Anomalous Diffusion of Extracellular Vesicles in an Extracellular Matrix for Molecular Communication

Hamid Khoshfekr Rudsari, Mohammad Zoofaghari, Martin Damrath, Mladen Veletić, *Member, IEEE*, Jacob Bergsland, Ilangko Balasingham, *Senior Member, IEEE*

Abstract—Anomalous diffusion of extracellular vesicles (EVs) occurs because of the natural stiffness and stress relaxation of the extracellular matrix (ECM). This phenomenon has not been considered so far in attempts of computational modeling of the biodistribution of EVs, which is used as a powerful tool in pre-clinical and clinical practice. Here we present a novel model of the anomalous EV diffusion based on a 3-dimensional partial differential equation from the molecular communications theory, and solve it using the Green's function theorem. We also verify our analytical results using a particle-based simulation (PBS). The model encompasses a source function for the EV release from cells, their degradation through natural half-life, and extracellular binding. Our findings reveal that different anomalous schemes lead to various propagation patterns and can be used for providing insights into designing EV-based drug delivery systems.

Index Terms—Molecular communication, extracellular vesicle, extracellular matrix, anomalous diffusion, drug delivery.

I. INTRODUCTION

EXTRACELLULAR vesicles (EVs) are nano-sized carriers of different biomolecules which can be used as agents for therapeutic purposes [1]. They are secreted by most cells and diffuse throughout the extracellular matrix (ECM). The ECM is an active and dynamic part of a tissue made of non-cellular compartments formed via filamentous proteins, polysaccharide compounds and other biomolecules [2]. We study the heart as the selected organ and focus here on the cardiac ECM. The cardiac ECM serves the heart tissue for organ development and homeostasis. It contributes to multiple processes, such as cell migration in response to chemical and mechanical signals, conducting signals in the heart and contraction of cardiomyocytes [2]–[4]. The natural

Hamid Khoshfekr Rudsari is with the Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, 0316 Oslo, Norway, and the Intervention Centre, Oslo University Hospital, 0372 Oslo, Norway. e-mail: h.k.rudsari@studmed.uio.no

Mohammad Zoofaghari is with the Department of Electrical Engineering, Yazd University, Yazd 89195-741, Iran, and the Intervention Centre, Oslo University Hospital, 0372 Oslo, Norway. e-mail: zoofaghari@yazd.ac.ir

Martin Damrath is with the Department of Electronic Systems, Norwegian University of Science and Technology, 7491 Trondheim, Norway. e-mail: martin.damrath@ntnu.no

Mladen Veletić and Ilangko Balasingham are with the Department of Electronic Systems, Norwegian University of Science and Technology, 7491 Trondheim, Norway, and the Intervention Centre, Oslo University Hospital, 0372 Oslo, Norway. e-mail: {mladen.veletic@ntnu.no, ilangko.balasingham@ntnu.no}

Jacob Bergsland is with the Intervention Centre, Oslo University Hospital, 0372 Oslo, Norway. e-mail: jacob.bergsland@ous-hf.no

stiffness, as well as stress relaxation of the cardiac ECM, result in anomalous diffusion of EVs which is experimentally demonstrated [5]. Also, cardiovascular diseases (CVDs) can be caused by fibrosis, a result of aging or other diseases or injuries, leading to stiffened ECM and finally anomalous diffusion of EVs [6]. This means that computational models purely based on the Brownian motion fail in accurately describing the biodistribution of EVs in the cardiac ECM. This motivates us to study the anomalous diffusion of EVs in the heart with greater detail. The main concepts presented here could be extended to other organs. For example, anomalous diffusion can happen in the brain ECM due to the presence of dead-space microdomains [7].

The distribution of first passage time in anomalous diffusive media has been studied in the molecular communications (MC) theory [8] wherein bit error rate and inter-symbol interference for static and mobile transceivers were considered [9]–[12]. The described anomalous diffusion was based on (α, β)-propagation modeling in a space-time fractional diffusion equation with the different values of α and β determining the anomalous features of the propagation. The propagation medium of molecules was radially symmetric 3-dimensional (3D) free space [9]–[11]. In addition, a concentration Green's function for modeling anomalous diffusion in a cylindrical-shaped medium as part of an MC system has been studied [13], considering a fractional diffusion equation for modeling the anomalous diffusion in MC.

These previous approaches cannot be used for modeling the anomalous diffusion and biodistribution of EVs in the cardiac ECM due to its unique properties of hindrance. Also, the release of particles in the available works is based on a point source release scheme which is not plausible in a realistic biological setting. Furthermore, the degradation of EVs in the cardiac ECM has not been considered previously [14], [15].

In this letter, we take up the challenge of studying anomalous EV diffusion by utilizing the MC theory as a methodology. We analyze the scenarios displayed in Fig. 1, by considering specific features of the ECM such as tortuosity and volume fraction, natural degradation of EVs through their half-life, and interactions between the ECM and EVs by extracellular binding. We model the anomalous EV diffusion by a power-law function for the mean square displacement (MSD). Our approach utilizes a 3D partial differential equation (PDE) which we analytically solve with a time-dependent diffusion coefficient matrix in an unbounded ECM. We also verify our analytical solution using a particle-based simulation (PBS). The PBS used in this letter is adapted for the release of EVs
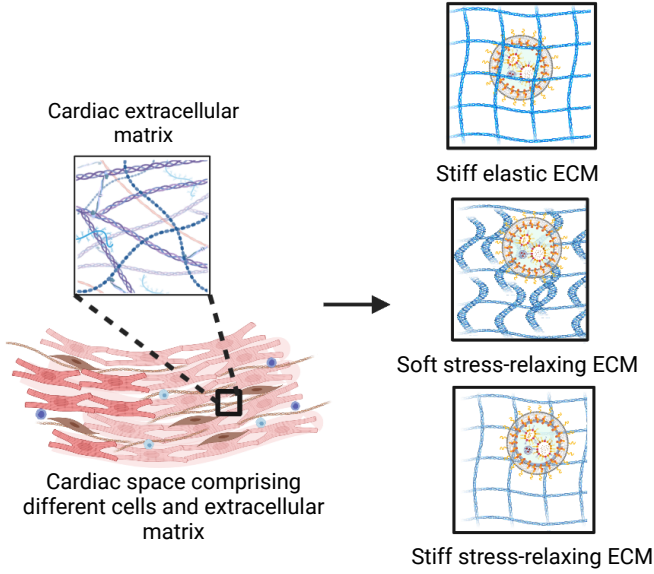
Fig. 1. Cardiac space is comprised of different types of cells such as cardiomyocytes, fibroblasts, lymphocytes, and macrophages, and the non-cellular extracellular matrix (ECM) which is mainly based on collagen type I and type III. Extracellular vesicles (EVs) can be distributed by their water permeation feature in the cardiac ECM while the matrix mesh size is larger than the EV's diameter. EVs have less movement in stiff elastic ECM whereas matrix stress relaxation helps EVs to escape matrix confinement. Stiff stress relaxation in the ECM matrix allows EVs to alter transport motions and improve their capability to transport biomolecules, which increases the mean square displacement of EVs.

which is based on a volume source function. Our analytical solution can be extended for the bounded media with different boundary conditions (BCs) such as Neumann, Dirichlet, and Rubin with respect to desired applications. Of note, more concepts from the MC theory could be used to analyze the EV-based drug delivery by applying the similarities between the delivery of EV therapy to the delivery of information [16].

In the remainder of this letter, in Section II, we model the anomalous diffusion of EVs in the cardiac ECM and analytically solve the 3D PDE. In Section III, we present the numerical results coming out of the presented model and discuss real scenarios of the cardiac ECM that can be modeled using our method. Finally, we conclude the paper in Section IV.

II. EXTRACELLULAR VESICLE BIODISTRIBUTION

Diffusion of EVs in the cardiac ECM follows a non-Brownian behavior. This happens for other biomolecules in different biological environments such as plasma fluids, nucleus, and cytoplasm [17]. The anomalous diffusion changes the MSD of EVs in the hindered ECM to follow a power-law function as [5]

$$\langle \text{MSD}(t) \rangle = D_0 t^\phi, \tag{1}$$

where D_0 is the generalized diffusion coefficient and ϕ can determine the anomaly; it ranges $0 < \phi < 1$ for subdiffusion, $\phi = 1$ for normal diffusion, and $\phi > 1$ for super-diffusion. Particles have less tendency to diffuse in a subdiffusive medium and vice versa in a super-diffusive medium [18].

We extend our previous EV biodistribution computational model [19] by addressing the challenge of the anomalous diffusion. The 3D PDE for EV concentration C in the cardiac ECM is

$$\frac{\partial C(\bar{r}, t)}{\partial t} = \nabla \cdot (D(t)\mathbf{H} \cdot \nabla C(\bar{r}, t))$$
$$- k_e(t)C(\bar{r}, t) + S(\bar{r}, t), \quad \text{in } \Omega \times T \tag{2a}$$
$$\text{IC: } C(\bar{r}, 0) = 0, \quad \text{in } \Omega \tag{2b}$$

where $\bar{r} = (x, y, z)$ is a point in the spatial domain Ω and $T = (0, t_R)$ is the time domain. The initial condition (IC) in (2b) assigns no EVs at the initial time of the simulation. The first part of (2a) models the movement of EVs according to the subdiffusion behavior in the cardiac ECM. The non-linear diffusion coefficient and the diffusivity tensor in (2) are given by

$$D(t) = D_0 t^{\phi-1}, \tag{3a}$$
$$\mathbf{H} = \begin{bmatrix} \dfrac{1}{\lambda_x^2} & \dfrac{1}{\lambda_y^2} & \dfrac{1}{\lambda_z^2} \end{bmatrix} \times \mathbf{I}, \tag{3b}$$

where $\lambda_i\Big|_{i \in \{x,y,z\}}$ is the tortuosity which models the hindrance of the cardiac ECM in three directions. The main difference between subdiffusion and normal diffusion in our model is highlighted by the power-law function given in (3a). This changes the linearity of diffusion and enable us to avoid considering the Brownian motion for the EV biodistribution. Eq. (3b) models the natural anisotropicity of the cardiac ECM [20] which models different tortuousness in different spatial directions.

The degradation of EVs modeled by $k_e(t)$ in (2) is given by [19]

$$k_e(t) = \frac{1}{\alpha}(k_h + k_d(t)), \tag{4a}$$
$$k_h = \frac{1}{\sigma}, \tag{4b}$$
$$\sigma = \frac{\Lambda_{1/2}}{\ln(2)}, \tag{4c}$$

where k_h models the half-life of EVs and k_d models the extracellular binding of EVs to the non-cellular compartments of ECM. The extracellular binding can be a function of time due to dynamic behavior of the cardiac ECM [2]. The half-life of EVs is 2-30 min and the extracellular binding is mainly happening due to interaction of EVs receptor with matrix molecules of the ECM [14], [15]. Also, α is the volume fraction of the cardiac ECM and determines the space for EV propagation in the cardiac ECM compared to the total volume of heart.

The source function $S(\bar{r}, t)$ is based on the EV release $\gamma(t)$ from cells secreting EVs as

$$S(\bar{r}, t) = S_x(x)S_y(y)S_z(z)S_t(t), \tag{5}$$

where

$$S_i(i)\Big|_{i \in \{x,y,z\}} = \exp\left(\frac{-(i - i_L)^2}{2\sigma_i^2}\right), \tag{6a}$$
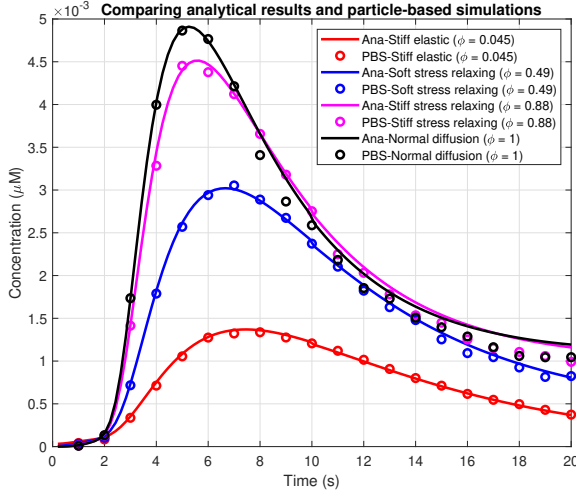$$S_t(t) = \frac{\gamma(t)}{\alpha}, \tag{6b}$$

Fig. 2. The concentration of EVs as a function of time for different anomalous diffusion regimes for comparing analytical results (Ana) and particle-based simulation (PBS), given by considering the degradation as $k_d = 0.1$ s^{-1} and the view point at x direction as $x = 5$ μm while $y = 0$ and $z = 0$. The types of anomaly are based on the parameter ϕ where $\phi = 0.045$ for stiff elastic, $\phi = 0.49$ for soft stress relaxing, and $\phi = 0.88$ for stiff stress relaxing schemes.

where i_L represents the location of the source in each direction and σ_i determines the spatial extension of the source through a Gaussian function. The release function can be designed with any type of practical functions with respect to the application.

To reach a closed form solution, we first change (2a) into a form with constant coefficients. Hence, an auxiliary function $K(\bar{r}, t)$ is defined as

$$K(\bar{r}, t) = C(\bar{r}, t)\beta(t), \tag{7a}$$

$$\beta(t) = \exp\left(\int_0^t k_e(t')\mathrm{d}t'\right). \tag{7b}$$

Then, the time derivative of $K(\bar{r}, t)$ is

$$\frac{\partial K(\bar{r}, t)}{\partial t} = \frac{\partial C(\bar{r}, t)}{\partial t}\beta(t) + C(\bar{r}, t)k_e(t)\beta(t). \tag{8}$$

By incorporating (8) in (2a), we yield

$$\frac{\partial K(\bar{r}, t)}{\partial t} = \nabla \cdot (D(t)\mathbf{H} \cdot \nabla K(\bar{r}, t)) + \beta(t)S(\bar{r}, t). \tag{9}$$

We introduce a new temporal parameter $\tau(t)$ as

$$\tau(t) = \int_0^t D(t')\mathrm{d}t', \tag{10}$$

Then, (9) is transformed by using the chain differentiation rule in terms of $\tau(t)$

$$\frac{\partial K(\bar{r}, \tau)}{\partial \tau} = \nabla \cdot (\mathbf{H} \cdot \nabla K(\bar{r}, \tau(t))) + \frac{\beta(t)S(\bar{r}, t)}{D(t)}. \tag{11}$$

It is worth noting that (11) can also be employed for bounded media with different types of BCs such as Neumann, Dirichlet, and Rubin BCs by using the auxiliary function, $K(\bar{r}, t)$.

Eq. (11) demonstrates an nonhomogeneous PDE in which the coefficients are no longer time-dependent and whose closed form solution is

$$C(\bar{r}, t) = \frac{1}{\beta(t)} \int_0^t \Big[(G^x (x, \tau(t) - \tau_0(t_0)) * S^x (x))$$
$$\times (G^y (y, \tau(t) - \tau_0(t_0)) * S^y (y))$$
$$\times (G^z (z, \tau(t) - \tau_0(t_0)) * S^z (z)) \Big]$$
$$\times \beta(t_0)S^t(t_0)\mathrm{d}t_0, \tag{12}$$

where

$$G^\nu (\nu, \tau(t) - \tau_0(t_0)) \Big|_{\nu \in \{x, y, z\}}$$
$$= \frac{1}{\sqrt{4\pi D_\nu (\tau(t) - \tau_0(t_0))}} \exp\left(\frac{-\nu^2}{4D_\nu (\tau(t) - \tau_0(t_0))}\right), \tag{13a}$$

$$\tau_0 = \int_0^{t_0} D(t')\mathrm{d}t', \tag{13b}$$

where $D_\nu \Big|_{\nu \in \{x, y, z\}} = \frac{D_0}{\lambda_\nu^2}$. Eq. (13a) demonstrates the Green's function of diffusion problem with the diagonal diffusion matrix. In (12), the operator $*$ denotes the spatial convolution which can be effectively calculated [19].

III. NUMERICAL RESULTS

We present the numerical results for the EV biodistribution in the cardiac ECM by considering the anomalous diffusion. The simulations are performed in MATLAB. We set the following values of the parameters: $D_0 = 1$ μm^2/s [5], $\{\lambda_x, \lambda_y, \lambda_z\} = \{1.1, 1.4, 1.7\}$ [5], $\alpha = 0.6$ [21], and $\{\sigma_x, \sigma_y, \sigma_z\} = 1 \times 10^{-6}$. We also set a fixed value of the EV half-life to 2 min. In our simulation, we consider the release rate $\gamma(t)$ presented in [22] by considering the heart rate of 120 beats per minute and the control signal of 25 μM/s. We assess different anomalous diffusion schemes in the cardiac ECM by assigning $\phi = 0.045$ for stiff elastic scheme, $\phi = 0.49$ for soft stress relaxing scheme, $\phi = 0.88$ for stiff stress relaxing scheme [5], and we set $\phi = 1$ for normal diffusion. The values of ϕ allocated to subdiffusion behavior for the cardiac ECM can be associated to cardiac disorders. Excessive accumulation of cross-linked collagenoufs ECM leads to myocardial stiffness which can be a result of an expansion in the cardiac ECM and promotes diastolic dysfunction [23]. For example, a stiffened cardiac ECM modeled by $\phi = 0.045$ can relate to how the EV biodistribution is affected by diastolic dysfunction. However, values of ϕ close to 1 can model a less stiffened cardiac ECM.

Fig. 2 verifies the analytically derived solution by a PBS for different anomalous regimes for the observation point at $x = 5$ μm and $k_d = 0.1$ s^{-1}. For this purpose, $S_t(t)$ is discretized with a temporal step size of $\Delta t = 10$ ms and 8511 particles. The spatial characteristic of the source function is represented by 203 equally spaced point sources. To determine the concentration at the observation point, the particles are counted in a spherical volume with 50 nm radius. The measured concentrations are averaged over 10^5
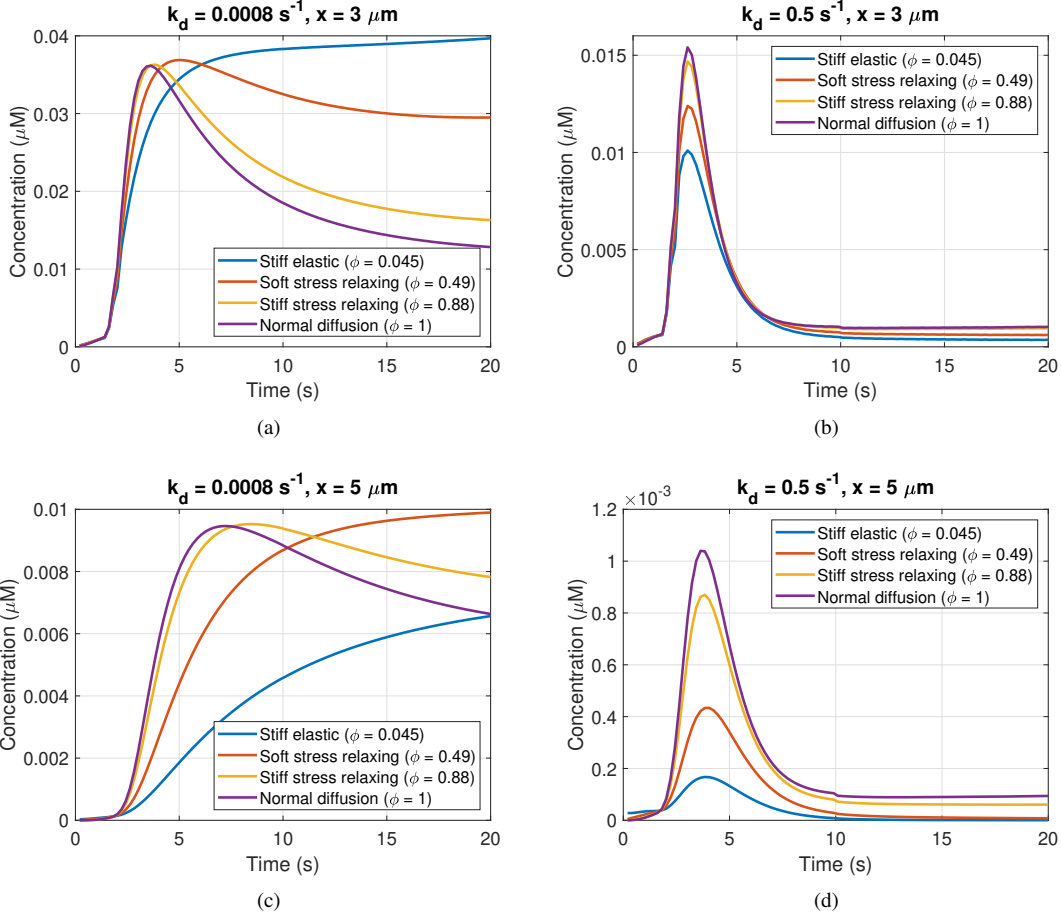
Fig. 3. The concentration of EVs are given as a function of time for two different values of $x = 3$ μm in (a) and (b) and $x = 5$ μm in (c) and (d) by considering $y = 0$ and $z = 0$ with various values of the extracellular binding rates k_d and different types of anomaly in the cardiac ECM.
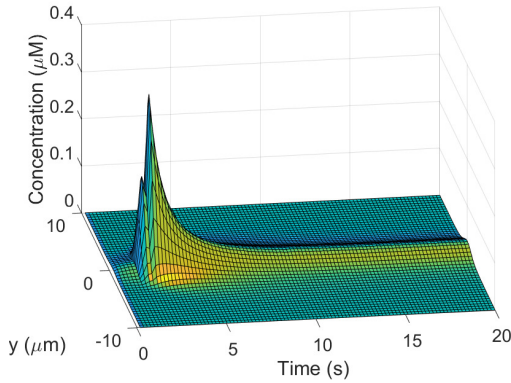

Fig. 4. 3D representation of the concentration of EVs over y direction in the Cartesian coordinate system as a function of time by setting $x = 0$ and $z = 0$. The degradation rate is $k_d = 0.1$ s^{-1} and $\phi = 0.88$. The EV concentrations over x and z directions are similar to this figure due to zero velocity.

realizations. The small deviations in Fig. 2 are caused by the limitations due to the unavoidable discretizations in time, space, and particles in PBS.

Fig. 3 shows the concentrations of EVs as a function of time for different view points and degradation rates. To assess the EV biodistribution, Figs. 3(a)-3(d) show that the EV concentration peak values for stiff stress relaxing scheme are greater than two other schemes. This behavior is expected since the stress relaxation of the ECM helps EVs to escape the matrix confinements and stiff stress relaxation of the ECM improves the EV transport motion and their capability to move faster [5]. On the other hand, stiff elastic scheme limits the EV propagation as Figs. 3(a)-3(d) present. Comparing different anomalous diffusion schemes with the normal diffusion, the EV concentration in normal diffusion is mostly smaller than the other anomalous scheme for $x = 3$ μm; however for $x = 5$ μm, the EV concentration for normal diffusion is higher than the other anomalous schemes because EVs move faster in normal diffusion toward the view point. Also, Fig. 3 presents that by increasing the degradation rate k_d: I) longer tails of concentration for all of the anomalous schemes occur due to a more extracellular binding of EVs, and II) a negative time shift of the concentration peak values occur.

By changing the view points from $x = 3$ μm in Figs. 3(a)-3(b) to $x = 5$ μm in Figs. 3(c)-3(d), we observe that the EV concentration decreases for different anomalous schemes due to inability of EVs to reach the longer view point in the cardiac ECM. The subdiffusive environment provides more time for EVs to bind to the ECM compartments which leads to more EV dissipation especially at farther observation points.

Anomaly also causes the EVs to remain longer in the environment which yields higher level of concentration levels. Also, the peak values of the concentrations of different anomalous schemes are departed from each other especially for smaller values of the degradation coefficient. This is because a stiff elastic matrix leads to less movement of EVs compared to soft and stiff stress relaxation matrix. Also, we observe that the peaks of the EV concentration for different anomalous schemes happen in more longer time by increasing the view point distance which is expected due to the longer distance for EVs to propagate in the ECM.

Fig. 4 shows a 3D view of the EV concentration for stiff stress relaxing regime in y direction over time. The source releases the EVs based on the rate given in [22] which has two peaks. Accordingly, Fig. 4 shows two peaks in the concentration for short distance view points. Also, the EV concentration profile for x and z directions are similar to Fig. 4 due to zero velocity in the cardiac ECM.

IV. Conclusion

Extracellular vesicles (EVs) are lipid-bilayered nano-carriers of biomolecules and have been used for drug delivery purposes. As experiments suggested, EVs anomalously diffuse in cardiac extracellular matrix (ECM) and follow non-Brownian movement. In this letter, we modeled the anomalous diffusion of EVs in the cardiac ECM by partial differential equations with a time-dependent diffusion coefficient, in which we considered the degradation of EVs through their natural half-life and extracellular binding. We also incorporated unique properties of the cardiac ECM like tortuosity and volume fraction. An analytical solution to the differential equations was derived based on Green's function theorem. We verified our analytical solution by particle-based simulation. We observed in the numerical results that anomalous diffusion can change the biodistribution patterns of EVs in the cardiac ECM by altering the amplitude and time of peak values in concentrations at different view points. Also, the degradation of EVs impacted their concentrations for different types of anomalous schemes in the cardiac ECM. Our method can be used to further model cardiac ECM for EV biodistribution with respect to the contraction and relaxation of cardiomyocytes which can finally change the pressure in the myocardium. Our findings can help prototyping practical drug delivery systems to prevent and treat cardiovascular diseases and potentially other types of disorders. Fine-tuning and verification of the suggested model can be done with experimental results in future works.

References

[1] S. Fu, Y. Zhang, Y. Li, L. Luo, Y. Zhao, and Y. Yao, "Extracellular vesicles in cardiovascular diseases," *Cell death discovery*, vol. 6, no. 1, pp. 1–9, 2020.

[2] G. del Monte-Nieto *et al.*, "Basic biology of extracellular matrix in the cardiovascular system, part 1/4," *Journal of the American College of Cardiology*, vol. 75, no. 17, pp. 2169–2188, 2020.

[3] A. C. Silva, C. Pereira, A. C. R. Fonseca, P. Pinto-do Ó, and D. S. Nascimento, "Bearing my heart: The role of extracellular matrix on cardiac development, homeostasis, and injury response," *Frontiers in Cell and Developmental Biology*, vol. 8, p. 1705, 2021.

[4] C. Spadaccio *et al.*, "The role of extracellular matrix in age-related conduction disorders: a forgotten player?," *Journal of geriatric cardiology: JGC*, vol. 12, no. 1, p. 76, 2015.

[5] S. Lenzini, R. Bargi, G. Chung, and J.-W. Shin, "Matrix mechanics and water permeation regulate extracellular vesicle transport," *Nature nanotechnology*, vol. 15, no. 3, pp. 217–223, 2020.

[6] S. Hinderer and K. Schenke-Layland, "Cardiac fibrosis–a short review of causes and therapeutic strategies," *Advanced drug delivery reviews*, vol. 146, pp. 77–82, 2019.

[7] F. Xiao, J. Hrabe, and S. Hrabetova, "Anomalous extracellular diffusion in rat cerebellum," *Biophysical Journal*, vol. 108, no. 9, pp. 2384–2395, 2015.

[8] T. Nakano, M. J. Moore, F. Wei, A. V. Vasilakos, and J. Shuai, "Molecular communication and networking: Opportunities and challenges," *IEEE Transactions on NanoBioscience*, vol. 11, no. 2, pp. 135–148, 2012.

[9] T. N. Cao, D. P. Trinh, Y. Jeong, and H. Shin, "Anomalous diffusion in molecular communication," *IEEE Communications Letters*, vol. 19, no. 10, pp. 1674–1677, 2015.

[10] D. P. Trinh, Y. Jeong, H. Shin, and M. Z. Win, "Molecular communication with anomalous diffusion in stochastic nanonetworks," *IEEE Transactions on Communications*, vol. 67, no. 12, pp. 8378–8393, 2019.

[11] D. P. Trinh, Y. Jeong, and S.-H. Kim, "Molecular communication with passive receivers in anomalous diffusion channels," *IEEE Wireless Communications Letters*, vol. 10, no. 10, pp. 2215–2219, 2021.

[12] L. Chouhan and M.-S. Alouini, "Rescaled brownian motion of molecules and devices in three-dimensional multiuser mobile molecular communication systems," *IEEE Transactions on Wireless Communications*, vol. 21, no. 12, pp. 10472–10488, 2022.

[13] S. Dhok, P. Peshwe, and P. K. Sharma, "Cognitive molecular communication in cylindrical anomalous-diffusive channel," *IEEE Transactions on Molecular, Biological and Multi-Scale Communications*, vol. 8, no. 3, pp. 158–168, 2022.

[14] C. Charoenviriyakul *et al.*, "Cell type-specific and common characteristics of exosomes derived from mouse cell lines: Yield, physicochemical properties, and pharmacokinetics," *European Journal of Pharmaceutical Sciences*, vol. 96, pp. 316–322, 2017.

[15] E. I. Buzás, E. Á. Tóth, B. W. Sódar, and K. É. Szabó-Taylor, "Molecular interactions at the surface of extracellular vesicles," in *Seminars in immunopathology*, vol. 40, pp. 453–464, Springer, 2018.

[16] Y. Chahibi, "Molecular communication for drug delivery systems: A survey," *Nano Communication Networks*, vol. 11, pp. 90–102, 2017.

[17] M. J. Saxton, "A biological interpretation of transient anomalous subdiffusion. i. qualitative model," *Biophysical Journal*, vol. 92, no. 4, pp. 1178–1191, 2007.

[18] R. Metzler, J.-H. Jeon, A. G. Cherstvy, and E. Barkai, "Anomalous diffusion models and their properties: non-stationarity, non-ergodicity, and ageing at the centenary of single particle tracking," *Physical Chemistry Chemical Physics*, vol. 16, no. 44, pp. 24128–24164, 2014.

[19] H. K. Rudsari, M. Zoofaghari, M. Veletić, J. Bergsland, and I. Balasingham, "The end-to-end molecular communication model of extracellular vesicle-based drug delivery," *IEEE Transactions on NanoBioscience*, 2022.

[20] W. L. Stoppel, D. Hu, I. J. Domian, D. L. Kaplan, and L. D. Black, "Anisotropic silk biomaterials containing cardiac extracellular matrix for cardiac tissue engineering," *Biomedical materials*, vol. 10, no. 3, p. 034105, 2015.

[21] C. A. Miller *et al.*, "Comprehensive validation of cardiovascular magnetic resonance techniques for the assessment of myocardial extracellular volume," *Circulation: Cardiovascular Imaging*, vol. 6, no. 3, pp. 373–383, 2013.

[22] H. K. Rudsari, M. Veletić, J. Bergsland, and I. Balasingham, "Targeted drug delivery for cardiovascular disease: Modeling of modulated extracellular vesicle release rates," *IEEE Transactions on NanoBioscience*, vol. 20, no. 4, pp. 444–454, 2021.

[23] A. D. Bradshaw *et al.*, "Pressure overload–induced alterations in fibrillar collagen content and myocardial diastolic function," *Circulation*, vol. 119, no. 2, pp. 269–280, 2009.

Hamid Khoshfekr Rudsari received the B.Sc. degree in electrical engineering major in telecommunications engineering from K. N. Toosi University of Technology, Tehran, Iran, and the M.Sc. degree in biomedical engineering from Tarbiat Modares University, Tehran, Iran, in 2017 and 2020, respectively. Currently, he is perusing the Ph.D. degree with the Department of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway. He is also doing his Ph.D. degree research work with the Intervention Centre, Oslo University Hospital, Oslo, Norway. Hamid is also a visiting adjunct scholar at the Michigan State University, East Lansing, MI USA, where he is doing a research visit at the Institute of Quantitative Health Science and Engineering. His main research interests include mathematical modeling and computer simulations of biological systems and the design and analysis of molecular communication-based networks for biomedical and health applications.

Mohammad Zoofaghari was born in Isfahan, Iran, in 1986. He received B.S. and M.S. degrees in Electrical Engineering from the Isfahan University of Technology, Isfahan, Iran, in 2009 and 2011, respectively, and the Ph.D. degree from the Amirkabir University of Technology, Tehran, Iran, in 2017. He is currently an Assistant Professor at the Department of Electrical Engineering, Yazd University, Yazd, Iran. In 2022, he also worked with the Intervention Center, Oslo University Hospital, Oslo, Norway as a visiting researcher. His current research interests include channel modeling and estimation in molecular communication using analytical and numerical methods, applied electromagnetic and microwave imaging.

Martin Damrath received the B.Sc., M.Sc., and Dr.-Ing. (Ph.D.) degree in electrical engineering from the Faculty of Engineering, Kiel University, Germany, in 2012, 2014, and 2020, respectively. From 2014 to 2021, he worked as a Research and Teaching Assistent at the Chair of Information and Coding Theory, Kiel University. He is currently a Postdoctoral Research Scientist at the Department of Electronic Systems, Norwegian University of Science and Technology (NTNU), Norway, and at The Intervention Center, Oslo University Hospital, Norway. His research interests include modeling of biological systems, molecular communications, and wireless communications.

Mladen Veletić is a researcher at the Department of Electronic Systems, NTNU, and the Technology and Innovation Clinic (The Intervention Centre), Oslo University Hospital. He is the author of 40+ academic papers published in leading journals and conferences of communications engineering, bio-engineering, and medicine. In his earlier career, Mladen Veletić completed a Ph.D. in Electronics and Telecommunications at the Faculty of Information Technology and Electrical Engineering, NTNU, and worked as a Senior Teaching and Research Assistant at the Faculty of Electrical Engineering, University of Banja Luka. He currently holds a Visiting Assistant Professor position at the Department of Telecommunications at the Faculty of Electrical Engineering, University of Banja Luka.

Jacob Bergsland received the MD degree in the Medical Faculty, University of Oslo in 1973. He had the following roles: the General Surgery Specialist at State University of New York, Buffalo, NY USA in 1981, Cardiothoracic Surgery Specialist at State University of New York, Buffalo, NY USA, in 1983, the Chief Centre for Minimally Invasive Cardiac Surgery at Kaleida Health, Buffalo NY in 1996, the Chief Centre for Heart Transplantation, Kaleida Health, Buffalo, NY in 1994, the International Director, Cardiovascular Surgery, University Clinical Centre, Tuzla, Bosnia in 1998, the Medical Director, BH Heart Centre, Tuzla, Bosnia in 2008. He is now a Cardiac Surgeon and Researcher in Intervention Centre, Rikshospitalet, Oslo University Hospital since 2002 and the Medical Director Cardiomech AS, Trondheim/Minneapolis since 2015.

Ilangko Balasingham is Professor of Medical Signal Processing and Communications at the Department of Electronic Systems, Norwegian University of Science and Technology (NTNU) in Trondheim, and Section Manager for Medical ICT Research at the Intervention Center, Oslo University Hospital. His research interests include super robust short-range communications for both in-body and on-body sensors, body area sensor networks, short-range microwave sensing of vital signs, short-range localization and tracking mobile sensors, and nanoscale communication networks. He has authored/co-authored 305 journal and conference papers and 9 book chapters and holds 6 patents. He has given 30 invited/keynotes at international conferences. In addition, he is active in organizing conferences (General Chair of the 2019 IEEE Int. Symposium of Medical ICT and the 2012 Body Area Networks (BODYNETS) conference; TPC Chair of the 2015 ACM NANOCOM) and editorial board (Area Editor of Elsevier Nano Communication Networks since 2013 and Specialty Chief Editor of Frontiers in Communications and Networks since 2020). He is a Senior IEEE member.