APPLYING SYSTEM DYNAMICS TO THE STUDY OF
PHARMACOKINETICS AND PHARMACODYNAMICS

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ABSTRACT

As an effective method of understanding the dynamic behavior of
complex systems, system dynamics has great potential in the study
of the dynamic course of drug absorption, distribution, metabo-
lism, excretion and effect, which is the content of the discip-
lines called pharmacokinetics and pharmacodynamics. Two ways of
applying SD are discussed: using DYNAMO to solve the traditional
pharmacokinetic models --- compartment models and combining
knowledge of pharmacokinetics and pharmacodynamics to set up
advanced models under the paradigm of system dynamics. The
apllication of the method, technique and modeling view of system
dynamics to pharmacokinetics and pharmacodynamics can be very
helpful and fruitful.

INTRODUCTION

Due to its effectiveness and convenience of studying the dynamic
problems of complex systems [4], system dynamics (SD) has been
made great application and development in China recent years. But
the application of SD in China is mainly limited to such systems
as socio-economic technology-ecology. Its application in biologi-
cal science and pharmacological study still requires more ef-
forts, it may be fruitful and promising since SD is very suitable
to be applied in these fields. This paper studies the drug absor-
ption, distribution, metabolism, excretion, effect and their
interactions in the human body in terms of the technique and
modeling method of system dynamics, and intends to initiatelly
the application of system dynamics in pharmacokinetics and phar-
macodynamics.

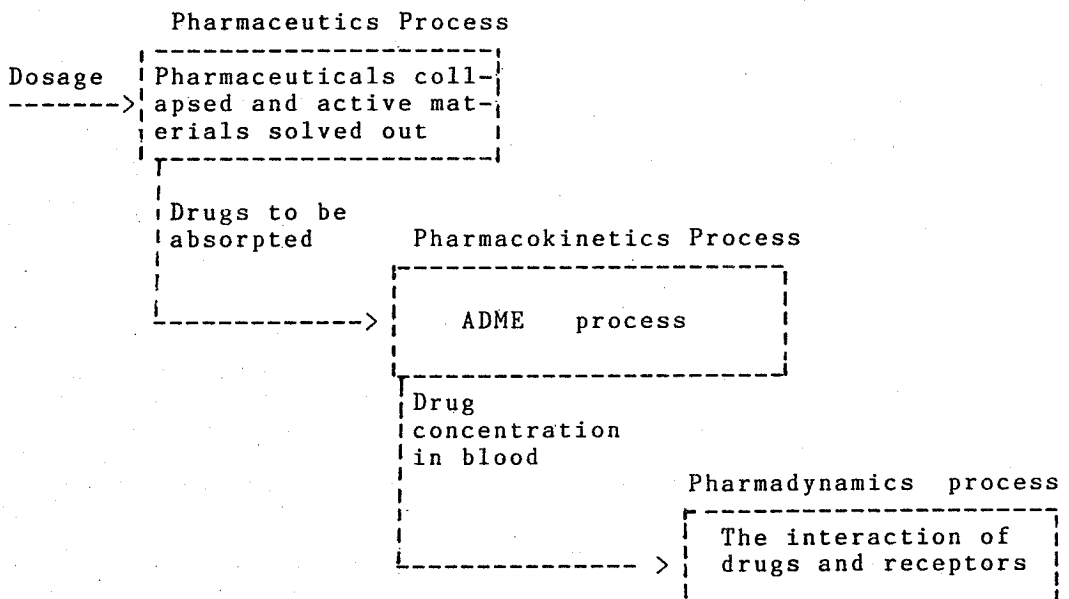## PHARMACOKINETICS, PHARMADYNAMICS AND SYSTEM DYNAMICS

Pharmacokinetics is the study of the process of drug absorption,
distribution, metabolism, and excretion (abbreviated ADME) . It
is a quantative study as well as a biologic study. By the first
appearance, it seems that the relationship of pharmacokinetics to
system dynamics, which is the study of dynamic behavior of gene-
ral complex systems, is only that of particularity to generaliza-
tion, that pharmacokinetics is only the application of the SD's
principles of studying general complex system to the study of a
specific system --- the human body. But in fact it is not the
case.

Pharmacokinetics was first a branch of pharmacology. Then it develops as the combination of mathematics (esp. defferential calculus and statistics) and pharmacology. Thus its approach is to establish the mathematical equations, or more specifically, differntial equations about the drug process, use experimental data and statistical method to determine the parameters of the equations and then solve the equations analytically. [3]

System dynamics, founded by professor Forrester at M.I.T., is a field which analyzes and studies information feedback system. It combines ideas from three fields --- control engineering (the concepts of feedback and system self-regulation), cybernatics (the nature of information and its role in control systems), and organizational theory (the structure of human organizations and the forms of human decision making). From these basic ideas, Forrester developed a guiding philosophy and a set of representational techniques for modeling complex, nonlinear, multiple loop feedback systems. [2] We can be sure to say that the current pharmacokinetics models nearly make no use of the SD techniques, let alone use its modeling philosophy. And we know that even studying the same problem, different philosophies, different methods can result in different achievements.

Pharmadynamics concerns the relationship of drugs to the intensity and course of pharmacologic (therapeutic and toxicologic) effects on the human body. Generally speaking, from dosing to generating effects, it will experience three processes: pharmaceutics process, pharmacokinetics process and pharmadynamics process. See Figure 1: [8]

Figure 1: The Drug Process

Pharmaceutics Process

Dosage
-------> Pharmaceuticals coll-
apsed and active mat-
erials solved out

Drugs to be
absorpted   Pharmacokinetics Process

------------->   ADME   process

Drug
concentration
in blood

                                Pharmadynamics   process

                                The interaction of
------------- >   drugs and receptors

It is necessary to point out that there exit close-loop feedback interactions between the processes, especially between the pharmacokinetics process and pharmadynamics process. The current models are not so ready to take into account of such close-loop feedback interactions because of the limitation of the paradigm and technique they employ. Most of them just simply ignore these interactions. This simplification is necessary to facilitate the traditional scientific study approach which just focuses atten- tion to one part of the system while assumes "other things being equal". This study proves to be fruitful and sometimes it is allowable and sometimes it is the only effective way to go. A lot of knowledges and data are acumulated in this way.

But the human body is a system, no doubt that if we include those close-loop feedback interactions in one model and thus organize available knowledges of pharmadynamics and pharmacokinetics in a systematic way, it will bring about a breakthrough in this area. However, as we will see later, it will result in a high-order, multiple-loop, nonlinear feedback structure model. Then what prevent us to do so?

The barrier to progress is not lack of data or knowledges. As Forrester points out: we have vastly more information than we use in an orderly and organized way. The barrier is deficiency in the existing theories of structure. Furthermore, the structuring of a proper system theory must be done without regard to the boudaries of conventional intellectual disciplines, [1] in our case that of pharmadynamics and pharmacokinetics. Professor Forrester not only points out the barrier but also provides the facility to overcome it, that is, System Dynamics.

Nonlinear, high-order, lagged feedback relationships are notoriously difficult to handle mathematically. This explains partly why current models evade them even when encountered. Forrester and his associates developed a computer simulation language called DYNAMO that allows nonlinearities and time delays to be represented with great ease, even by persons with limited mathematical training --- this is especially meaningful in our case since most doctors, pharmacology experts in China belong to this group due to the deficiecy of our education system. DYNAMO is a very specialized language developed to express the basic postulates of the system dynamics paradigm and to be easily understandable to laymen. It is widely used by system dynami- cists. But DYNAMO can also be used to program linear open-system models that are not philosophically system dynamics models at all. [3]

Now we first discuss how to use DYNAMO to solve the common pharmacokinetic models --- compartment models. They are mainly linear, open-system models. But as we will see that the employ- ment of DYNAMO is still helpful and useful because of its clarity and convenience. Furthermore, this discussion provides us a basis on which we can build advanced models under system dynamics

paradigm.

COMPARTMENT MODELS SOLVED USING DYNAMO

The most commonly employed approach to the pharmacokinetic
characterization of a drug is to represent the body as a system
of compartments, even though these compartments usually have no
physiologic or anatomic reality, and to assume that the rate of
transfer between compartments and the rate of drug elimination
from compartments follow first-order or linear kinetics.
Compartments can be considered as a body cavity or an assumptive
theoretical storage in which the drug are well-distributed. So
compartments are just like "levels" in SD's terms and transfer
rates connected to them are also SD's "rates". There are so
called one-compartment model, two-compartment model and multicom-
partment models, thus they correspond to one-order (or one
level), two-order and high-order models. [2] [5]

Drug elimination from the body can and often does occur by
several pathways, including urinary and biliary excretion,
excretion in expired air, and biotransformation in the liver or
other fluids or tissues. If the body and these parts work
normally or healthfully (we will abandon this assumption later)
and at low concentrations of drug (i.e., concentration typically
associated with therapeutic doses), the rate of these enzymatic
processes can be approximated very well by first-order or linear
dynamics. [2]

For example, the intravenous injection one-compartment model:
drugs such as antipyrine when intravenous injected have the
following characteristics: [5]

  (1) Distributed evenly and rapidly throughout the body after
      injected.
  (2) The drug process in the body mainly equals the elimination
      process.
  (3) The rate of elimination of drug from the body at any time is
      proportional to the amount of drug in the body at that time.

Using flow diagram we can dipict above case like Figure 2:

Figure 2: One-compartment Model
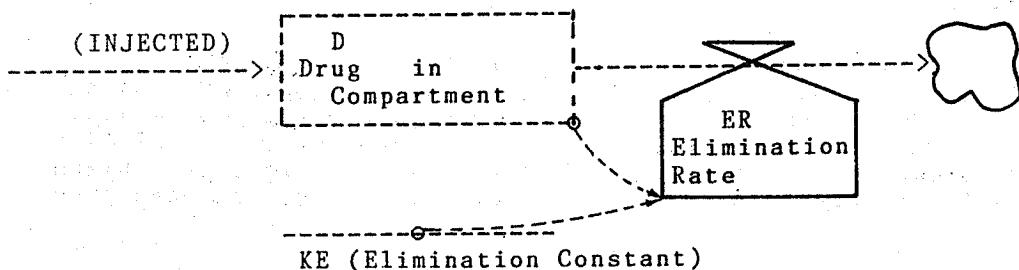
Represented by DYNAMO:

```
L  D.K=D.J-DT*ER.JK                               (1)
N  D=D0                                           (2)
R  ER.JK=D.K*KE                                   (3)
C  KE=_____  (Specific value)                    (4)
```

Where
  D --- Drug amount in the compartment (mg)
  D0 --- The initial drug amount injected (mg)
  ER --- Elimination Rate (mg/hr)
  KE --- Rate constant (dimensionless)

Even readers with primary calculus knowledge will be able to give
the analytical solution:

```
D(t)=D0*exp(-KE*t)                                (A)
```

This example is so simple that we can see no advantage of using
DYNAMO over searching for analytical solution. But the following
cases make full sense for the solutions other than analytical
one:

a.Multicompartment models:

The one-compartment model requires that drugs are evenly and
rapidly distributed through out the body. That is not necessarily
the reality. The transfer of many drugs between tissues, organs
and bones differs greatly. Thus multicompartment models are
needed to study the change of drugs in the body precisely. For
example, the two-compartment model assumes a central compartment,
whose apparent volume of distribution is relatively larger, and a
peripheral compartment, whose apparent volume is smaller, eg:
blood as central compartment and tissues as peripheral compart-
ment. [5]

From the view point of mathematics adding a compartment means
adding one equation and the order of the equations will increase
by one. This will increase the difficulty for solution. But with
DYNAMO, we can easily add level variables and corresponding rate
variables.

b.Extavascular (e.g., oral, intramuscular, etc.) dosing:

Unlike intravenous injection, there is an absorption process and
the drug enters the blood circulation gradually. This can be
treated by adding a material delay in DYNAMO.

c.Multiple dosing:

This is more frequently the practical case. Most drugs are
administered with sufficient frequency that measurable and often
pharmacologically significant levels of drug persist in the body

when a subsequent dose is administered. For drugs administered in a fixed dose at a constant dosing interval (e.g., every 12 hours), we can use PULSE function in DYNAMO to deal with but it is difficult to solve analytically. And even for cases administrated in a variable dose at a inconstant dosing interval, in which analytical solutions are nearly impossible, we can still handle them by the TABLE function of DYNAMO. To achieve therapeutic concentration more quickly, in clinical administration the first dosage is sometimes increased, this presents no problem either.

Now we take an extravascular dosing, two-compartment model to demonstrate above discussion.

A group of experts in Chengdu City, China, have done an experiment: they had ten persons take 500 milligram tetracycline fluid orally. Then they recorded the drug quantity in their urine, then averaging the data. [5]

The flow diagram is like figure 3 (see next page).

For the absorption compartment (or a material delay instead):

$$L \quad DA.K=DA.J-DT*AR \qquad (6)$$
$$N \quad DA=DO \qquad (7)$$
$$R \quad AR.KL=DA.K*KA \qquad (8)$$
$$C \quad KA=0.6597 \qquad (9)$$

Where
  DA --- Drug amount in the absorption compartment (mg)
  AR --- Rate from absorption compartment to central compartment (mg/hr)
  KA --- Rate constant for DA, Pharmacologic constant (dimensionless)
  DO --- Dosing amount at time zero (mg), for taking fluid orally we can assume the absorption delay equals zero, and the absorption is complete, so

$$C \quad DO=500 \qquad (10)$$

Figure 3: Flow Diagram of the Two-compartment Model
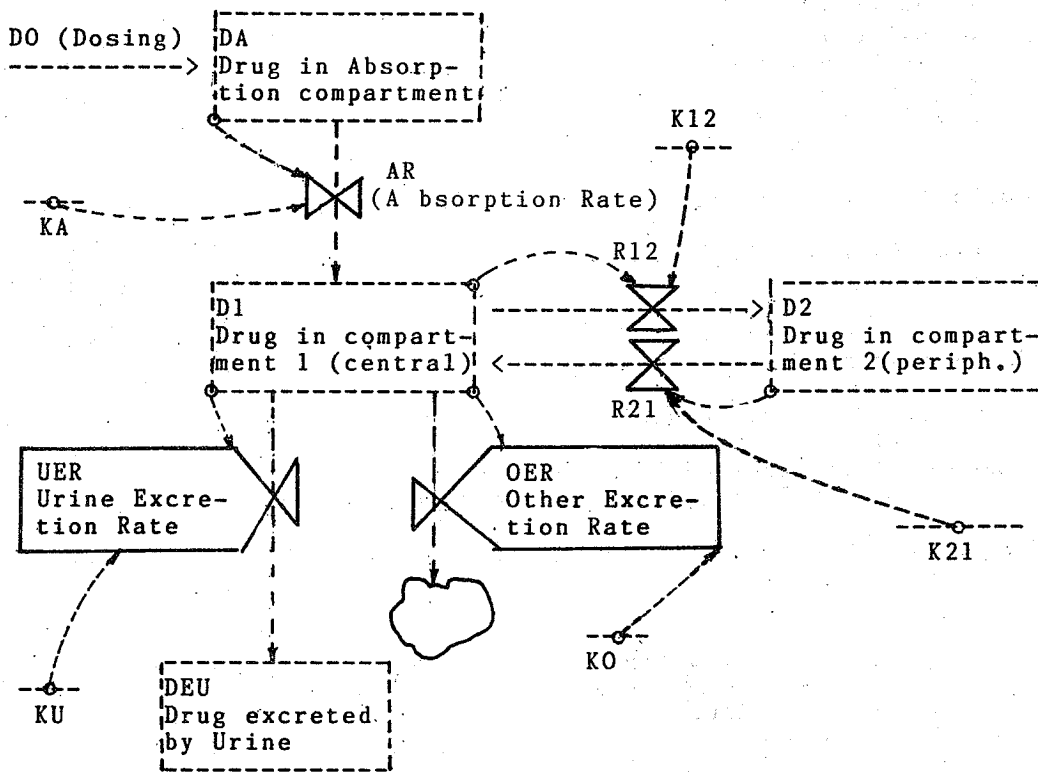
For central compartment (compartment 1) and peripheral compart-
ment (compartment 2), the corresponding equations are similar
except that the number of rates and rate constants are different.

Central dempartment:

    L D1.K=D1.J+DT*(AR.JK+R21.JK-R12.JK-UER.JK-OER.JK)   (11)
    N D1=0   (12)

  D1   --- Drug in central compartment, i.e., compartment 1 (mg)
  AR   --- See equation (8)
  R12 --- Rate of transfer from compartment 1 to 2 (mg/hr)
  K12 --- Rate constant for R12' (dimensionless)
  R21 --- Rate from compartment 2 to 1 (mg/hr)
  K21 --- Rate constant for R21 (dimensionless)
  UER --- Urine Exception Rate (mg/hr)
  KU   --- Rate constant for UER (dimensionless)
  OER --- Other Exception Rate (mg/hr)
  KO   --- Rate constant for OER (dimensionless)

Based on the linear assumption, all the R equations have the same
form:

```
R  R12.KL=D1.K*K12                                              (13)
C  K12=0.05249                                                  (14)
R  UER.KL =D1.K*KU                                              (15)
C  KU=0.05705                                                   (16)
R  OER.KL=D1.K*KO                                               (17)
C  KO=0.3461                                                    (18)
R  R21.KL=D2.K*K21                                              (19)
C  K21=0.15256                                                  (20)
```

Similarly, for peripherial compartment:

```
L  D2.K=D2.J+DT*(R12.JK-R21.JK)                                 (21)
N  D2=0                                                         (22)
```

Since the experiment recorded the drug excreted by urine, we use DEU to represent it:

```
L  DEU.K=DEU.J+DT*UER.JK                                        (23)
N  DEU=0                                                        (24)
DEU --- Drug Excreted by Urine (mg)
UER --- Urine Excretion Rate, see equation (15) (mg/hr)
```

The simulation results and the experiment data are listed as follows:

Time(hr)	DEU (mg) Recorded Value	DEU (mg) Computed value	Error (Computed-Recorded)/ Recorded*100%
1	7.608	7.19	-5.5%
2	24.175	22.89	-5.3%
3	42.386	41.48	-2.1%
4	61.309	60.33	-1.6%
6	98.745	94.90	-3.9%
8	128.452	123.97	-3.6%
14	189.307	185.59	-2.0%
24	240.845	242.90	0.01%
48	291.660	307.16	0.01%
72	302.909	307.16	0.01%

We can see that the validity of the model is of little problem. We can then be confident to use this model in clinical administration. Yet we can search for analytical solutions for this problem. But the DYNAMO software parckage has many obvious advantages. Its clarity and transparency make the mechanics of modeling so easy that even doctors with little mathematical training can do the work. This is particularly meaningful in China where the education system lacks a general, cross-discipline education, so doctors and pharmaceutical experts usually know little mathematics. But one or two week training will make it possible for them to use DYNAMO. And it is very convenient to deal with the multicompartments, multiple dosing, entravascular dosing and even nonlinear transfer rate which is impossible to solve analytically.

We give an example of using the above model. From clinical pharmaceutic handbook we know that the effective concentration of tetracycline is from 1.2 to 1.9 mg/1. [6] Now let's see the result of different dosing policies.

In clinical practice we are usully concerned with the concentration which equals the drug amount divided by the apparent volume.

The apparent volume of central compartment is V1=73.485 litre.

The apparent volume of periphercal compartment is V2=10.482 litre.

The usually tetracycline dosing policy is: first dose 200 mg and then 100 mg every 12 hours. [7] We then add

```
R  DR.KL=PULSE(DPT,TO,T)                                      (25)
C  DPT=100                                                    (26)
C  TO=12                                                      (27)
C  T=12                                                       (28)
A  C1.K=D1.K/V1                                               (29)
A  C2.K=D2.K/V2                                               (30)
C  V1=73.485                                                  (31)
C  V2=10.482                                                  (32)
```

Where

```
DR   --- Dosing Rate (mg/hr)
DPT  --- Dose Per Time (mg)
TO   --- Beginning time for periodic dosing (hr)
T    --- Time period of dosing (hr)
C1   --- Concentration of compartment 1 (mg/1)
V1   --- Volume of compartment 1 (1)
C2   --- Concentration of compartment 2 (mg/1)
V2   --- Volume of compartment 2 (1)
```

And we change formulation (6) and (10) to

```
L  DA.K=DA.J+DT*(DR.JK-AR.JK)                      (6a)
C  DO=200                                          (10a)
```

The simulation result shows that the blood concentration in central compartment bellows the lowerest effective concentration or 1.2 mg/1. And the maximum concentration is about 1.7 mg/1, less than 1.9 mg/1. (Figure 4)

Figure 4: First dosage 200 mg and then 100 mg every 12hours.
The concentration of central compartment over time.

C1
(mg/1)

1.5

1.2

10   20   30   40   50   60 TIME(hr)
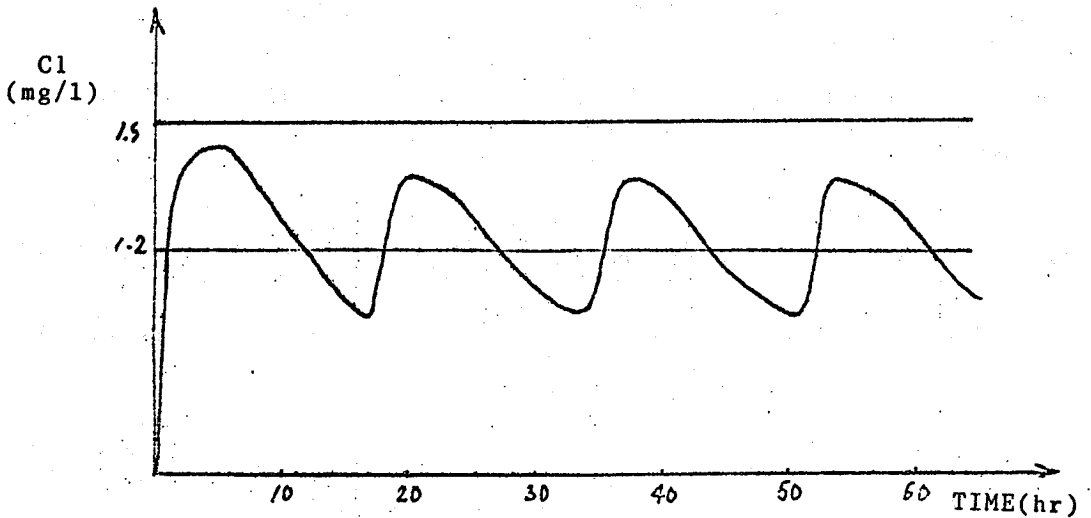
We can see that if we only seek to make the blood concentration
between the effective band, the policy that first dosage 220 mg
and then 120 mg every 12 hours seems more reasonable. (Figure. 5)

Figure 5: First dosage 220 mg, then 120 mg every 12 hours, the
concentration of central compartment.

C1
(mg/1)
1.9

1.2

10   20   30   40   50   60 TIME(hr)
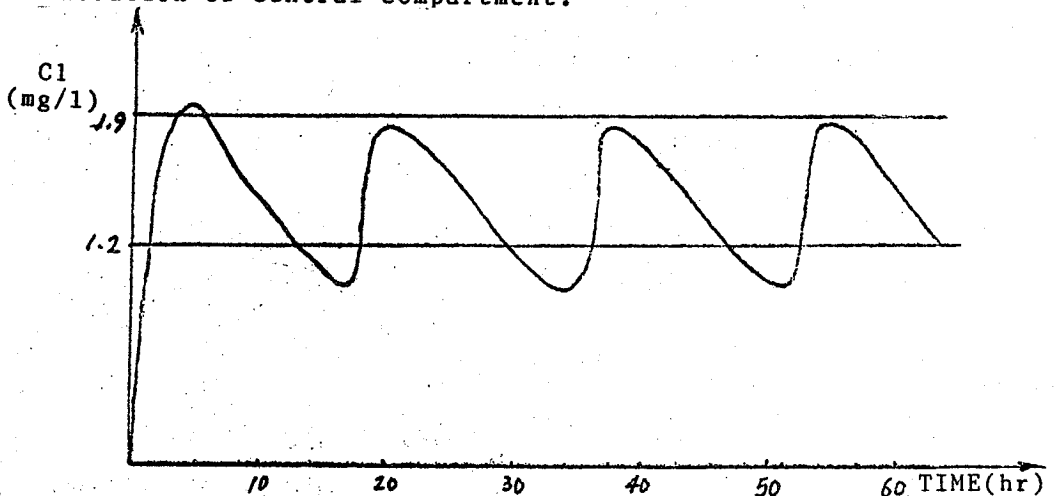
Of course, we should not only search for the goal to let the
blood concentrtion lie within the effective band. Other factors,
such as tetracycline is easy to accumulate in bones, teeth, liver
and other organs, should be considered. This papar does not mean
to provide a guidebook for clinical administration, rather it
mainly introduces how to use the model written in DYNAMO.

Up to this step, we only solve the problems that have been solved analytically more ingeniously and convenniently. As we said before, System dynamics has developed a guiding philosophy. It is a kind of structure-function simulation. And it can handle with system problems of high-order, nonlinear, and multiple-feedback. Next, we roughly inquire into this subject, i.e., modeling drug process under the system dynamics paradigm.

SYSTEM DYNAMICS DRUG MODELS

The linear, open-system compartment models represent the normal cases. By normal we mean that the parameters are measured from heathy human bodies. Now the clinical study has proved the dynamic parameters vary not only from the healthy to the sick but also from one phase of the disease to another with the same patient. [5] And from the system dynamics point of view this variation is structural.

The parameters such as KA, K12, K21,KU and KO in above example represent certain physiological ability or physiological function. As said before, under "normal" conditions, they are stable. But unfortunately the "normal" conditions are frequently broken by diseases, and our drug receivers are of course persons with diseases usually. Diseases cause a series of change in the physiological functions so that the pharmacokinetic parameters will change obviously.

Diseases such as gastric ulcer and depression can influence the absorption of drugs by changing stomach emptying time, small intestinal absorption function, intestinal lumen concentration gradient of drugs and/or inhabiting the secretion of bile, especially for oral administration. Diseases such as low albumin (burn, tumor, heart-failure, inflamation, heptitis, renal diseases, etc., usually accompanied by this) can influence the distribution of drugs by changing content of plasma protein, by preventing the decomposation of drugs and so on. Through changing the activity of drugs, bile and renal excretion function, diseases can change the metabolism and excretion rate of drugs. [9]

For example, most drugs are eliminated from the body by renal excretion, the elimination rate is determined by the renal function of the drug receiver. Quantitatively, the excretion rate

$$QE=C*GFR+QT \qquad (*)$$

Where
  QE   --- Quantity excreted in a period (mg/hr)
  C   --- Concentration of the drug in blood (mg/1)
  GFR --- Glomerular filtration rate (1/hr)
 QT   --- Quantity secreted by renal tubular

When the kidney has diseases such as glomerrulonephritis and/or renal tubular disorders, the renal function (reflected by GFR and

QT) will be influenced, thus the excretion rate and therefore the drug blood concentration will be influenced.

On the other hand, drugs are designed to cure or alleviate the diseases. They will influence the functions of the body or some of its subsystems. And the effect or the intensity of the effect is related to the amount of drug in the body or in specific organs, tissues and fluids, e.g., blood concentration of the drug. The relationship of the drug to its effect is called dose-effect relationship in pharmadynamic terms.

Again we take the renal function as an example. Drugs called diuretics such as funrosemide can make the kidney excrete water and sodium more rapidly. (Figure 6)

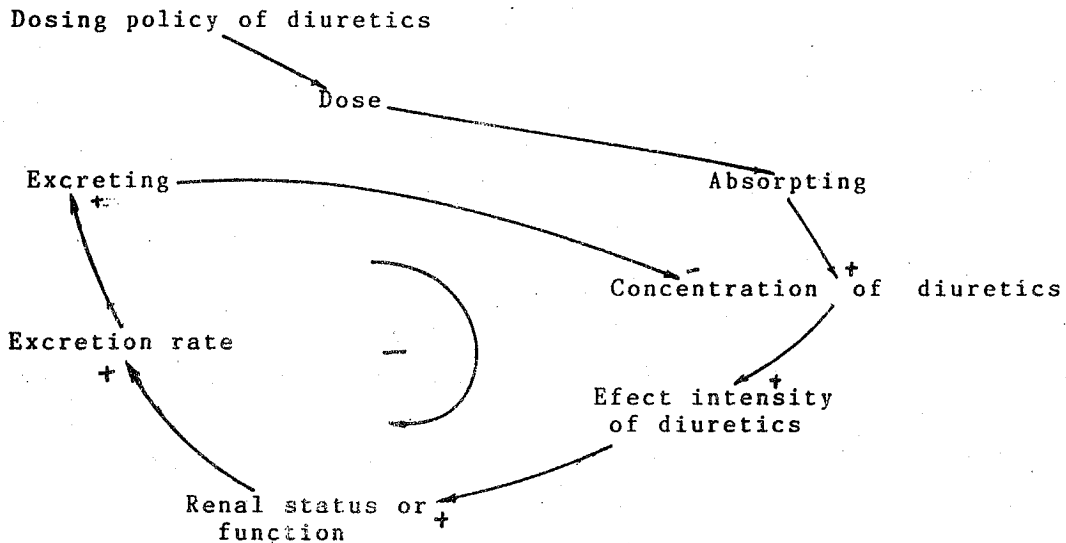Figure 6: Furoseminde's effect on renal excretion of Na
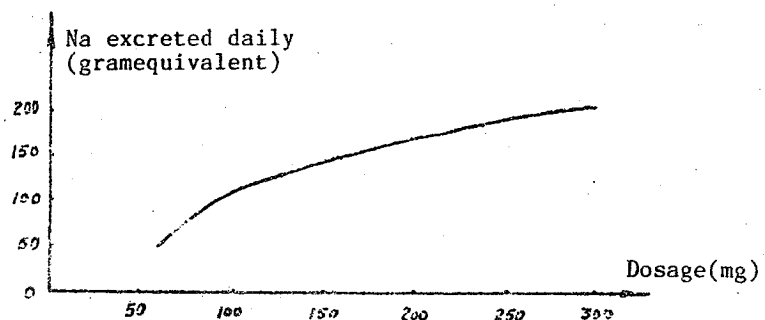
Thus these relationships form a close-loop feedback: under a certain dosing policy, the drug influences the physiologic status and function of the body, the presence or absence of the effect and the intensity of the effect if present are determined by the amount or concentration of the drug given the quality of the drug and the receiver. Thus it influences the absorption, distribution, metabolism and excretion (ADME) of the drug, and this inversly influences the drug amount or drug concentration and thus the effect or effect intensity of the drug.

Figure 7: Causal-loop diagram of the feedback
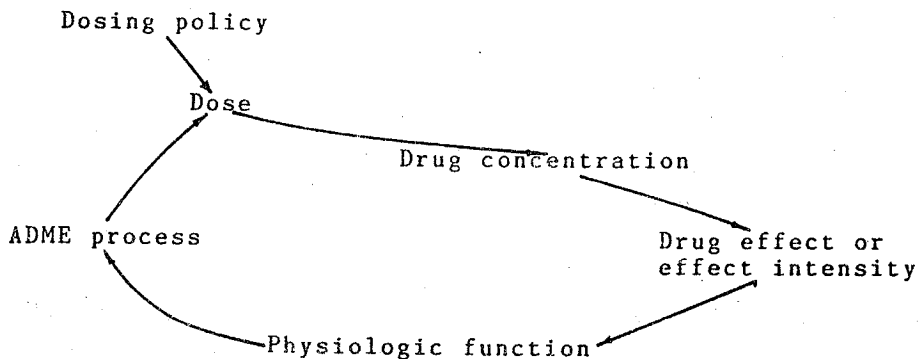
Whether the influence is positive or negative depends on the specific situation --- what kinds of drugs and patients are under consideration. For above example we have Figure 8.

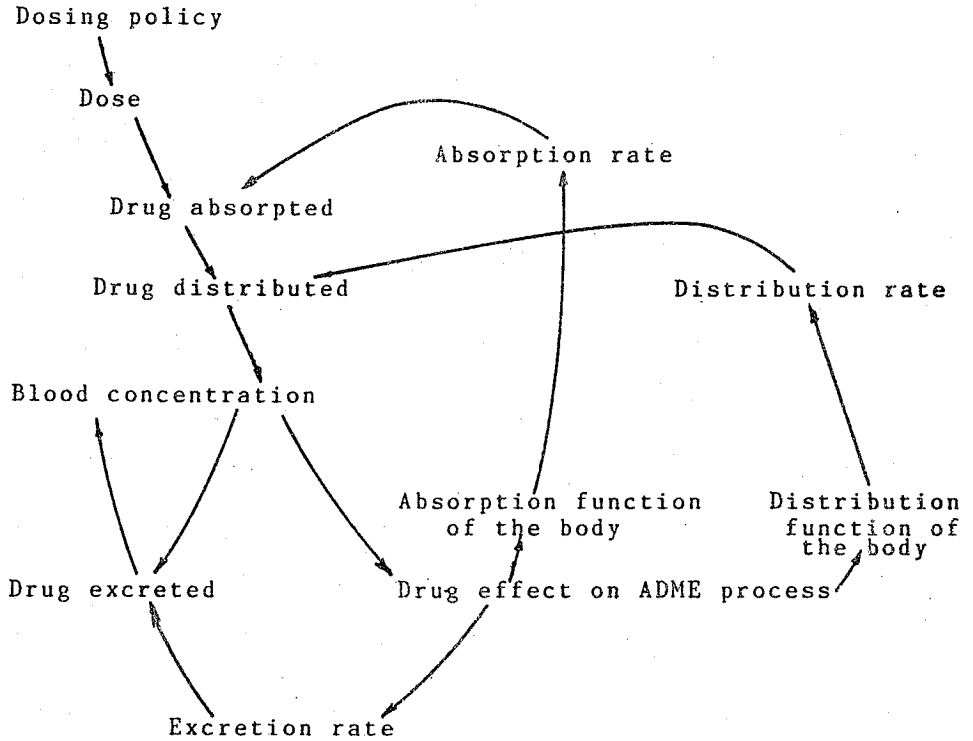Figure 8: Causal loop diagram for diuretics effect

Dosing policy of diuretics

Dose

Excreting

Absorpting

Concentration of diuretics

Excretion rate

Efect intensity
of diuretics

Renal status or
function

If the drug under study influences not only excretion, but absorption, distribution, metabolism as well, that will make the case extremely complex (see Figure. 9). But so long as the direction and intensity of the influence can be known quantitatively (such as the dose-effect curve like Figure 6), system dynamics can deal with the problem with few difficulties. Thus, we combine the knowledges of pharmacokinetics, pharmadynamics and even physiology, clinical sciences together under the system dynamics' paradigm into one model, which may be a breakthrough in these areas.

And there are time delays for the drug effects, for ADME processes and so on. It is also of no problem if the lengths of the time delays can be known.

Pharmacologic experts have already noticed the difference of pharmacokinetic parameters between healthy persons and patients and they have done some corrections to their models accordingly. For example they correct the dose for patients with renal diseases in this way: [5]

Figure 9: Causal loop digram (Assuming no metablism)

Dosing policy

Dose

Absorption rate

Drug absorped

Drug distributed

Distribution rate

Blood concentration

Absorption function
of the body

Distribution
function of
the body

Drug excreted

Drug effect on ADME process

Excretion rate

DC=DN*(KER/KE)   (**)

DC --- Dosage corrected for renal diseases (mg)
DN --- Dosage under normal conditions (mg)
KER --- Excretion constant with renal diseases, which is tested
(dimensionless)
KE --- Normal excretion constant (mg)

But this method ignores the dynamic interaction of pharmadynamic
effect and phsiologic functions. Furthermore, this is not the
approach of system dynamics. It is the approach of relying on
statistical data to verify the model structure and model
parameters. [3] It does not do the structural analysis. As we
said before, the primary assumption of the system dynamics para-
digm is that the persistent dynamic tendencies or the dynamic
macro-behavior of any complex system arise from its feedback
structure --- physiological structure, physiological self-regula-
tion goals, rewards and pressures that cause the body and its

subsystmes (organs, tissues, blood and so on) to behave the way
they do and to generate cumulatively the dominant dynamic tenden-
cies of the total system. Now we get to another advantage of
system dynamics, i.e., through micro-structure analysis the re-
searchers can improve the understanding of the system of interest
--- the body in our case.

At last, there is a need of adjustment. The compartment models
often have important clinical application, particularly in the
development of dosage regiment. However, these modles are
inherently limited in the amount of information they provide
because, in the usual case, the compartments and the parameters
have no obvious relationship to anatomical structure or physiolo-
gical function of the species under study. Now that with the help
of DYNAMO we need not pay much attention to problems in terms of
mathematical operation, we can add "compartments" or levels
according to our need, to the physiologic function or anatomical
structure. These detailed models are elaborated on the basis of
the known anatomy and physiology of human bodies. Thus, system
dynamics helps bridge the gap between mathematical description
and physiological reality.

Because we lack specific data or we, who are almost laymen in
such diciplines as pharmacology, physiology, pharmadynamics,
etc., lack the ability to collect and organize existing data, we
can not give an example as we do with compartment modles. Our
purpose is just to point out the direction and the approach. But
we believe that the cooperation of pharmacologic experts,
clinical doctors and system dynamists will achieve the goal.

CONCLUSION

We have discussed two kinds of application of system dynamics to
drug process study. The first application, i.e., using DYNAMO to
solve the open-system compartment modles, has practical value.
The development direction of clinical drug administration is
individulizing and floating administration, i.e., deciding the
dosage according to different patients and different disease
stages of the same patient. [10] With the help of mathematical
models, doctors can use drugs more reasonablly and consciously.
Some ones may argue that most compartment models can be solved
analytically. But remember that the computer augments the human
brain the way a steam engine augments human muscle. And DYNAMO
may be the best candidate among computer languages such as
FORTRAN, BASIC, etc. to solve compartment modles. We would like
to recommend DYNAMO to docters, pharmacological researchers.

The advanced application is representing the closed loop interac-
tion feedback relationship of drugs to the human body in the
model structurally, organizing knowledges of pharmacokinetics,
pharmacodynamics, physiology, clinical sciences, etc. together in
the model and thus simulating the process endogenously. The
studying and modeling is under the guidance of the system dyna-
mics paradigm. It is of both practical value and theoretical

value. It may bring about breakthrough in these areas.

ACKNOWLEDGEMENTS

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