BIOPHARMACEUTICS MODELING AND SIMULATIONS

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Theory, Practice, Methods, and Applications

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To Hitomi

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PREFACE

> "Science is built of facts the way a house is built of bricks; but an accumulation of facts is no more science than a pile of bricks is a house."
>
> —Henry Poincare

The aim of this book is to provide a systematic understanding of biopharmaceutical modeling. Probably, this is the first book challenging this difficult task.

Biopharmaceutical modeling demands a wide range of knowledge. We need to understand the physical theories, the physiology of the gastrointestinal tract, and the meaning of drug parameters. This book covers the wide range of scientific topics required to appropriately perform and evaluate biopharmaceutical modeling. In this book, oral absorption of a drug is mainly discussed. However, the same scientific framework is applicable for other administration routes such as nasal and pulmonary administrations.

Oral absorption of a drug is a complex process that consists of dissolution, precipitation, intestinal wall permeation, and gastrointestinal transit. In addition, drug metabolism can also occur in the intestinal wall and the liver before drug molecules enter into systemic circulation.

Historically, a reductionist approach has been taken to understand the oral absorption of a drug. Each process of oral absorption was reduced to its subprocesses up to the molecular level. However, understanding each piece of the puzzle is insufficient in understanding the whole picture of oral absorption. It is critically important to reconstruct the whole process of oral absorption and understand the interrelationship between each piece that comprises oral absorption of a drug.

In the field of biology, computational systems biology has been emerging since the millennium [1]. In systems biology, the interactions between biological molecules are investigated in both reductionist and constitutive approaches to

understand the quantitative relationship between a disease state and each molecular process. In this book, a similar approach is applied for the oral absorption of a drug.

In the first section of this book, the whole picture of oral absorption is discussed. As the central dogma of oral drug absorption, the interplay of dissolution rate, solubility, and permeability of a drug is discussed in a comprehensive manner without using mathematics. Even though the discussion in the first section is only a conceptual and qualitative outline, correct understanding of this central dogma will be of great benefit for drug discovery and development. The central dogma of oral drug absorption is the basis of the biopharmaceutical classification system (BCS), which is widely used in drug discovery and development [2].

We then move forward to each theory that comprises the entire oral absorption model. In this book, the entire mathematical framework is called the "gastrointestinal unified theoretical framework (GUT framework)." The concept of "concentration" is first discussed in detail, as it is critically important for understanding biopharmaceutical modeling. Then, theories of solubility, dissolution, precipitation, membrane permeation, and drug metabolisms are discussed. Each theory is described based on the unified definition of drug concentration and then incorporated into the GUT framework.

We then move forward to the physiological and drug property data that is used for biopharmaceutical modeling. The quality of biopharmaceutical modeling heavily relies on the quality of input data. The input data are roughly categorized into drug property and physiological parameters. These data are reviewed from the viewpoint of their use in biopharmaceutical modeling.

Before moving on to the discussions about practical applications of biopharmaceutical modeling in drug research, the validity of biopharmaceutical modeling is critically reviewed. A step-by-step approach has been taken to validate the biopharmaceutical modeling employing Occam's razor as a leading principle.

As the applications of biopharmaceutical modeling in drug research, biopharmaceutical classification system, dose/particle size dependency prediction, selection of solid form and enabling formulation, food effect prediction, etc. are then discussed.

Next, the strategy to use biopharmaceutical modeling in drug research and regulatory application is discussed. Introduction of good simulation practice for biopharmaceutical modeling would be an emergent issue for regulatory application.

Many figures and tables are provided to make it easy to understand biopharmaceutical modeling. In addition, more than 900 references are cited. I hope that readers will enjoy reading this book and that this book will be a helpful reference for biopharmaceutical modeling.

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KIYO SUGANO

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2. Kitano, H. (2002). Computational systems biology. *Nature*, 420, 206–210.

LIST OF ABBREVIATIONS

API	Active pharmaceutical ingredient
A to B	Apical-to-basal
BA	Absolute bioavailability
BCS	Biopharmaceutical classification system
B to A	Basal-to-apical
CER	Ceramide
CFD	Computational fluid dynamics
CHO	Cholesterol
CM	Carrier mediated
CNT	Classical nucleation theory
CSSR	Critical supersaturation ratio
DDI	Drug–drug interaction
DRL	Dissolution-rate limited
DSC	Differential scanning calorimeter
DTA	Differential thermal analysis
FFA	Free fatty acid
FaSSIF	Fasted stated simulated intestinal fluid
FeSSIF	Fed stated simulated intestinal fluid
FIH	First in human
GET	Gastric emptying time
GI	Gastrointestinal
GUT framework	Gastrointestinal unified theoretical framework
HH	Henderson–Hasselbalch
IVIVC	*In vitro* (dissolution)–*in vivo* correlation
LCT	Long-chain triglyceride
LHS	Left-hand side

MCT	Medium chain triglyceride
MMC	Migrating motor complex
NBE	Nernst–Brunner equation
NS	Navier–Stokes
PAMPA	Parallel artificial membrane permeation assay
PC	Phosphatidylcholine
PDE	Particle drifting effect
PE	Phosphatidylethanolamine
PG	Phosphatidylglycerol
PI	Phosphatidylinositol
PK	Pharmacokinetics
PL	Permeability limited
PLM	Polarized light microscopy
PPS	Prediction process step
PS	Phosphatidylserine
PXRD	Powder X-ray diffraction
RHS	Right-hand side
RPM	Revolution per minute
SC	Stratum corneum
SEDDS	Self-emulsifying drug delivery system
SITT	Small intestinal transit time
SL-E	Solubility–epithelial membrane permeability limited
SL-U	Solubility–UWL permeability limited
SPIP	Single-pass intestinal perfusion
TC	Taurocholic acid
TG	Thermal gravity
USP	United state pharmacopeia
UWL	Unstirred water layer
A_H	Hydrogen-donor strength
AUC	Area under the curve (subscript indicates administration route, etc.)
$A_{\text{blood vessel}}$	Surface area of the blood vessel in the villi
Acc	Accessibility to villi surface
C_D	resistance coefficient
CF_{SSR}	Steady-state reduction correction factor
CL_h	Hepatic clearance
$CL_{h,int}$	Intrinsic hepatic clearance
CL_{perm}	Permeation clearance
$CL_{subepithelial}$	Permeation clearance of subepithelial space
CL_{tot}	Total clearance
CR	Controlled-release function
C_{active}	Effective concentration for active transport
C_{bile}	Concentration of bile acid
C_{bm}	Concentration of bile-micelle bound drug

$C_{dissolv}$	Dissolved drug concentration
$C_{dissolv,ss}$	Steady-state concentration
C_{nc}	Number of critical cluster per volume
C_p	Plasma concentration
C_{pd}	Particle-drifting coefficient
$C_{subepithelial}$	Concentration of drug in subepithelial space
C_{tot}	Total drug concentration
$C_{u,z}$	Concentration of unbound drug with charge z
C_{water}	Concentration of water (55.6 M)
DF	Degree of flatness of intestinal tube
$D_{albumin}$	Diffusion coefficient of albumin-bound drug
D_{bm}	Diffusion coefficient of bile-micelle-bound drug
D_{eff}	Effective diffusion coefficient
Disp	Dispersion coefficient for GI transit
$D_m(x)$	Local diffusion coefficient at position x in membrane
D_{mono}	Diffusion coefficient of monomer drug
Dn	Dissolution number
Do	Dose number
D_{oct}	Octanol–water distribution coefficient
Dose	Dose amount (subscript indicates administration route, etc.)
D_{paddle}	Paddle diameter
D_{vessel}	Diameter of vessel
F	Absolute bioavailability
Fa	Fraction of a dose absorbed (subscript indicates administration route, etc.)
Fa_{DRL}	Fa for the dissolution-rate-limited cases
Fa_{NI}	Fa calculated by numerical integration using the S1I7C1 model
Fa_{PL}	Fa for the permeability-limited cases
Fa_{SL}	Fa for the solubility-permeability-limited cases
Fa_{SS}	Fa calculated with steady-state approximation
$Fa_{min.\ limit}$	Minimum value of $Fa_{PL,}$ Fa_{SL}, and Fa_{DRL}
Fa_{sfo}	Fa calculated as sequential first-order processes of dissolution and permeation
F_{cn}	Frequency of addition of another molecule to critical cluster
Fg	Fraction not metabolized in intestinal epithelial cells
Fh	Fraction not metabolized in hepatic first pass
GIP	Position in GI tract
Gz	Graetz number
H_{paddle}	Height of paddle from vessel bottom
H_{viili}	Height of villi
J_{max}	Maximum flux by carrier-mediated transport
J_{nc}	Primary nucleation rate per volume per time
J_{perm}	Permeation flux

K_a	Dissociation constant
K_{bm}	Bile micelles–water partition coefficient
K_m	Michaelis–Menten constant
$K_{org}(x)$	Local partition coefficient at position x in membrane
K_{sc}	Partition coefficient into stratum corneum
K_{sp}	Solubility product
K_w	Ionic product for water
$K_{transit,k}$	First-order transition kinetic constant
L	Representative length
L_{GI}	Length of GI tract
N_A	Avogadro number
$N_{API,GI,k}$	Number of API particle bins in GI position k
N_n	Number of nuclei
N_p	Number of particles in one dose
P_{CM}	Carrier-mediated transcellular permeability
PE	Plicate expansion
P_{UWL}	UWL permeability in the GI tract
P_{WC}	Permeability by water conveyance
P_{app}	Apparent permeability of *in vitro* membrane permeation assay
P_{eff}	Effective intestinal membrane permeability
P_{ep}	Epithelial membrane permeability
P_{oct}	Octanol–water partition coefficient
P_{para}	Paracellular pathway permeability
$P_{plicate}$	Plicate surface permeability
P_{trans}	Transcellular pathway permeability
$P_{trans,0}$	Intrinsic transcellular pathway permeability of undissociated species
Q_{GI}	Flow rate along small intestine
Q_h	Hepatic blood flow
Q_{villi}	Villi blood flow
Q_{in}	Infusion rate
R_{GI}	Radius of GI tract
RK	Renkin function
R_{MW}	Apparent pore radius of paracellular pathway based on MW selectivity
RPM_{min}	Minimum agitation speed
R_{SA}	Ratio of drug particle surface area in UWL and villi surface area
Re	Reynolds number
R_{mucus}	Nominal pore radius of mucus layer
R_{para}	Apparent pore radius of the paracellular pathway
S_0	Intrinsic solubility of undissociated drug
$S_{0,rp}$	Solubility of particles with radius r_p

$S_{0,\infty}$	Solubility of particles with infinitely large particle size
SA_{API}	Particle surface area of API
SA_{GI}	GI surface area for absorption (based on smooth tube)
SA_p	Surface area for one particle
SRn	Steady state reduction number
S_{blank}	Solubility in a blank buffer (without micelles)
Sc	Schmitt number
$S_{cocrystal}$	Intrinsic solubility of cocrystal
$S_{dissolv}$	Solubility in a biorelevant media (unbound + micelle bound)
Sh	Sherwood number
Sh_{disk}	Sherwood number for rotating disk
Sh_p	Sherwood number for particle
Sh_{tube}	Sherwood number for tube
$Sn_{T_{si}}$	Saturation number at time T_{si}
Sn_{ini}	Initial saturation number (Sn_{ini})
S_{salt}	Intrinsic solubility of salt
$S_{surface}$	Solubility at solid surface
T_{DO1}	Time when drug amount remaining in small intestine gives Do = 1
T_m	Melting point (Kelvin)
Tn_{exss}	Extended steady-state duration number
U	Flow speed
U_e	Microeddy effect velocity
Ur	Urinary excretion fraction
$U_{rel,tot}$	Relative flow velocity
U_t	Terminal sedimentation velocity
VE	Villi expansion
V_{GI}	GI fluid volume
Vc	Velocity of intestinal fluid
V_{me}	Velocity representing microeddy effect
V_p	Volume of one particle
V_{rel}	Relative velocity between fluid and particle
V_t	Terminal (sedimentation) slip velocity
Vx	McGowans molecular volume
$W_{channel}$	Width of channel between villi
W_{villi}	Width of villi
X_{bm}	Bile-micelle-bound drug amount
$X_{dissolv}$	Dissolved drug amount
$X_{u,z}$	Amount of unbound drug with charge z
Z_{ch}	Zel'dovich number
Z_{para}	Paracellular pathway charge
d_{disk}	Disk diameter
d_p	Particle diameter

d_{tube}	Tube diameter
f_{PSB}	Volume percentage of each particle size bin in one dose
f_{bm}	Fraction of bile-micelle-bound molecule
f_{n},f_0	Fraction of undissociated species
$f_{\text{subepithelial}}$	Unbound fraction of drug in subepithelial space
f_{u}	Bile-micelle-unbound fraction
f_{up}	Plasma unbound fraction
f_{z}	Fraction of charged species
g	Gravitational acceleration constant
h	Unstirred water layer thickness
h_{HJ}	Criteria value for Hintz–Johnson model
h_{UWL}	Unstirred water layer thickness in the intestine
h_{WF}	Criteria value for Wang–Flanagan model
h_{fam}	Thickness of firmly adhered mucus layer
h_{UWLvitro}	UWL thickness in *in vitro* permeability assay
$h_{\text{subepithelial}}$	Thickness of subepithelial space
k_{B}	Boltzmann constant
k_{abs}	Absorption rate coefficient
k_{deg}	Degradation rate constant
k_{diss}	Dissolution rate coefficient
k_{el}	Elimination rate
k_{mass}	Mass transfer coefficient
k_{perm}	Permeation rate coefficient
l_{tube}	Tube length
m.p.	Melting point (Celsius)
m_{atom}	Number of atoms in molecule
r_{mono}	Molecular radius
r_{p}	Particle radius (at time t)
$r_{\text{p,PSB}}$	Particle radius for particle size bin
$r_{\text{p,ini}}$	Initial particle radius
$r_{\text{p,ini,PSB}}$	Initial particle radius for particle size bin
$r_{\text{p,nc}}$	Critical radius of nuclei
v_{atom}	Relative volume of atom
v_{m}	Molecular volume
z	Molecular charge
ΔC	Concentration gradient
ΔG_{nc}	Energy barrier for nucleation
ΔH_{m}	Enthalpy of melting
ΔS_{f}	Entropy of fusion
ΔS_{m}	Entropy of melting
Π	Particle shape factor
β	Lump constant (β) of foreign particle number, sticking provability, etc
γ	Interfacial tension between solid surface and fluid

ε	Agitation strength (Energy input per time)
η	Kolmogorov's minimum eddy scale
λ_{disso}	Dissociation resistance from solid surface (in length dimension)
λ_{nc}	Interfacial attachment resistance (in length dimension)
μ	Viscosity of fluid
ν	Kinematic viscosity of fluid
ρ_f	Density of fluid
ρ_p	True density of drug
ψ_{cn}	Interfacial reaction rate correction factor