Modelling the Drug Release Kinetics of Mesoporous Silica Nanoparticles

A. Ganhör*, J. Karoliny*, D. Lehner*, A. Noel‡, Y. Salinas†, O. Brüggemann†, A. Springer*, and W. Haselmayr*
*Institute for Communications Engineering and RF-Systems, Johannes Kepler University Linz, Austria
†Institute of Polymer Chemistry, Johannes Kepler University Linz, Austria
‡School of Engineering, University of Warwick, UK

I. Introduction

There are emergent applications, such as smart drug delivery or smart infrastructure monitoring, where conventional wireless communication using electromagnetic waves is impractical or detrimental. As an alternative approach, molecular communications (MC), using molecules for the information exchange, has been proposed and received increasing attention over recent years [1]. Inspired by natural MC systems, various release and reception mechanisms have been investigated under different propagation environments. For the propagation of the signaling molecules from the transmitter (TX) to the receiver (RX), passive (free diffusion) and active (e.g., bacterial or molecular motors) transport mechanisms have been considered. The reception at the RX can also be classified as passive or active, where the former only observes the molecules and the latter affects the movement of the molecules (e.g., through absorption). The molecule release at the TX is affected by its geometry and the particle generation, where the information can be encoded in the concentration/number, type, and release time of the signaling molecules.

The prevalent TX considered in literature is the point TX [1]. Due to its zero-dimension, the impact of the geometry is not included in the model. Moreover, most works assume that the signaling molecules are produced instantaneously and released immediately into the environment. In [2], two spherical TXs with different initial molecule distributions have been investigated: i) the molecules are uniformly distributed over a virtual sphere; and ii) the molecules are initialized uniformly over the surface of a solid, impenetrable, and reflective sphere. The molecules are produced instantaneously and released immediately. In [3], the TX is modeled as a sphere with a point source at its center and the outer surface is covered by nanopores. Therein, the molecules leave the TX space through the nanopores, which is modeled by a modified diffusion coefficient. A TX with molecule storage has been presented in [4]. The molecules can exit the storage through an outlet, where the size of the outlet determines how many molecules diffuse into the environment. In [5] an ion-channel based TX has been presented, corresponding to a spherical object with ion-channel embedded in its membrane. By applying a voltage across the membrane, the ion-channels open and molecules can leave the TX.

The MC paradigm has been proposed as a promising approach to model drug delivery systems (DDSs) [1]. To model such a system, finding a good model for practical carriers of drug molecules is a crucial step. Silica nanoparticles with mesopores, so-called mesoporous silica nanoparticles (MSNP), are such promising drug carriers (see Fig. 1), possessing unique features such as biocompatibility, high loading capacity, and a plethora of surface functionalizations [6]. In DDSs it is important to assess the drug delivery performance, i.e., to determine the number of expected molecules at the receive site (e.g., tumor). Hence, in this work we derive an analytical expression for the number of drug molecules released from a fully loaded MSNP into the propagation channel (see Fig. 1). This is the first step towards the end-to-end impulse response, from loading the drug molecules to their observation at the RX.

The first three authors contributed equally to this work.

Fig. 1. Illustration of the drug molecules' release using MSNPs: i) first the MSNP is fully loaded with drug molecules, i.e., the molecules are encapsulated in the MSNP; ii) once the drug molecules' release is triggered the molecules diffuse through the mesopores into the environment.

II. Drug Release Kinetics of MSNPs

In this section, we mathematically describe the number of drug molecules entering the physical channel, starting from a fully loaded MSNP. First, we introduce the underlying system model and the prerequisites, and then we describe the drug release kinetics.

A. System Model and Prerequisites

We consider a three-dimensional unbounded fluid environment, with uniform temperature and viscosity. The MSNP has a spherical shape with radius r_{TX}. At time $t = 0$ the mesopores of the MSNP are fully loaded with drug molecules, which are released at $t > 0$. In the following, we use the Higuchi model [7] to describe the release kinetics of MSNPs, which requires that the following prerequisites are ensured: i) the concentration of the drug molecules inside the MSNP C_{m} is much higher than their solubility in the surrounding fluid C_{s} (written as a concentration), i.e. $C_{\mathrm{m}} \gg C_{\mathrm{s}}$; and ii) the concentration outside the MSNP is zero (perfect sink condition).

B. Release Kinetics

We start by deriving the release kinetics of a homogeneous matrix system, where the drug molecules are encapsulated in a homogeneous matrix (e.g., in a polymer). Once the matrix system is immersed in a dissolution medium, the drug molecules at the surface will be dissolved in this medium. This results in a linear concentration gradient and drug molecules diffuse from the inner to the outer layers of the sphere. Fig. 2 illustrates a sphere with a homogeneous matrix, where r_{TX} denotes the radius of the sphere and $r^{\star}$ refers to the unextracted part, i.e., the region where the molecules haven't yet start diffusing.

The total residual number of drug molecules in a sphere having a homogeneous matrix corresponds to the sum of that

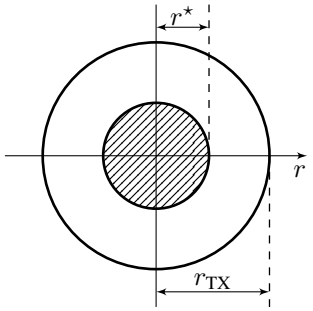

Fig. 2. Drug distribution in a sphere with a homogeneous matrix.

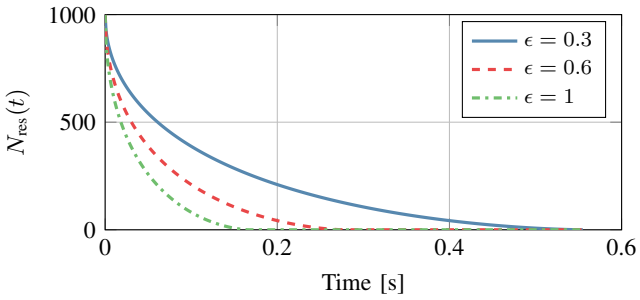

Fig. 3. Residual number of drug molecules in MSNP $N_{\mathrm{res}}(t)$ (obtained through (1) and (5)) for different porosity values ϵ and with $N_{\mathrm{res}}(t=0) = N_{\mathrm{res}}(r_{\mathrm{TX}}) = 10^3$ molecules.

in the unextracted portion ($r < r^\star$) and that in the region no longer saturated with the drug molecules ($r^\star < r < r_{\mathrm{TX}}$) [7]

$$N_{\mathrm{res}}(r^\star) = \frac{4}{3}\pi {r^\star}^3 C_{\mathrm{m}} + \int_{r^\star}^{r_{\mathrm{TX}}} 4\pi r^2 C_{\mathrm{a}}(r)\mathrm{d}r$$
$$= 4\pi\left[\frac{r^{\star 3}}{3}C_{\mathrm{m}} + \frac{C_{\mathrm{s}}}{6}r^\star\left(r_{\mathrm{TX}}^2 + r^\star r_{\mathrm{TX}} - 2r^{\star 2}\right)\right], \quad (1)$$

with $C_{\mathrm{a}}(r) = r^\star(r_{\mathrm{TX}} - r)/(r(r_{\mathrm{TX}} - r^\star))C_{\mathrm{s}}$, i.e., $C_{\mathrm{a}}(r^\star) = C_{\mathrm{s}}$ and $C_{\mathrm{a}}(r_{\mathrm{TX}}) = 0$. Hence, the change in the residual number of drug molecules with respect to the unextracted part $r^\star$ can be written as [7]

$$-\frac{\mathrm{d}N_{\mathrm{res}}(r^\star)}{\mathrm{d}r^\star} = 4\pi\left[r^{\star 2}C_{\mathrm{m}} + \frac{C_{\mathrm{s}}}{6}\left(r_{\mathrm{TX}}^2 + 2r^\star r_{\mathrm{TX}} - 6r^{\star 2}\right)\right]. \quad (2)$$

It is important to note that the relation in (2) is equal (with opposite sign) to the total flux over the time $\mathrm{d}t$ [7], i.e.,

$$\frac{4\pi D C_{\mathrm{s}}}{\left(\frac{1}{r^\star} - \frac{1}{r_{\mathrm{TX}}}\right)}\mathrm{d}t = \frac{\mathrm{d}N_{\mathrm{res}}(r^\star)}{\mathrm{d}r^\star}\mathrm{d}r^\star$$
$$DC_{\mathrm{s}}\mathrm{d}t = \left(\frac{r_{\mathrm{TX}} - r^\star}{r_{\mathrm{TX}}r^\star}\right)\left[r^{\star 2}C_{\mathrm{m}} + \frac{C_{\mathrm{s}}}{6}\left(r_{\mathrm{TX}}^2 + 2r^\star r_{\mathrm{TX}} - 6r^{\star 2}\right)\right]\mathrm{d}r^\star. \quad (3)$$

Through integration from r_{TX} to $r^\star$ and using the assumption $C_{\mathrm{m}} \gg C_{\mathrm{s}}$, we obtain

$$r_{\mathrm{TX}}^3 - 3r_{\mathrm{TX}}r^{\star 2} + 2r^{\star 3} \approx \frac{6r_{\mathrm{TX}}}{C_{\mathrm{m}}}DC_{\mathrm{s}}t. \quad (4)$$

This relation enables us to determine $r^\star$ as a function of time, i.e. $r^\star(t)$. Hence, substituting $r^\star$ by $r^\star(t)$ in (1) leads to the the residual number of drug molecules as a function of time, i.e., $N_{\mathrm{res}}(t)$,

Next, we consider a porous matrix system, where the drug molecules are encapsulated in a porous polymer (e.g., MSNP). In such systems, once the matrix is immersed in a dissolution medium the mesopores are filled with this medium. Thus, the shape and volume of the mesopores have a great impact on the release kinetics. As for the homogeneous matrix in (4), the following relation was derived for the porous matrix [7]

$$1 + 2\left(\frac{r^\star}{r_{\mathrm{TX}}}\right) - 3\left(\frac{r^\star}{r_{\mathrm{TX}}}\right)^2 = \frac{6D\epsilon C_{\mathrm{s}}t}{\tau r_{\mathrm{TX}}^2}, \quad (5)$$

where ϵ denotes the porosity of the matrix and τ is the tortuosity factor of the capillary system (i.e., within the pores). Similar as above, this expression can be used to derive $r^\star(t)$, which can then be substituted into (1) to obtain $N_{\mathrm{res}}(t)$. Due to the limited space, we omit the final closed-form expression of $N_{\mathrm{res}}(t)$ and just present the numerical evaluation in the next section.

III. Numerical Results

For the numerical results we used a TX with a radius of $1\,\mu$m that is initially loaded with $N_{\mathrm{res}}(t=0) = N_{\mathrm{res}}(r_{\mathrm{TX}}) = 10^3$ molecules. The diffusion coefficient and the tortuosity factor were chosen to be $10^{-9}\,\mathrm{m}^2/\mathrm{s}$ and 1, respectively. Fig. 3 illustrates the residual number of drug molecules for various porosity values ϵ over time. In particular, we numerically evaluated (1) using $r^\star(t)$ which was obtained from (5). We observe that the higher the porosity (i.e., more mesopores), the faster the release of the drug molecules.

IV. Future Directions

In this work, we have mathematically described the release kinetics of MSNPs, which are a promising carrier for drug molecules in DDSs. This initial work paves the way for many future works including: i) investigation of alternative models describing the release mechanism of porous matrix systems; ii) derivation of an end-to-end response, from loading the drug molecules to their observation at the receive site; iii) design of controlled drug release systems using (mobile) MSNPs; and iv) validation of the theoretical expression through practical experiments.

References

[1] N. Farsad, H. B. Yilmaz, A. Eckford, C. B. Chae, and W. Guo, "A comprehensive survey of recent advancements in molecular communication," *IEEE Commun. Surveys Tuts.*, vol. 18, no. 3, pp. 1887–1919, thirdquarter 2016.

[2] A. Noel, D. Makrakis, and A. Hafid, "Channel impulse responses in diffusive molecular communication with spherical transmitters," in *Proc. Biennial Symp. Commun.*, 2016. [Online]. Available: http://arxiv.org/abs/1604.04684

[3] U. A. K. Chude-Okonkwo, R. Malekian, and B. T. Maharaj, "Diffusion-controlled interface kinetics-inclusive system-theoretic propagation models for molecular communication systems," *EURASIP Journal Adv. Signal Process.*, vol. 2015, no. 89, pp. 1–23, Oct. 2015.

[4] R. Mosayebi, H. Arjmandi, A. Gohari, M. Nasiri-Kenari, and U. Mitra, "Receivers for diffusion-based molecular communication: Exploiting memory and sampling rate," *IEEE J. Sel. Areas Commun.*, vol. 32, no. 12, pp. 2368–2380, Dec 2014.

[5] H. Arjmandi, A. Ahmadzadeh, R. Schober, and M. Nasiri-Kenari, "Ion channel based bio-synthetic modulator for diffusive molecular communication," *IEEE Trans. Nanobiosci.*, vol. 15, no. 5, pp. 418–432, July 2016.

[6] S. Giret, M. Wong Chi Man, and C. Carcel, "Mesoporous-silica-functionalized nanoparticles for drug delivery," *Chemistry – A European Journal*, vol. 21, no. 40, pp. 13 850–13 865, 2015.

[7] T. Higuchi, "Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices," *Journal of Pharmaceutical Sciences*, vol. 52, no. 12, pp. 1145–1149, 1963.