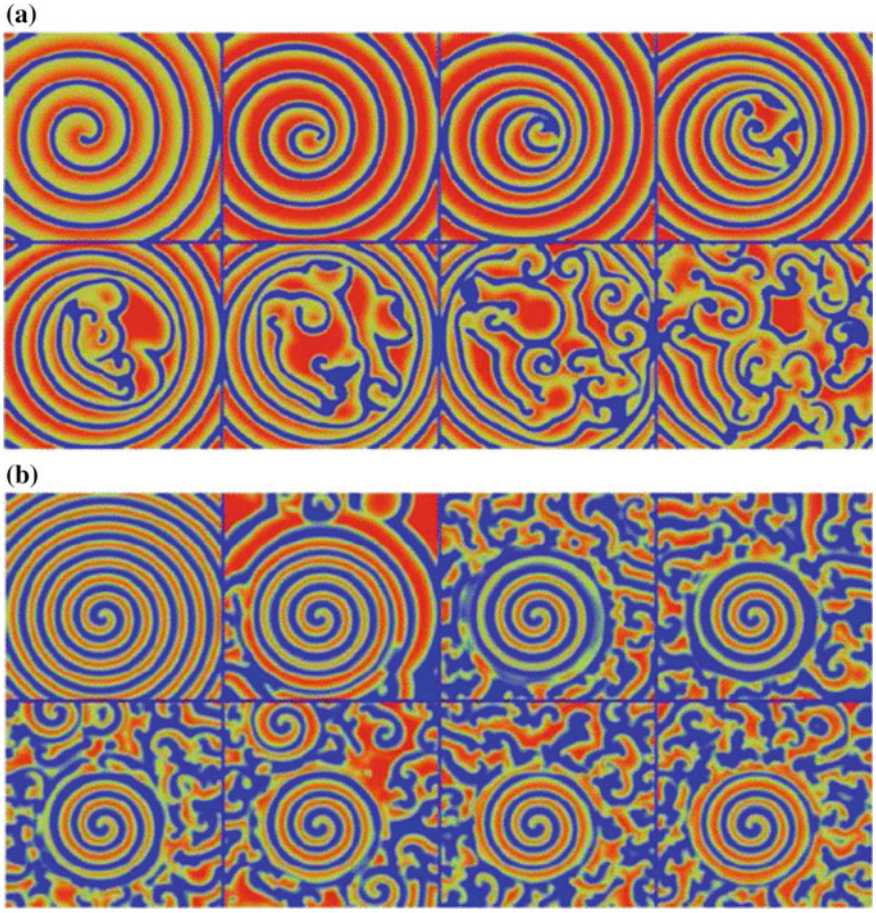

Fig. 3 Two different scenarios of spiral breakup shown at different stages in time. Both scenarios lead to irregular dynamics. **a** The breakup appears first close to the center and spreads then outward. **b** The breakup appears first far away from the center. At the end, a stable spiral fragment with finite radius is left, surrounded by a "turbulent" bath. The figures show simulations of the model, Eq. 4. (Taken from [47])

3.2 Breakup of 3D Scroll Waves

The natural extension of spiral waves in two dimensions are scroll waves in three dimensions. Straight scroll waves rotate with constant frequency. However, under certain conditions the filament of the scroll is not straight but takes a helical shape under meandering or when an external twist is imposed. Complex unstable dynamics may occur if the tension of the filament is negative. Three-dimensional waves rotate around the center filament.

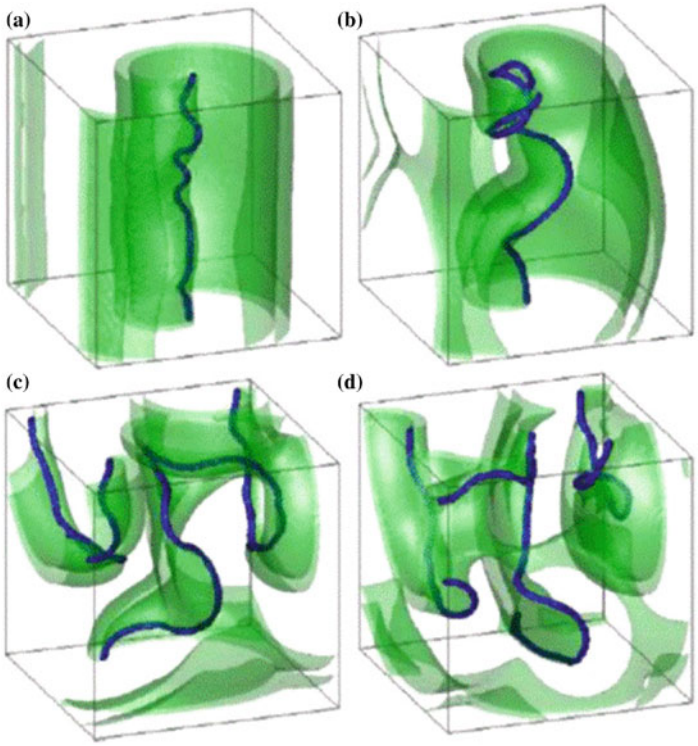

Fig. 4 Numerical simulations of a scroll wave with negative filament tension: **a** initial deformed filament, **b** bending of the filament, **c** breakup of the filament at the boundaries, **d** stationary chaotic dynamics. Simulations done with the Luo-Rudy model for excitation propagation in cardiac tissue (taken from [45])

Even if the scroll filaments are just convenient mathematical entities, their dynamics permits to assign them physical magnitudes like tension. An illustration how negative line tension of filament leads to scroll wave breakup and subsequent turbulent dynamics is given in Fig. 4. An initial almost straight filament develops a wiggly structure whose amplitude grows in time. Once, the filament hits the boundaries of the container the scroll waves break and irregular dynamics ensues (cf. Fig. 4); for a more extensive discussion see e.g. [45].

3.3 Breakup in Heterogeneous Excitable Media

Small-scale heterogeneities are inevitable and omnipresent in cardiac tissues. This is due to the variability of individual cells, the presence of different cell types as well as the potential inclusion of non-functional fibrotic cells inside otherwise

healthy tissue. Another factor is the discrete nature of the tissue that is composed of myocytes separated by extracellular space filled with interstitial fluids. If the fraction of non-conducting cells reaches fractions close to the percolation threshold where the conducting parts of the tissue become disconnected. An example how reentry appears in a discrete heterogeneous model for cardiac tissue near the percolation threshold is shown in Fig. 5 [51].

The wave has already quite an irregular shape with a rough interface and many holes. For the realization of a random medium shown in Fig. 5, a large non-conducting cluster appears (see Fig. 5a). In its vicinity the excitation wave is broken and reentry appears, which leads to an overall persistent irregular dynamics.

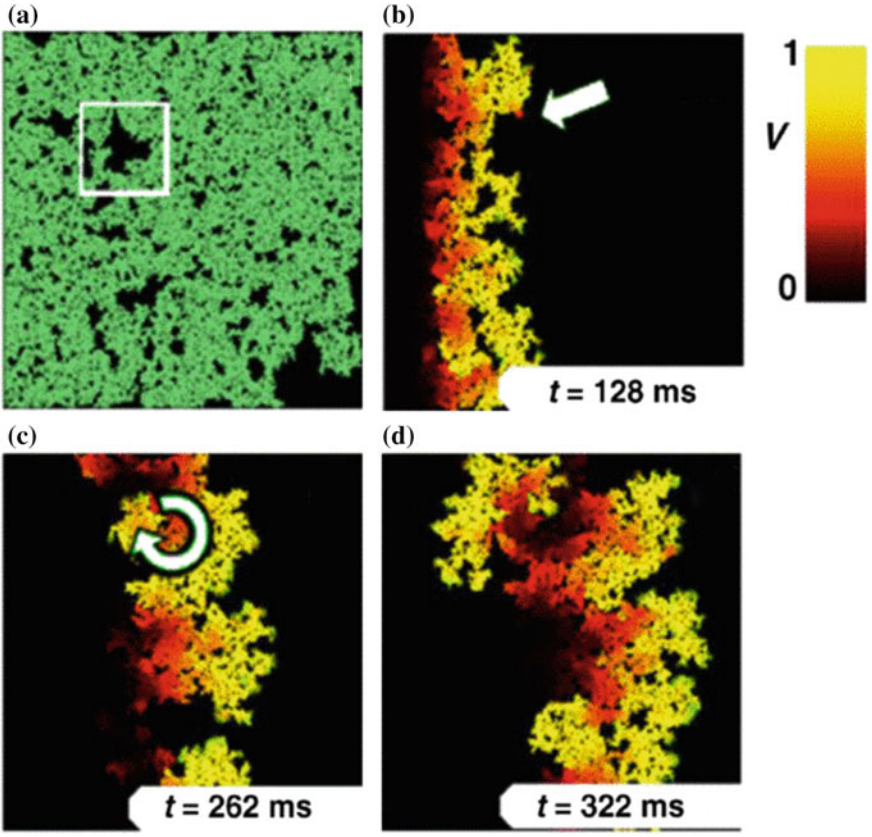

Fig. 5 Heterogeneities induce breakup of an initially planar wave in a two-dimensional simulation of a variant Fenton-Karma-model for cardiac tissue (taken from [51]). Panel **a** shows non-conducting areas (black) embedded into the conducting area (green). White square marks a large cluster responsible for the reentry and the wave breakup in the heterogeneous medium seen in simulations in panels **b**–**d**. Straight arrow in **b** marks the place of reentry and circular arrow in **c** follows the reentry direction

In this section, we have discussed three different mechanisms for transition from regular spiral or scrolls to irregular, chaotic dynamics. While in chemical systems these mechanism could be explored separately, the challenge in biological systems like the heart is that all three aspects may contribute simultaneously or even cooperatively.

4 Conclusion

Reaction-diffusion systems enter the stage in 1952 with the publication of the two seminal papers by Turing, that suggested a potential role for reaction-diffusion processes in morphogenesis, and by Hodgkin and Huxley, who based on experimental data developed a first model for impulse propagation in neurons that became a cornerstone of mathematical physiology. During the 1960s and 1970s Prigogine, Nicolis and co-workers extended the early concept of Turing by introducing the notion of "dissipative" structures. In parallel, experimental studies of the Belousov–Zhabotinsky reaction revealed rotating spiral waves as a particular beautiful example of such structures. In the 1990s, the field of chemical pattern formation reached maturity by introducing open reactors and experimental systems that showed a large variety of patterns both in homogeneous and heterogeneous catalysis including the realization of chemical Turing patterns. A concise summary of the history of chemical complexity was recently provided by Ertl and Mikhailov [52]. Improved imaging techniques in cell biology have subsequently led to the discovery of protein patterns in the late 1990s. A number of important unsolved questions concern the role that vortices namely rotating spiral and scroll waves play in the emergence of cardiac arrhythmias and potential strategies to control and suppress such dangerous physiological states. Here, recent progress in imaging of electrical and mechanical waves in cardiac muscle fuels hope for future discoveries [53].

References

1. M.C. Cross, P.C. Hohenberg, Pattern formation outside of equilibrium. Rev. Mod. Phys. **65**, 851 (1993)
2. A.M. Turing, The chemical basis of morphogenesis. Phil. Trans. Roy. Soc. Lond. B **237**, 37 (1952)
3. A.L. Hodgkin, A.F. Huxley, A quantitative description of membrane current and its application to conduction and excitation in nerve. J. Physiol. Lond. **117**, 500 (1952)
4. J. Keener, J. Sneyd, *Mathematical Physiology* (Springer, New York, 1998)
5. E. Meron, Pattern formation in excitable media. Phys. Rep. **218**, 1 (1992)
6. R. FitzHugh, Impulses and physiological states in theoretical models of nerve membrane. Biophys. J. **1**, 445 (1961)
7. A. Gierer, H. Meinhardt, Theory for biological pattern formation. Kybernetik **12**, 30 (1972)
8. D. Barkley, A model for fast computer simulation of waves in excitable media. Physica D **49**, 61 (1991)

9. M. Bär, M. Eiswirth, Turbulence due to spiral breakup in a continuous excitable medium. Phys. Rev. E **48**, 1635 (1993)
10. R. Kapral, K. Showalter (eds.), *Chemical Waves and Patterns* (Kluwer, Dordrecht, 1994)
11. A. Goldbeter, *Biochemical Oscillations and Cellular Rhythms: The Molecular Bases of Periodic and Chaotic Behavior* (Cambridge University, Cambridge, 1996)
12. A.N. Zaikin, A.M. Zhabotinsky, Concentration wave propagation in 2-dimensional liquid phase self-oscillating system. Nature **225**, 535 (1970)
13. A.T. Winfree, Spiral waves of chemical activity. Science **175**, 634 (1972)
14. R.J. Field, R.M. Noyes, E. Körös, Oscillations in chemical systems 2: Thorough analysis of temporal oscillations in Bromate-Cerium-Malonic acid system. J. Am. Chem. Soc. **94**, 8649 (1972)
15. S.C. Müller, Th. Plesser, B. Hess, The structure of the core of the spiral wave in the Belousov-Zhabotinsky reaction. Science **230**, 661 (1985)
16. V. Castets, E. Dulos, J. Boissonade, P. de Kepper, Experimental evidence of a sustained standing turing-type nonequilibrium chemical pattern. Phys. Rev. Lett. **64**, 2953 (1990)
17. Q. Ouyang, H.L. Swinney, Transition from a uniform state to hexagonal and striped turing patterns. Nature **352**, 610 (1991)
18. K.J. Lee, W.D. McCormick, Q. Ouyang, H.L. Swinney, Pattern formation by interacting chemical fronts. Science **261**, 183 (1993)
19. K.J. Lee, W.D. McCormick, J. Pearson, H.L. Swinney, Experimental observation of self-replicating spots in a reaction-diffusion system. Nature **369**, 215 (1994)
20. A. Hagberg, E. Meron, Complex patterns in reaction-diffusion systems: a tale of two front instabilities. Chaos **4**, 477 (1994)
21. S. Jakubith, A. von Oertzen, W. Engel, H.H. Rotermund, G. Ertl, Spatiotemporal concentration patterns in a surface reaction - propagating and standing waves, rotating spirals, and turbulence. Phys. Rev. Lett. **65**, 3013 (1990)
22. R. Imbihl, G. Ertl, Oscillatory kinetics in heterogeneous catalysis. Chem. Rev. **95**, 697 (1995)
23. Q. Ouyang, J.M. Flesselles, Transition from spirals to defect turbulence driven by a convective instability. Nature **379**, 143 (1996)
24. Q. Ouyang, H.L. Swinney, G. Li, Transition from spirals to defect-mediated turbulence driven by a Doppler instability. Phys. Rev. Lett. **84**, 1047 (2000)
25. L.Q. Zhou, Q. Ouyang, Experimental studies on long-wavelength instability and spiral breakup in a reaction-diffusion system. Phys. Rev. Lett. **85**, 1650 (2000)
26. G. Gerisch, Periodic signals control pattern formation in cell aggregations. Naturwissenschaften **58**, 430 (1971)
27. F. Siegert, C. Weijer, Three dimensional scroll waves organize *dictyostelium* slugs. Proc. Natl. Acad. Sci. USA **89**, 6433 (1992)
28. E. Ben-Jacob, I. Cohen, H. Levine, Cooperative self-organization of microorganism. Adv. Phys. **49**, 395 (2000)
29. J. Lechleiter, S. Girard, E. Peralta, D. Clapham, Spiral calcium wave propagation and annihilation in *Xenopus laevis* oocytes. Science **252**, 123 (1992)
30. M. Falcke, Reading the patterns in living cells: the physics of Ca^{2+} signaling. Adv. Phys. **53**, 255 (2004)
31. D.M. Raskin, P.A. De Boer, Rapid pole-to-pole oscillation of a protein required for directing division to the middle of *Escherichia Coli*. Proc. Natl. Acad. Sci. USA **96**, 4971 (1999)
32. M. Loose, E. Fischer-Friedrich, J. Ries, K. Kruse, P. Schwille, Spatial regulators for bacterial cell division self-organize into surface waves in vitro. Science **320**, 789–792 (2008)
33. C. Beta, K. Kruse, Intracellular oscillations and waves. Ann. Rev. Cond. Math. Phys. **8**, 239–264 (2017)
34. J. Halatek, F. Brauns, E. Frey, Self-organization principles of intracellular pattern formation. Phil. Trans. R. Soc. B **373**, 20170107 (2018)
35. V.K. Vanag, I.R. Epstein, Pattern formation in a tunable medium: the Belousov-Zhabotinsky reaction in an aerosol OT microemulsion. Phys. Rev. Lett. **87**, 228301 (2001)

36. S. Alonso, F. Sagués, A.S. Mikhailov, Taming winfree turbulence of scroll waves in excitable media. Science **299**, 1722 (2003)
37. A.S. Mikhailov, K. Showalter, Control of waves, patterns and turbulence in chemical systems. Phys. Rep. **425**, 79–194 (2006)
38. T. Bánsági Jr., O. Steinbock, Nucleation and collapse of scroll rings in excitable media. Phys. Rev. Lett. **97**, 198301 (2006)
39. C. Luengviriya, U. Storb, G. Lindner, S.C. Müller, M. Bär, M.J.B. Hauser, Scroll wave instabilities in an excitable chemical medium. Phys. Rev. Lett. **100**, 148302 (2008)
40. T. Bánsági, V.K. Vanag, I.R. Epstein, Tomography of reaction-diffusion microemulsions reveals three-dimensional turing patterns. Science **331**, 1309–1312 (2011)
41. A.T. Winfree, *When Time Breaks Down: The Three-Dimensional Dynamics of Electrochemical Waves and Cardiac Arrhythmias* (Princeton University, Princeton, 1987)
42. S.V. Pandit, J. Jalife, Rotors and the dynamics of cardiac fibrillation. Circ. Res. **112**, 849 (2013)
43. A. Karma, Physics of cardiac arrhythmogenesis. Ann. Rev. Cond. Math. Phys. **4**, 313 (2013)
44. Z. Qu, G. Hu, A. Garfinkel, J.N. Weiss, Nonlinear and stochastic dynamics in the heart. Phys. Rep. **543**, 61 (2014)
45. S. Alonso, M. Bär, B. Echebarria, Nonlinear physics of electrical wave propagation in the heart: a review. Rep. Prog. Phys. **79**, 096601 (2016)
46. A.T. Winfree, Electrical turbulence in three-dimensional heart muscle. Science **266**, 1003 (1994)
47. M. Bär, L. Brusch, Breakup of spiral waves caused by radial dynamics: Eckhaus and finite wavenumber instabilities. New J. Phys. **6**, 5 (2004)
48. F.H. Fenton, E.M. Cherry, H.M. Hastings, S.J. Evans, Multiple mechanisms of spiral wave breakup in a model of cardiac electrical activity. Chaos **12**, 852 (2002)
49. P. Wheeler, D. Barkley, Computation of spiral spectra. SIAM J. Appl. Dyn. Syst. **5**, 15777 (2006)
50. I.S. Aranson, L. Kramer, The world of the complex Ginzburg-Landau equation. Rev. Mod. Phys. **74**, 92 (2002)
51. S. Alonso, M. Bär, Reentry near the percolation threshold in a heterogeneous discrete model for cardiac tissue. Phys. Rev. Lett. **110**, 158101 (2013)
52. A.S. Mikhailov, G. Ertl, *Chemical Complexity - Self-Organization Processes in Molecular Systems* (Springer International Publishing Company, Cham, 2017)
53. J. Christoph, M. Chebbok, C. Richter, J. Schröder-Schetelig, P. Bittihn, S. Stein, I. Uzelac, F.H. Fenton, G. Hasenfuß, R.F. Gilmour Jr., S. Luther, Electro-mechanical vortex filaments during cardiac fibrillation. Nature **555**, 667 (2018)