MATHEMATICAL AND STOCHASTIC MODELLING OF MOLECULAR COMMUNICATION SYSTEMS FOR ADVANCED DRUG DELIVERY APPLICATIONS

by

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A dissertation submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

Faculty of Engineering and Information Technology

University of Technology Sydney

July 2020

Certificate of Original Authorship

I, Muneer Al-Zubi declare that this thesis, is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the School of Biomedical Engineering at Faculty of Engineering and Information Technology at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise reference or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This document has not been submitted for qualifications at any other academic institution.

This research is supported by the Australian Government Research Training Program.

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Date: 06/07/2020

Abstract

Molecular communication (MC) is an emerging nanoscale communication paradigm, biologically inspired by the cellular communications via biochemical molecules in the living organisms. The MC paradigm is highly suitable for modelling and abstraction of the underlying complex processes in the drug delivery systems (DDSs) over wide spatiotemporal scales. Targeted and implantable DDSs are advanced and engineered technologies for effective delivery of anticancer drugs to the cancerous tumors without affecting other healthy parts in the body. This approach offers an efficient alternative or adjunctive therapy to other treatment techniques, such as conventional chemotherapy, thermal ablation, and surgical resection. In-Silico (mathematical and stochastic) models are key tools to understand and quantify the various parameters and processes in the DDSs, including drug transport, release processes, reaction, and other physicochemical interaction processes in the biological microenvironments inside the body. These models play an essential role in the design and development of the DDSs which in order can reduce the animal experiments and can save time and reduce cost.

The focus of my Ph.D. research is to develop novel mathematical and stochastic simulation models using MC paradigm for localized targeted and implantable DDSs over nano- and micrometer scales in complex biological microenvironments. Using the MC paradigm, the drug delivery process is abstracted as a communication mechanism where the drug source acts as a transmitter while the target site (e.g., cancer cell) acts as a receiver and the biological environment through which the molecules get transported acts as a propagation channel. The anticancer drug molecules represent the information carriers that contain the physicochemical properties of the drug. We use system analysis approach using the channel impulse response (CIR) coupled with the signal processing technique (convolution) for modelling the targeted and implantable DDSs in tumor microenvironments (TME). This approach provides more general and flexible models compared to other modelling approaches.

The thesis made original contributions in the following four major aspects:

(1) Generalized mathematical and stochastic simulation models are developed for diffusion-based molecular communications (MC) in complex fluidic microenvironments that include multilayered physical structures, ligand-receptor reaction, anisotropic diffusion, and the effect of reactive obstacles. These generalized models are developed for modelling and design of both the targeted drug delivery systems (TDDS) as well as the molecular communication systems between bio-nanomachines or cells in such complex environments over microscopic scale. (2) The proposed multilayer MC models have been extended for modelling the intravascular TDDS including anticancer drug release from the nanocarriers (NCs) and drug transport across the endothelial barrier of the tumor vasculature in tumor microenvironments. (3) Novel mathematical and stochastic simulation models are developed for modelling the implantable drug delivery system (IDDS) in tumor by predicting and characterizing the release process and drug distribution in the surrounding tumor tissue. (4) Pharmacokinetic /Pharmacodynamics models are developed for modelling the combination therapy using local implantable drug delivery systems in solid tumors following thermal ablation therapy.

Acknowledgments

First and foremost, I would like to express my sincere thanks to my principle supervisor **Prof. Ananda Sanagavarapu** for the continuous support and help in my PhD study and related research, and for his patience, motivation, and huge knowledge. He helped me at all the times of my research and with writing of this thesis. I could not have imagined having a better advisor for my PhD study. Discussions with him helped me to work in this emerging topic besides producing this high-quality dissertation. Without him, the road towards the completion of this research would have been difficult. Also, I would like to thank my co-supervisor **Dr. Steve Ling** for his unceasing encouragement during my PhD study.

I am also grateful to University of Technology Sydney (UTS) for awarding me full prestigious international scholarships to undertake my PhD study.

Dedication

*To **my parents and my family** for their love, endless support and encouragement. I am forever indebted to my parents, who have always kept me in their prayers and taught me the meaning of life. Moreover, this thesis is dedicated to my beloved wife, **Duaa**, who has been a constant source of support and encouragement. Without them, the completion of this work would not have been possible.*

Abbreviations

AUC	Area Under the Curve
CIR	Channel Impulse Response
CT	Computed Tomography
DDD	Drug Delivery Device
DDS	Drug Delivery System
DOX	Doxorubicin
DTI	Diffusion Tensor Imaging
ECS	Extracellular Space
ECM	Extracellular Matrix
EPR	Enhanced Permeability and Retention
FDA	Food and Drug Administration
HT	Hyperthermia
IBP	Intervascular Blood Pressure
IDDS	Implantable Drug Delivery System
IFF	Interstitial Fluid Flow
IFP	Interstitial Fluid Pressure
ISFI	In-Situ Forming Implant
IVF	Interstitial Velocity Field
IVIVC	In Vitro - In Vivo Correlation
MC	Molecular Communication

MCvD	Molecular Communication via Diffusion
MEC	Minimum Effective Concentration
MRI	Magnetic Resonance Imaging
MSD	Mean-Square Displacement
MW	Molecular Weight
NC	Nanocarrier
PTX3	Pentraxin-3
PD	Pharmacodynamic
PK	Pharmacokinetic
PLGA	Poly (Lactic-co-Glycolic Acid)
QS	Quorum Sensing
RDME	Reaction-Diffusion Master Equation
RF	Radio Frequency
RFA	Radiofrequency Ablation
RMSE	Root-Mean Square Error
RN	Receiving Nanomachine
TDDS	Targeted Drug Delivery System
TME	Tumor Microenvironment
TN	Transmitting Nanomachine
TSL	Thermosensitive Liposome

List of Publications

Journals:

1. M. Al-Zubi and A. Sanagavarapu, "Modelling of Implantable Drug Delivery System in Tumor Microenvironment using Molecular Communication Paradigm", *IEEE Access,* vol. 7, pp. 141929-141940, 2019.
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4. M. Al-Zubi and A. Sanagavarapu, "Modelling of multilayer biological medium under molecular communication paradigm", *IEEE Life Sciences Conference (LSC)*, Australia, pp. 31-34, 2017.

Table of Contents

List of Figures

List of Tables