Implementation of Fractal Pharmacokinetic in the Compartmental Modeling

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BACKGROUND

Demands for pharmacokinetic / pharmacodynamic modeling

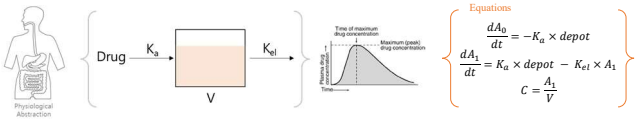
- Regulatory affair: bioequivalence (generic drugs, formulation change), Drug repurposing, First-in-human dose and some other tasks…
- Modifications in formulations are vigorously made on existing drugs
- From oral drug to topical applications, other forms of injection…
  ex) Extended / Controlled release, Burst release etc…

*Considerations of methods in various fields

Fields	Classical	Nonclassical
Geometry	Euclidean	Fractal
Topology	Ordered media	Disordered media
Diffusion	Regular	Anomalous
Kinetics	Deterministic	Stochastic
Dynamics	Linear	Nonlinear

CA (compartmental analysis)

- Compartment model analysis: Description of drug mechanistic in body / formulation is made
- Can provide a precise diagnostics based on variability identification (in non-linear mixed effect modeling)
- Population pharmacokinetics / Physiologically-based pharmacokinetics
- Homogeneity assumption is dogmatic in compartmental analysis, which means an instant blending. Not really happening in the nature, particularly in micro-environments.
- Fixed rate constant is true only under the homogeneity assumption. It bears no anatomical or physiological connotation other than referring to the ensemble of all the tissues



In time-varying rate problem

following modeling techniques are not sufficient to represent kinetic mechanism in real:

- Michaelis-Menten kinetics:
  Mostly used for describing drug-transporter relationships, could be applied to this kind of problem, but it lacks explainability when characterizing passive movement of target drugs
- Change-point based approaches:
  Used to control drug flows by applying modeled times, activating functions etc., can be unnatural depending on the situation it is used
- Separating compartmental spaces:
  Does not happening in real-world, descriptive modeling only, difficulties in expending the meaning of the model to other application

Suggested kinetic expression

- Fractal-like kinetics in consideration of compatibility with conventional ODE solver-based software
- Introduction of non-classical concepts onto the classical CA approach to reflect heterogeneity in real clinical settings
- Fractal-like kinetics (transient): Use of fractal exponent, 'heterogeneous' exponent for the trajectories of the process

Equation: "$\text{rate} = \frac{\theta}{time^h}$"

- Technically, fractal exponent 'h' in given equation decides the power of rate reduction over time

OBJECTIVES

To where, this fractal pharmacokinetic pattern could be applied?

1. Simulation Study
- Exploration of fractal-like kinetics on essential elements in the pharmacokinetics:
Absorption, Distribution, Metabolism, Excretion
2. Modeling Study
Modification of existing pharmacokinetic models with fractal rate inclusion to see its effect on performance

METHODS

1.1. Simulation study

- Exploration of fractal-like kinetics on essential elements in the pharmacokinetics: ADME (Absorption, Distribution, Metabolism, Excretion)
- Typical PO 2-compartment model was tested in this study, fractal-like rate coefficient was applied to the following parameters in the compartment model: Ka, CL, Q, V1, V2

1.2. Simulation Scenario

- Fractal exponent on fractal-like rate coefficient was changed by 0.01 in every iterations to visualize the parameter's contribution to the PK profile
- Simulations were done with three different conditions between Ka and CL, two different conditions between Vc and Vp which is presented as difference of Kcp and Kpc
- The values of parameters used in the simulations are as follows:

Simulation	A (Kcp < Kpc = Vc > Vp)			B (Kcp > Kpc = Vc < Vp)		
Condition	Ka < CL	Ka = CL	Ka > CL	Ka < CL	Ka = CL	Ka > CL
Ka	0.033	0.1	0.3	0.033	0.1	0.3
CL	0.3	0.1	0.033	0.3	0.1	0.033
Q	-	3	-	-	3	-
V1	-	10	-	-	10	-
V2	-	1	-	-	100	-
h	-	0 – 1.00	-	-	0 – 1.00	-

2.1. Estimation study

- Modification of existing pharmacokinetic models with fractal rate inclusion
- NONMEM (7.5.0); Saddle point reset, PsN (5.2.6); Method of parallel retries (parameter perturbation)
- Diagnostics: Visual Predictive Check (VPC), Goodness of fit (GOF), Bootstrap method
- Estimation condition: FOCEI (First-Order Conditional estimation with interaction) method was chosen for estimation

2.2. Modeling case

Five cases of model were collected. Fractal-like equations were applied to the Case 1 and 2 for transdermal patch, case 3 for intramuscular injection, case 4 and 5 for antibody drug injection. Performances of models were evaluated with Goodness of Fit Plot (GOF), Visual Predictive Check (VPC), Normalized-Prediction Distribution Error (NPDE)

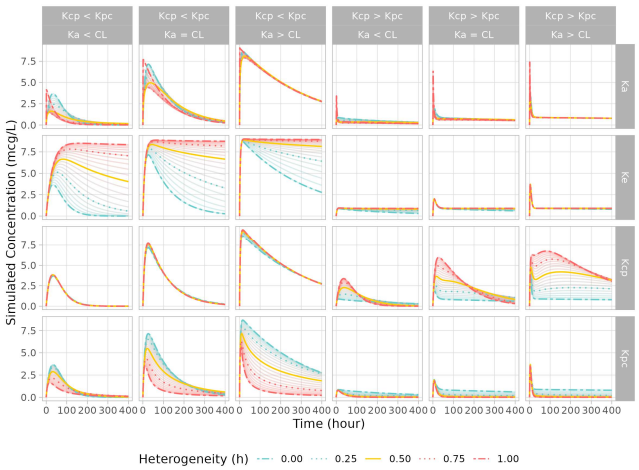
2.3. Model evaluation metrics

- OFV (Objective function value), AIC and AICc (Akaike's Information Criterion, and Corrected AIC)
  - AIC = OFV + 2k (k: number of free parameters)
    AICc = AIC + (2k(k+1))/(n-k-1) (n: number of observations, Erik Olofsen et al., 2014)
  - Sensible criterion for comparing models with different number of parameters
- Coding implementation for equation (in repeated dose for case 2)
  - Kfrac = EXP(LOG(K) - H*LOG(TIME - TAD + TAU))
    → K: conventional rate constant, TIME: time, TAU: For preventing 0 value in log, TAD: time after dose

RESULTS

1. Simulation study

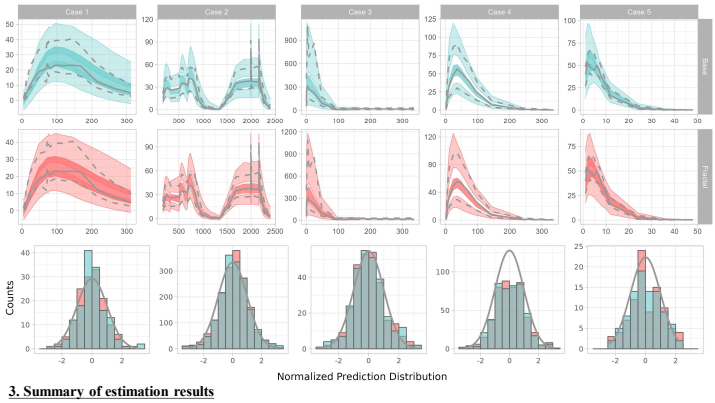
- Upper gray labels: Left 3 columns for simulation A conditions, another 3 columns for simulation B conditions
- Right gray labels: Fractal-like kinetics were applied to Ka (absorption rate), Ke (elimination rate), Kcp (rate central to peripheral), Kpc (rate peripheral to central)



- By addition of fractal rate, a distinguishable double peak was observed under the condition where peripheral volume is much larger than central's. In addition, IV like patterns in PO dose were observed in fractal absorption, and amount trapping was observed in fractal elimination
- Fractal rate on absorption is thought to be the most observable in real situation (applied to the next estimation study)

2. Estimation study

- Prediction corrected Visual predictive Checks were made to each case (upper two rows of figures). Both model showed good agreement in between observations and predictions but slightly different in variability. In most cases, the confidence intervals of predictions were decreased
- NPDE (lowest figures), GOF results were slightly improved, OFVs improved in most cases



3. Summary of estimation results

Model		Case 1	Case 2	Case 3	Case 4	Case 5
No. of subjects		18	44	20	40	8
No. of observations		383	3024	339	472	93
No. of parameters – Base model		12	13	16	21	10
No. of parameters – Fractal model		13	14	18	22	12
Estimate of fractal exponent (h)		0.32	0.894	0.0268	0.277	0.139
OFV	OFV – Base model	1443.70	13977.10	2155.43	1556.43	358.47
	OFV – Fractal model	1410.08	13592.00	2153.54	1539.64	350.13
	Difference (Δ)	-33.62	-385.10	-1.89	-16.79	-8.34
AIC	AIC – Base model	1467.70	14005.10	2187.43	1598.43	378.47
	AIC – Fractal model	1436.08	13624.00	2189.54	1583.64	374.13
	Difference (Δ)	-31.62	-381.10	2.11	-14.79	-4.34
AICc	AICc – Base model	1468.54	14005.24	2189.11	1600.48	381.15
	AICc – Fractal model	1437.07	13624.18	2191.67	1585.89	378.03
	Difference (Δ)	-31.47	-381.06	2.55	-14.58	-3.12

CONCLUSION & DISCUSSION

- The core model structure was not changed to test pure outcome of fractal kinetic for a single process. If the structure can be modified, it is expected to be a better descriptive model for all
- For two cases of transdermal patch, the OFV has decreased in greater level when compared to the antibody cases. OFV for IM injection has scored almost identical. Still, the model was improved with structure modification.
- Application of fractal kinetics to the drug absorption phase can offer mechanically-suitable PK interpretation with better agreement between observations. Because of its nonlinearity behavior, it could affect subsequent simulation results like dose-optimization
- Another fractal-like equations will be tested (ex. Steady state fractal-like kinetics, fractal-Menten kinetics)

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