8.22 BIOENGINEERING AND MEDICAL PHYSICS

G. Bagheri, G. Bertens, E. Bodenschatz, B. Hejazi, S. Hussaini, M. Kalhöfer-Köchling, H. Khodamoradi, H. Kim, S. Luther, R. Majumder, A. Mamane, J. Moláček, F. Nordsiek, S. Salekdeh, O. Schlenczek, K. Stieger, B. Thiede, L. Turco, Y. Wang, Y. Zhang, V. Zykov

S. Christiansen (Fraunhofer IKTS Forchheim), A. Panfilov (Ghent University), A. Helmke (HAWK), M. Pöhlker, C. Pöhlker (MPI for Chemistry), T. Salditt (University of Göttingen), S. Clauberg, H. Kaba, J. Kosub, N. Kucheryava, W. Leszczynski, J. Lotz, T. Meyer, S. Scheithauer, M. Uecker, K. Walter, W. Zimmermann (University Medical Center Göttingen), S. Spindeldreier(Leibniz University Hannover), S. Boretius, R. Hinkel (German Primate Center), R. Müller, K. Wogram (Institute for Music and Aerosols, part of Blasmusikverband Nordrhein-Westfalen), C. Wille (InoxAir GmbH)

After decades of development in biophysics and biomedical engineering, we now understand far more about the physics of living matter and are rapidly developing new technologies for human health and safety. This is a topic central to the department of Prof. E. Bodenschatz.

On the one hand we investigate problems in cardiac function, like fibrillation mechanisms and their avoidance, mechanics of the contracting heart, and helping in the development of Engineered Heart Muscle (EHM) and its placement on a patient's heart. To this end based on cellular electrophysiology, we studied how spiral waves in cardiac tissue can be controlled with light and temperature. In the German Centre for Cardiovascular Research (DZHK) funded project "Alliance for the Regeneration of the Heart", we developed a computational model for the heartbeat and investigated the mechanical properties of heart muscle both theoretically and experimentally, in collaboration with the group of Prof. W. Zimmermann at the University Medical Center Göttingen (UMG). In the Federal Ministry for Education and Research (BMBF) funded project IndiHEART, we are helping developing with our partners fibre-based 3D bioprinting for patient specific EHM.

On the other hand the pandemic has shown that we know too little about the mechanisms and pathways of airborne disease transmission, a topic which has been studied deeply by us over the past 1.5 years. In collaboration with Prof. S. Scheithauer from the UMG we have measured the human exhaled particles from more than 130 volunteers, have investigated aerosol emission from wind instruments and mask efficacy in collaboration with R. Müller and Dr. K. Wogram from the Institute for Music and Aerosols. We have developed the web app HEADS, https://aerosol.ds.mpg.de, that allows the calculation of the infection risk by human pathogens. HEADS relies on a new theoretical model for poly-pathogen infection risk. In collaboration with MPI-C and Fraunhofer IKTS we measure the constituents of human droplets.

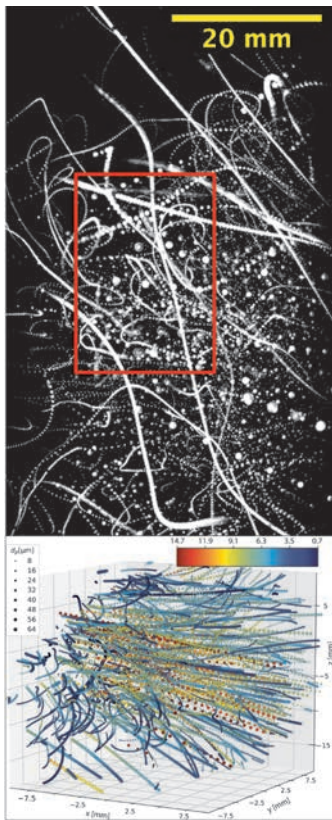## 8.22.1 Human exhaled particles and risk of infection from airborne diseases

Figure 8.63: (Top) Particle emission from mouth during speaking (35 years old male subject, mouth 4 cm below top left corner and outside field of view), visualized by laser light illumination and a high-speed camera. (Bottom) Figure shows 3D track of particles inside the red square shown in the top image obtained by three high-speed cameras looking at this volume from different angles while recording droplet motions at 15000 frames per second. Detected particles produced during speaking are between 8 and 64 micrometers (circle size) and can have velocities as high as 14.9 m/s (color in m/s) of the exhaled particles.

(G. Bagheri, F. Nordsiek) The COVID-19 pandemic has demonstrated how little we know about the mechanisms and pathways of airborne disease transmission and prevention strategies, despite decades of research. Uncertainties and knowledge gaps about the size and concentration of exhaled particles during various activities, the suitability of infection models used, the effectiveness of masks in preventing disease transmission, and the dispersion and dilution dynamics of infectious particles indoors or outdoors, to name a few, have severely compromised our ability to contain the spread of the virus. The physics of infectious particle dispersion carried by turbulent exhalation flow is reminiscent of cloud physics, for which we have developed sophisticated analytical and experimental tools. We have measured directly the size and concentration of exhaled particles from more than 130 subjects aged 5-80 years using aerosol size spectrometers and in-line holography from nanometres to millimetres. With this we have filled the most important knowledge gap, i.e. the source term, for assessing the risk of infection in airborne disease transmission. We have found age to be an important parameter influencing the concentration of particles <5 μm, while gender, body mass index, smoking and exercise habits had no discernible influence. We have also investigated the physics of the exhalation flows during different respiratory manoeuvres using size-resolved three-dimensional particle tracking imaged at 10-15 kHz, which are furthermore complemented by two-dimensional optical flow measurements. We have collected and analysed 200 h of exhalation samples with the spectrometers, 12000 holograms, and more than three million images from the high-speed cameras. From this data and direct measurements we obtained the shrinkage of particles by drying. With this knowledge, we are now able to predict risk of infection from human exhaled particles in well-mixed indoor environments in our web application HEADS. We have further improved risk assessment models to account for particles containing multiple pathogens [1]. We also assessed dispersion of aerosols in two German hardware stores. It was found that in such environments near field exposures are dominant [2]. We find for a typical SARS-CoV-2 parameters that social distancing alone, even at 3 meters between two talking individuals, leads to a more than 90% infection risk after a few minutes. With surgical masks, the upper bound on the person-to-person risk of infection with infectious speaking remains below 26% even after 60 minutes. For well-fitting FFP2 mask, this is reduced by 60% compared to surgical masks. We conclude that wearing appropriate masks in the community provides excellent protection for others and oneself and makes social distancing less important [3].

8.22.2 From cardiac mechanics simulations and printing of engineered heart muscle towards repairing a patient specific failing heart

(Y. Wang) The human heart is one of the most important organs of our body, responsible for pumping oxygenated blood and receiving deoxygenated blood. Heart failure is a common and potentially fatal condition in which the heart muscle cannot pump sufficient blood to meet the body's needs. Current options for patients with end-stage heart failure include mechanical support devices and heart transplants. Alternatively, EHM may offer new avenues to repair the failing heart. Within the IndiHEART project with our collaborators from the UMG, the German Primate Center (DPZ) and the Leibniz University of Hanover, we won second place (out of three) in the national innovation competition "Organ Replacement from the Laboratory" of the BMBF. In IndiHEART we aim to build a patient specific organ-like engineered myocardium consisting of porous, interwoven and microfiber-based tissue by using different micro-fluidic technologies. In this way we create a tissue that has optimized fibers. Cells and extracellular matrix are incorporated into a Ca-alginate shell and extruded via bioprinting (Fig. 8.64). Employing fiber-based tissue not only increases nutrient and oxygen exchange throughout thick constructs but also may induce cell orientation via contact guidance and enhance cell maturation. After being very promising in animal studies the first successfully in man studies have been conducted by our collaborator Prof. W. Zimmermann and his colleagues.

To obtain a functionally synchronized native heart muscle tissue, both deep understanding of cardiac mechanics and muscle fiber orientation are required. Myocardium, as a complex active soft matter, typically displays anisotropic mechanical behavior due to their fibrous nature. In constitutive modeling, fiber families are often assumed to be unidirectional. However, recent related studies show the need to incorporate dispersion of fiber orientation. Taking fiber dispersion into account, we have proposed a new class of constitutive laws, which compute faster, are easier to implement, and more stable than their counterparts [4]. The proposed laws are used with the finite element method to model the infarcted heart. *In silico* EHMs are introduced and how the pump function changes with different EHM configuration is evaluated (Fig. 8.65). Within the DZHK, we also study the mechanical properties of myocardium with rheometer (Prof. W. Zimmermann) and understand the fiber architecture using phase-contrast micro-CT (Prof. T. Salditt, U Göttingen) and DT-MRI (Prof. S. Boretius, DPZ). All of these, enable us to provide a directed orientation for extruded cell-loaded microfibers into the patch. The personalized EHM design generated in modeling will be used to guide the production of personalized patch, which will be produced by 3D bioprinting.

8.22.3 Control of electric turbulence in the heart

(Y. Wang, V. Zykov) Self-organisation in complex excitable systems often results in the formation of spiral waves or vortices. In the heart they can cause lethal rhythm disorders which predispose to sudden cardiac death. Restoration of normal heart function requires the timely termination of theses singular structures. This is best possible by
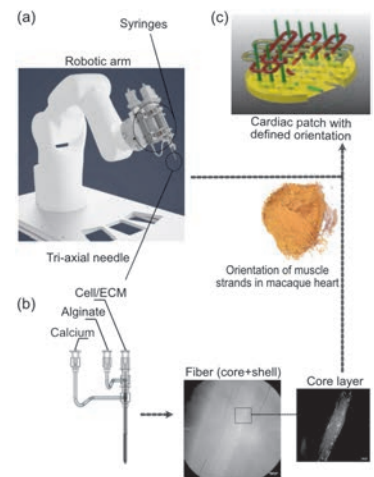

Figure 8.64: Generation of engineered human myocardium incorporating defined oriented cell-laden microfibers. (a) Schematic illustration of 6-axias robotic arm integrated with a (b) tri-axial needle to fabricate core–shell microfibres composed of cardiomyocites-ECM encapsulated in Ca-alginate hydrogel. (c) Employing 3D-robotic arm technology can provide a cardiac patch template which can be used as a guidance to create 3D construct base on a continuous well-defined organization of core-shell microfibers.
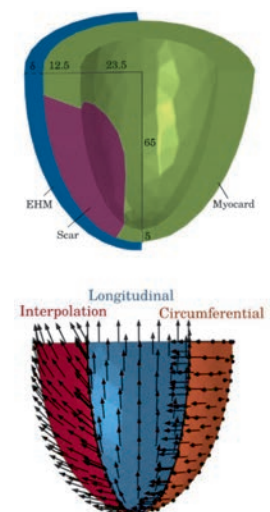

Figure 8.65: (Top) Schematic illustration of an infarcted left ventricle with EHM patch. (Bottom) Three different fiber configurations considered in the *in silico* EHM patch.
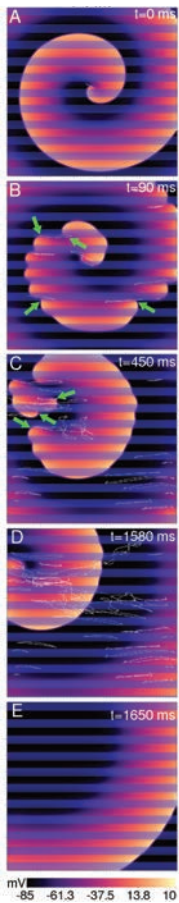
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Figure 8.66: Termination of spiral waves by transient break-up with spatio-temporal modulation of tissue excitability using a moving zebra-like pattern.
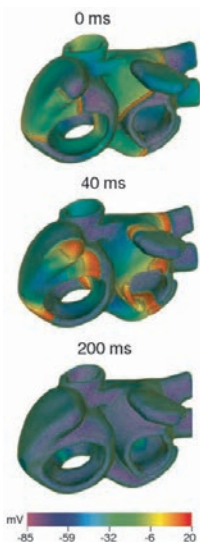

Figure 8.67: Scroll wave dynamics in the remodeled human atria, under the effect of global cooling at 5°C.

tools that allow precise, safe and at best painless control of the wave dynamics. Optogenetics offers such a possibility. We have shown *in silico* with numerical simulations that inhomogeneous illumination of optogenetically modified cardiac tissue can detach anchored spirals from inhomogeneities [5], and global, time-periodic, light-based sub-threshold perturbations lead to the controlled triggering of wave breaks [6]. The spatio-temporal modulation of tissue excitability by moving zebra-like illumination patterns at sub-threshold light intensity over optogenetically modified tissue can suppress spiral wave activity in a domain by way of transient chaos. In line with our previous findings [6], we observe reshaping of the spatial profile of the wave as we illuminate the stripes (Fig. 8.66). The initial state of the spiral in the domain is shown in Fig. 8.66(A). Here blue highlighted stripes indicate illuminated regions moving upwards. Wave breaks occur at a boundary between the illuminated and non-illuminated regions (Figs. 8.66(B-D)). Bold green arrows indicate the positions of the wave breaks. The created spirals are then constrained to propagate along the moving light stripes towards the in-excitable domain boundary and disappeared. Finally, the self-sustained spiral wave activity can be completely suppressed, as shown in Fig. 8.66(E) [7]. Thus, we have found a robust method to suppress spiral wave activity without prior information about the location and dynamics of the spiral. The method relies on introducing a transient chaotic state that survives for about 1-2 s.

With an alternative approach, we study numerically how temperature can be used to remove scroll waves from the heart, i.e. defibrillation of the atria by temperature. Ambient temperature has a profound influence on cellular electrophysiology through direct control over the gating mechanisms of different ion channels. We performed the first, detailed, systematic *in silico* study of the electrophysiological characterization of cardiomyocytes from different regions of the human atria ([8], Fig. 8.67), based on the effects of ambient temperature ($5 - 50°C$) and the Courtemanche-Ramirez-Nattel cellular model. Our studies show that different parts of the atria react differently to the same changes in temperature. We show how this heterogeneous response can provide an explanation for the development of a proarrhythmic substrate during mild hypothermia. We use the above concept to propose a treatment strategy for atrial fibrillation that involves severe hypothermia in specific regions of the heart for a duration of only ~ 200 ms (Fig. 8.67).

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