hello everyone and thank you for the
more compartmental and complemental
approaches to phenetic data analysis my
name is Pao Vini and I would like to
acknowledge also my colleague David
Foster who originally was responsible
for this content when the course was put
together at the beginning heres my my
current
disclosures and I think its helpful to
start with the with some background in
terms of the the words and the glossery
that were going to use in the remainder
of this presentation so we refer often
of course to pharmokinetics which in a
very simple way is what the body does to
the drug and then uh in the to place
this in the proper context well also
sometimes talk about pharmacodynamics
which is drug does to the body
uh and this is all in the context of
temporal disease progression and
measurable therapeutic effect that a
drug has a goal to modify and uh uh
running alongside this on the background

is the idea of variation so the data
that we measure are subject to noise and
variability and so theyre not
necessarily a perfect picture of the
biological system that we are trying to
um to to estimate and to study so PK MPD
um PK again is what the body the drug is
fairly well known and its required to
understand pharmacodynamics PD which is
actually um part of the ultimate goal of
drug Discovery and development to
understand what the drug does to the
body uh which is sometimes unknown often
unknown but has true clinical relevance
and so the questions in this area that
were going to tackled relate to both PK
and PD and like I mentioned earlier PK
and PD are based
are they operate or they are based in
the context of disease progression uh so
a certain uh time course of the patient
status worsening that the drug uh would
like to to impact and to change this is
the broader context of what were going
to talk about but in the remainder of
this presentation we will talk about

pharmokinetics so

PK so P can be very complex uh you know

a drug in the body is constantly

undergoing change concentrations in

various body spaces rise and fall

depending on the particular

characteristics of the molecule and the

biological system that is being studied

uh because this behavior is so complex

there is a need to summarize it in a way

that can be easily

communicated and uh that can be used for

example to compare molecules on to the

other or to properly evaluate and

estimate the effect of a certain drug or

a certain therapeutic and so thats how

these complex curves this complex

Behavior can be summarized in terms of

parameters that can be derived from

these time courses so a a PK parameter

is something that we can use to

summarize what is a very complex

Behavior time dependent data that is due

to the interplay or race of distribution

elimination accumulation these

parameters are informative on the

characteristics of drug molecule

and they can be descriptive or

observational or they can be uh

quantitative so well actually see what

the differences between these in a few

minutes and to estimate these parameters

we use mathematical models and the two

important classes of these models are

the compartmental modeling class and the

non compartmental modeling class and so

as far as the goals of this lecture what

the goals of this hour or so that we

spend together are is that that wed

like to understand a little bit to what

these model assumptions are what are the

assumptions that inform every one of

these models what are the parameters of

interest that we distill from PKA curves

and what to expect from these estimates

and so we by the end of this time we

should be able to understand clearly

what each model assumptions are and how

we can choose the most appropriate

method depending what information is

required what data are available uh

were not going to uh make any

conclusions in terms of which method is
better than one another because of
course the answer to that depends on the
question being asked and the context of
where the model is being
used so um we talked about PK and what
it means for a drug in the body to be
constantly undergoing change a drug
molecule whenever its administered uh
follows processes of of absorption
transport in the circulation or across
membranes transformation by about
chemistry and elimination and you may
have heard the moniker adme adme Al
distribution metabolism extion to to be
being used to refer to this collection
of changes and like I mentioned earlier
depending on the on the um on the space
where the drug is introduced or where it
gets and how its transformed drug
molecules um describe or or undergo
several changes and so the concentration
time profile depending on how the drug
is given intravenously intravascularly
orally uh and where it goes um can have
several different profiles several

different shapes some which can be very complex and so we refer to this collection of time and space dependent changes as kinetics so kinetics in general not just for drugs but in general for any sub NE biological system refers to its temporal and spatial distribution and in specifically for drugs or for xenobiotics pharmacokinetics is the collection of temporal and spatial distributions of a drug or drug combinations in a biological system so some of you may be experts in pharmacokinetics the definition of kinetics to core is a bit broader um because it doesnt just refer to changes over time it includes also changes on in space so a complete description of these concentrations that we have described described requires both an understanding of special distribution and temporal distribution so where in the system and when in the system now you you can you can appreciate how if we were going to describe this formally you know writing

the equations of this behavior in

spatial and temporal detail is quite

demanding in fact its quite difficult

uh for the mathematical inclin among you

it would boil down to write partial

differential equations IE rates of

change for the drug molecule in space

and time and however rigorous is not

really practical so while people in over

time have tried to develop special

realistic models of drug

distribution uh they soon realize that

this requires very detailed knowledge of

things like physical chemistry

thermodynamics ulatory Dynamics and even

if you are able to formulate them they

can be very difficult to solve and to

top it all is challenging to design an

experiment that can help us quantify the

parameter values for these time and

space behaviors while desirable often

not practical so um over the years the

uh discipline has developed several

other approaches that are a bit more a

bit more um tractable to describe a

change over time and space of drugs in a

biological systems and one that is now
the state of the art is what we call
physiologically based pharmokinetic
models or pbpk pbpk models are a
compromise between spatial realism and
temporal realism and tractability and
essentially they they boil down to uh
creating differential equations for the
various organ systems that a a human or
or animal body has and then building the
arrangement between these organ systems
in terms of circulatory flows so that
one can write organ level realistic
kinetics and this is not a fully
specially distributed model but it is a
good compromise because it bols down the
system to its most important components
which are the organs where the drug
distributes and like I said this
approach is now stateoftheart
and one can also use it for example to
translate among speces say from
preclinical studies to uh small human
studies to larger human studies and uh
because they are mechanistically more
realistic um or than other models that

we see they lend themselves well to

translation and to translation between

species and other

setting um theres Al as we go from more

realistic special distributions to

something that is a a hybrid which has

organ level kinetics there are also um

ways to sort of lump the components of a

system empirically based on their

behavior and when I say Behavior it can

mean um time location or combination of

the two its not mechanistically

realistic as a PPK model but it

essentially

lumps the components of the system into

um entities that behave together

similarly and so this could be based

like I said in time location or the

combination of the two and so we dont

necessarily talk about space in this

setting but we uh implicitly talk about

spatial distribution via changes that

occur in time and so these lamp

parameter models essentially discretize

the system through boiling it down into

a as small as possible number of

components um that is not as large as

PPK and is not as detailed as specially

um realistic models but it is trable and

so these models are um are called in the

most general setting compartmental

models and they can based on linear non

linear differential equations and an

incarnational comp model is a non

compartmental approach that is actually

based on algebraic equations so to make

it a bit more um intuitive uh on the

left we we have the pbpk model that we

described a few minutes ago and on the

right we have a compartmental model

where the um system has been reduced or

lumped to a relatively small set of

components that interact with with each

other but they but that are now losing

the direct connection with the organ

system or with the with the actual

system that was that is being

represented that correction that

connection is now IND

and based on uniformity of behavior and

lumping of tissues together because they

behave similarly as opposed to having

every tissue and organ represented in a way that is realistic and based on its behavior and mechanistic knowledge that we have that being said the models on the right are quite useful because they are small they are tractable they are fast to solve and so theyve been essentially the Workhorse for pharmokinetics for many years before PK models came along now how do we build these models on the right how do we uh formalize what this lamping process means and how do these compartments behave uh when they are by themselves when they are connected so there are two basic hypothesis or shall I say assumptions that comp complemental model models are based on one is that every compartment is kinetically homogeneous so molecules in in a given compartment um behave uniformly they have the same probability of living the compartment going in any direction of the system and so the this is uniformity of behavior so drag molecules in a compartment behave in a

way that is

similar um also compartments are

supposed to be well mixed so if there

are two samples in different locations

in the compartment the concentrations

that we get out of those samples has to

be the same so this is uniformity of

information every compartment um every

compartment is kinetically homogeneous

and well mixed meaning that the

molecules in the compartment behave

similarly and also the information the

in the compartment is distributed

uniformly and so thats the idea of

lumping we lump together spaces that may

be physically distinct but where the

drag molecule behaves in a way that is

similar and so we use that to build

models that are smaller than PPK models

or then especially realistic models but

like I said theyre much more

practical heres another um framework

that we find useful in the next few

minutes when we learn about the

biological system uh we can split it

into two parts there are and this is

based on the idea that only some components of an intact living biological system are amable to measurements so there are some compartments that are accessible they are available to the experimentalist for test input and or measurements and these are we call them accessible compartments or accessible pools there are parts of the system with the where we cannot either insert a drug molecule or measure from and these are inaccessible compartments or pools this is the whole rest of the system which is not available for test input and or for measurement what do by that heres a compartmental model on the left and I highlighted the accessible pool in yellow so thats basically the only space where we can make input or we can administer a drug or we can measure a drug everything else is invisible and so the idea is that um to develop these models properly a structure needs to be postulated for these models based on the limited information that is available

from the accessible compartment or the accessible pool similarly to how we would like for example to estimate or to qualify how many rooms there are in a house based on how many people at a party are standing in the backyard or are visible from the windows and so on were trying to reconstruct inaccessible features of the system from things that we can see and the effect of biomedical system investigation is that we dont have access to all the information that we would like and so we have to infer uh what happens in an intact biological system based on limited measurements limited measurements they are not just limited in time or in terms of sampling schedule or how many blood samples we can take but theyre limited uh in a sense of where we can take them from for example blood plasma is the only space that we can access easily in a biomedical system context so what is a compartmental model in this setting now to sort of summarize we we started with specially realistic models you know very

intractable partial differential

equations and so on and then we went to

pbpk which is a bit of a hybrid approach

where we arrange organs um based on how

the organ behaves and what we know about

the organ and mechanistically speaking

and we arrange them in a way that is

realistic and now we went down to a

further simplification which is a

compartmental model which is a

collection of compartments or pools that

are each one of them taken separately

kinetically homogeneous and

instantaneously well mixed so uniformity

of behavior and uniformity of

information and then a Arrangement and

connection of a of a finite number of

compartments is a compartmental mod and

this will be subject to a specified

input and and measurement location just

like the example that I showed earlier

where there was only one compartment

that was amable to measurement among the

five that comprise the entire the entire

model so to summarize the process one

last time we went from um a

conceptualization of time and space

changes of drug molecules in inex system

and we boil it down to temporal changes

only based on a certain arrangement of

the units in a model that we call

compartments and so this has been a very

popular coach uh in PH kinetics and had

enabled the discipline to quantify

several aspects of drug Discovery and

development to measure PK parameters of

interest to properly

characterize drugs and their behavior in

index systems over the years over the

decades so for those of you that are not

necessarily mathematically inclined I

would like to at least make an attempt

to

demystify differential equations

whenever you see differential equ

equations your eyes dont have to glaze

over this is just an approach to

modeling rates of change and rate of

change is a fancy name for slope um and

derivative is a fancy name for slope so

uh we write these differential equations

to model or to represent how a certain

time profile changes and so this uh
these models are based on differential
equations because the are ations in a
system for example change with time and
so these tools are perfectly amable to
represent temporal changes that occur uh
you know in the systems that weve been
talking about and so just remember you
know the differential equations or
derivative is a fancy name for a way to
describe rates of change or essentially
slopes and well have more to say about
that in a few
minutes I think it sort of helps to um
walk through a very simple example of
how we build these models um and so like
I think Ive alluded to um these models
are have two components mainly one is
the underlying model of the system the
system exists independently of how we
experiment on it so the system exists
independently of where we or whether we
introduce a molecule in the system or
where we sample from and so on thats
basically a summary of the principal
components of the biological system and

then on this model we superimpose an experimental design a certain input and a certain measurement function so for a drug the most common example is for example an oral or intravenous dosal drug uh either by mouth or into into the vein and then the measurement to be a canula that essentially samples uh blood samples over time from a certain location say in the forearm right so but that system exists and Moves In Time Changes in time independently of the experimental design that we have in terms of input and measurement and so we show this in practice now by building a very simple complemental model and in fact this is the simplest complemental model which is where the where the the distribution of a drug in the body is summarized by a single compartment that is a a a single space where drug molecules obey the principle of uniform to behavior uniform to information and so the idea here this is a good model for the drug and some drugs actually are quite well described by simple model

such as this where the body is

essentially single component and so when

we write this differential equation here

on the left what what Im what Im

saying there in mathematical terms is

that the rate of change of the amount q

in compartment one is equal to uh

whatever enters the compartment minus

whatever exits the compartment so in

this case the compartment has a

clearance or has an

elimination rate which we call k0 um

and then that times the amount in the

comparment describes how quickly drug

will leave that space once it it is

administered and heres my

Administration its a dose in the

compartment now I have a new component

in my differential equation dose of T

dose of T can be a pulse can be B an

infusion or a more complex pattern of

administration but the amount of drug in

the compartment the rate of change of

that amount is given by the balance of

what goes in the dose and what goes out

which is essentially this elimination

process that is described by this rate

constant a0 times the amount

itself and the last ingredient of the

model is the measurement often shown as

a dotted line from the from the uh the

measurement location and usually when we

work with drugs uh with ph kinetics we

measure concentrations and so the

concentration in this case is the amount

q divided by certain volume which is

the volume of distribution of

compartment one and so I just throw it

in here these um entities that I have

that Im talking about k0 and B these

are essentially parameters and they

describe and they they shape you know

the behavior of q of T depending on

their values right and depending on the

on the dose and the

input for a simple system such as this

one it has a simple solution the

solution of a sing of a single uh

compartmental model is a single

exponential time course so um the time

course of drugs described by

compartmental models um obeys

exponential exponential law and so uh

the concentration of drug in the

comparment will decrease exponentially

and I have it there on the on the right

and these parameters will be estimated

K 0 and V will be estimated by matching

the mathematical prediction of the

compartment which is the line to measure

data which are the the squares in the

graph that you have in front of you and

so the we can use matching model to data

but to derive parameters from the model

equation so the best fit of the model to

the Curve will provide values for the

parameters K 0 and d and then I can use

k0 and V for example to calculate

things that interest to me like for

example clearance rate uh clearance rate

of a certain drug is the times the

elimination rate and has units of volume

per unit time units are very important

in this business as you can imagine um

whatever you need to measurement you

useing your equations which can be much

more complex than this need to be

consistent and uh and so while V is

intuitive is basically it can be for

example liters or milliliters k0 is

inverse time because its the rate and

clearance which is the product of k0

and V is liter per hour or volume per

unit time so the volume cleared in the

unit time of the drug and so you can see

how helpful you know these approaches

can be because uh first I had you know

four data points measurements over time

or drug behavior and now I have numbers

that I can use not only to describe that

curve but also to compare it to others

for example if I have several different

black candidates I can compare their

clearance rates their volume and based

on criteria that I have independent of

that I can decide which candidate may be

better uh than the other to develop and

so Ill have more examples of that later

and so like I said the solution to a

compartmental model is an exponential

curve and this exponential curve can be

described by parameters and this very

simple example where where I uh that I

walked you through the parameters are

clearance and volume um and the the
curve is determined by two parameters so
I can choose to report for example
clearance and volume or k0 and volume
or k0 and clearance I can choose any
combination of any pair of these
parameters that I that I um think is
most useful and so some people talk
about primary versus D parameters so um
people would sometime report the model
in terms of clearance and volume because
they had theyre more intuitive in terms
of volume clear per unit time and and
volume itself as very intuitive
interpretation and mechanistic
interpretation uh k0 is usually a
little bit harder to grasp the sort of
rate of decrease so we tend to think of
it as a derived parameter another useful
parameter is for example
halflife uh which you sure have heard in
different context is the time it takes
for the amount to decrease by half and
so this is a very useful parameter that
we can derive from these models uh to um
help us not only determine how quickly

the drug leades the system but also for example what the dosing regimen should be how often should we dose the drug once a day twice a day three times a day once a week and also to compare drugs one to the other in terms of halflife um just so now this is very simple model right how can we make it a little bit more complex right some of these kinetics can be nonlinear um meaning nonlinear in in the sense that the elimination rate in this case k 0 is not necessarily constant but for example depends on concentration like for example what if k0 has a m m saturable um shape as opposed to being a constant so this gives rise to interesting behaviors right so and some of you may have seen this before certain drugs are cleared um using according to to such a model so um the these models nonlinear models end up being essentially the combination of several different behaviors only in one model like for example when concentration is

much lower than the km NIS M and

parameter then the compartmental amount

will decline at the at the rate

proportional to it which is first order

kinetics low concentration and then when

km is when concentration is much larger

than km then you will have something

called zero order kinetics right but

this is this is the same model it just

behaves differently depending where you

are in the concentration time curve so

we can have an example I I I can show

you what this means in terms of um how

this essentially looks like in practice

so if I were to solve this model and

simulated for certain instances of the

parameter values I would see exactly

what I mentioned earlier there is for

large concentration values which are

larger than km the kinetics is zero

order so it basically declines at a

constant rate independent of

concentration and then when I approach

the km and fall below it then the time

course becomes the the clearance becomes

first order so its linear on the

logarithmic Y axis so you can have several kinds of behavior several levels of complexity with nonlinear models you have all this in one place so the model has a range of behaviors a range of complexities depending on where you are in the concentration time curve and this is a very flexible Tool uh this kind models can be very flexible to accommodate the very broad range of behaviors that we can see in biological systems in practice now these examples are based on a single compartment but of course we can have models with several compartments where we arrange these homogeneous pools uh together um and they exch with exchanges between them they can be single directional B directional and so on and so we connect them using these these fluxes and so these are essentially movement these fluxes can be physical movements among the various compartments or could be a composite or metabolic activity

biochemical transformation transport the

important thing is that they occur

within a similar time frame so that the

compartments when theyre arranged they

uh are defined in in in a time frame

that is common there is common among

them and again for the mathematically

incline this can be written in terms of

differential equations where the in the

end is relatively simple it all all gos

down to accounting you have the rate of

change change of the amount in a given

compartment which is everything that

goes out plus everything that goes in

and so these equations can be written

for these models in a relatively

straightforward form and people have

been doing this for a long time luckily

these days there is software that does

it for you so you dont have to be

concerned with the details of these

differential equations or writing the

arrangement yourself there are several

ways to do that which are which are very

simple and uh if um we we we simp ify

the system further in a way that say all

the transfer rates are constant then

these boil down to ordinary differential

equations in steady state and if the

assumptions that are described earlier

in terms of good mixing and kinetic

homogeneity uh apply then the

differential equations can be further

simplified where the KJ in front of the

qs are all constant and then the

equation are quite straightforward to

solve and write and essentially they

boil down to a system of ordinary

differential equations that can be

written in Matrix form and just so I you

um this is an interesting uh feature of

this class of models um if I write the

Ki the transfer rates in in Matrix form

and I take the inverse of that Matrix I

basically have a description of the

resonance time of a Dr molecule in every

compartment in the system and so this

can be useful if youre interested for

example to estimate how much time a drug

molecule would spend in any one of those

one two four five n compartments that

you have

defined um and this was a quick overview

of this technology and of course uh the

field has been moving very quickly

especially over the last few decades and

these days compartmental models can be

very complex and very detailed like for

example for biologic monoclonal

antibodies you not only have to deal

with their kinetics in the center which

which often obeys a two compartment

model but also immune complex formation

of disposition due to antidrug

antibodies and disposition based on tar

drug disposition which is another is

another way the monocon antibodies can

be cleared and so this class of models

has a lot of flexibility and can

accommodate uh really detailed

complexity and biological plausibility

all the way without going to the um the

mechanistic detail the pbpk models have

or to the um rigorous detail that

special distributed models have like I

said its a bit of a

compromise so compartmental models are

are in their Essence a postulation of

how one behaves believes a system
actually functions and and and behaves
but the model is not only limited to the
compartment structure and their
Arrangement it also
requires uh the declaring right what the
experiment to be performed in that in on
that model is like I have we here for
example a five compartment Model Five
pools that are distributed in a certain
arrangement from left to right stomach
gut plasma an extravascular pool so I
can for example explore this system
using an an intravenous dose directly in
the plasma compartment this will bypass
entirely the stomach and gut model so
what whatever data I have from this
experiment will not be informative on
whatever happens in stomach and gut
because theyre being
bypassed on the other hand I could
choose to um
to experiment on the system using an
oral dose and so in this case my oral
dose would be given in the stomach we
Traverse the gut and appear in plasma

and the sampling the measurement is
still done in plasma and perhaps even in
one more extravascular pool pool the
time course that is derived from this
particular arrangement of experimental
design is different than is very
different what can be derived from this
other experimental Arrangements uh the
the location of the input is different
and there will give rise to different
behaviors but the underlying structure
of the system is unchanged the actual
biological system that is being studied
doesnt change what changes is just the
arrangement of input and output of those
measurements that I choose to Pro
it and so one word about experiments so
the idea of experimental design is that
I have this conceptual model that
represents the biological system I want
to experiment on it U and that the uh
conceptual or computer experiment has to
be the same or similar uh to the one
that I use to generate the actual data
so in terms of input and and measurement
and like I mentioned earlier its

crucial here that we account for units
properly so for example if those is in
migs in milligrams concentration will
often be milligrams per milliliter and
so every one of these model models and
model parameters have units that
describe how how they behave and how
they change so this accounting for units
is is crucial for building these models
correctly and especially to interpret
that output
correctly and so theres a whole
discipline built around parameter
estimation
and I did mention this a little bit
earlier so in terms of matching the
model prediction to data um conceptually
there are infinite values that I can
choose for k0 V and clearance and so on
but only a relatively small set of these
values will describe my data
appropriately so thats basically how we
estimate models we estimate model
parameters we calculate the output of
the mathematical model we match it to
data using parameter estimation and for

the statistically minded Its a form of
nonlinear regression most often and we
extract values that then we can use like
I mentioned earlier to summarize the
complex Behavior to compare um drugs to
one to the other to evaluate for example
different formulations or different
modes of administration and so on um and
so we the technical details are probably
for other lectures in this course but
there are techniques of model building
uh and selection and estimation methods
that one can spend a lot of time on but
we W today uh were just interested in
the output or the result of these
Technologies which are the model
parameters uh and like for the purpose
of this lecture these are from genetic
parameters volumes clearance residence
St remember what the body does to the
drug and I think I mentioned very
briefly how we we can rearrange or
reparameterize the model parameters for
example for rate constant to clearance
to make them more suitable to biological
interpretation and so this brings me to

um to know compartmental analysis maybe

some of you are wondering well its a

lot of work its a lot of um assumptions

and uh its lot of calculations that we

have to uh to make to estimate some of

these parameters is there a way that I

can do it without having to postulate

these complex structures right so this

me to non compartmental analysis so the

question here is is a compartmental

model always required to estimate

selected from PK parameters from a

certain curve and so then the question

is um probably not so which PK

parameters can we estimate based on only

the measurements in the accessible pool

the accessible portion of the system

that is aable to measurement and which

parameters are you know can we estimate

with the modum with the minimum number

of assumptions and what these

assumptions are right I mean clearly

every time that we estimate something

that cannot be directly measure uh a

model is required but in this case a

model is just a conceptualization of how

the system works and so um

noncompartmental approaches have

assumptions that limit their

applicability in some way but well show

in the next few minutes how they relate

to the complemental models that we have

described so

main message here is that between

compartmental and noncompartmental

Analysis the only difference between the

two methods in how they choose to

describe the nonaccessible portion of

the system and you may remember when we

buil a compartmental model we have to

make assumptions on the portion of the

system that we dont see we have to

describe the compartmental arrangement

how many compartments are there how are

they connected how do they uh clear to

the envir enironment and so on and we

have to do it only based on measurements

in the accessible pool in the accessible

portion right and nonc compartmental

model doesnt make any statement on that

it basically says it basically focus on

focuses on the accessible pool right um

and uh makes all its inferences on PK
parameters based on those measurements
and this is a very general uh statement
of a noncompartmental model uh that can
be used for like endogenous substances
for example like like hormones or or
metabolic substances uh but for drugs
and xenobiotics the only input is from
the outside there is no endogenous
production of of drug for example most
of the time its a new chemical so it
doesnt its not produced and
so model is essentially bows down to an
accessible pool a system which dont we
dont make any statement on an
elimination rate and an input in meure
so the the um accessible pool of a
noncompartmental system essentially has
characteristics that are the same as the
compartments that we have described so
the accessible pool has to be
kinetically homogeneous and
instantaneously well mixed um and most
of the time I mean its not its pretty
obvious by now the accessible pool is
plasma is the circulating blood which is

an ideal compartment most of the time

can be described very well by being

kinetically homogeneous and

instantaneously well mixed and so the

non compartmental

framework um partitions the system into

an accessible pool where we dose and we

measure from and a system that we make

no statement No statement on right

anything else is not is Undeclared right

its something that we dont necessarily

model explicitly

right so so heres a comparison of the

two modeling methods and Ive

highlighted the accessible pool in both

so for the compartmental model like I

mentioned earlier just to re

reiterate everything that talks with or

communicates with the accessible pool is

explicitly stated in this model is five

compartments some of them communicate B

directionally with accessible pool some

of them

unidirectionally um and some of them

clear to the environment and some others

dont the the non compartmental system

essentially summarizes

the um the whole system into an

accessible pool and something and the

rest of the system which is left like I

said undescribed and and Undeclared and

so um but there is actually one one

assumption that nonmental framework

makes on the rest of the system um and

this assumption is that there can be no

additional sources or syns within the

the system except where I make my

measurements or where I do my where I

administer my dose so this whole other

part of the system that communicates

with the accessible pool cannot have any

extra elimination extravascular for

example elimination or any additional

sources that are not accounted for in

the accessible pool so essentially this

uh recirculation Arrow here means that

anything that leaves the accessible pool

um except through that irreversible loss

that we see in in the graph has to come

back so there cannot be additional syns

so to speak within the system except

where measurements are made and so quite

simple right its relatively simple

model with respect to to the to having

to declare the individual components of

the system that we have here like in the

compartmental framework so if we use

this framework what can we estimate it

turns out we can estimate quite a bit if

the assumption that I mentioned of no

additional sync and Source are met so we

can still estimate clearance rates we

can estimate volume of distribution and

new residence time and the way that this

is done is that these parameters are

estimated directly from the measurement

without necessarily having to fit a

model or without necessarily having to

make assumptions on the Unseen part of

the system using algebraic techniques

um and so if theres no additional syn

additional Source if the ktic parameters

are constant then I can estimate them

using using this technology so for

example what about clearance rate uh the

formal definitional clearance rate as I

mentioned earlier is the elimination

rate divided by concentration but it can

be shown that if the noncompartmental assumptions are met I can have a pretty good estimate of clearance uh by doing those divided by area under the concentration curve Au and so this is a relatively simple calculation that can be made just based on the measurement that you have there on the right and um if these assumptions are met can give you a pretty robust and useful estimate of clearance phate without having necessarily to declare the um the the uh interconnections between the accessible andac and inaccessible portion of the system that we have to make in compartmental models um I will mention though I will start mentioning here and I will mention it again that when we use this relatively simple framework of course we lose something uh if we dont go through the effort of developing a more mechanistic model then of course we dont have the tools for example to extrapolate beyond the uh time uh the the the the range the time range of the

experiment we dont have tools for

example to scale between species and so

on but for an estimation that can be

useful in terms of decision making and

preliminary characterization this is

actually a pretty good approach so uh

several calculations can be made based

on this area under the curve that we

talked about um theres actually two

areas under the curve one is the

relatively

straightforward

um area that is delimited by the by the

trapez interpolation the concentration

curve the other one is something a bit

more esoteric which is the area under

the moment curve which is the area under

the concentration times time and thats

used actually to calculate another

nonmental parameter which is quite

useful which is the mean residance time

MRT um and we can think of MRT or the

mean residance time as the average time

that a molecular drug spends in the

system intuitive intuitively speaking is

the center of mass of the concentration

time curve and so this gives you essentially a typical time that a molecular drug will be in the biological system post Administration and this calculation that you have here on the screen may seem a little difficult but let me uh tell you that modern software tools do it uh you know almost instantaneously so thats another very useful parameter that I can estimate and in this case it doesnt require me to make assumptions on like I said the part of the that are not uh measuring so what is needed for these estimates essentially estimates of these area under the curve and under the moment curve and so these are quite um straightforward to obtain with modern software just to sort of tell you a little bit where these numbers come from because you will be using probably these softwares if you if you work in this area uh so its helpful to understand a little bit where this comes from and what the under pinnings are in terms of these estim ations uh integral is a

fancy name for area all right just like

derivative is a fancy name for slope

integral is a fantasy name for area and

so uh these areas that I talked about

can be estimated using integrals and

typically this would go from zero to

Infinity to to infinite time of course

no experiment is conducted for an

infinite time and so we have these areas

use a mix of interpolation and EXT ation

interpolation to calculate the area that

is given by Thea measure and

extrapolation to calculate the area that

is left you know all the way to infinite

time um and so people sometimes refer to

noncompartmental analysis as model

independent that is true in a way

because one doesnt have to make a lot

of assumptions on the inaccessible

portion of the system so model

development is at the minimum but there

is at least a um a a modeling assumption

or statement that is made when we

extrapolate beyond the confines of of

the experiment so when we go to infinite

time you need a little bit of a model to

do that and like we see in a minute the

most common of that is essentially a

single exponential function that is

extrapolated all the way to infinite

time and so these um I mean like I said

for interpolation when it comes to

calculating the area under the curve

that I measure you can we can use

various methods and these go by the

fancy name of trapezoidal L trapezoidal

combination the the trapezoidal rule is

nothing but an estimate of the area

based on the uh uh quite literally the

area under each pair of data points that

is connected by a straight line and then

you calculate the area under that

particular trapezoid and then you sum

them all up and you have you know the

area under the curve up to the last

train point you can for for curves that

change maybe you know that CH have a

different pattern of change for example

rising and falling log trapezoidal is a

little bit more useful but this is just

math and I think that suff to say that

there are ways to estimate the curve

under the data that we measured right so

these are it can be as simple as

calculating the area under each

trapezoid and then summing the

and then of course I need a way to

extrapolate further uh right uh so

extrapolation is always necessary let me

just say before we go to that that if I

estimate the Cur the area under the

curve with very limited data like the

one on the on the right chances are my

estim is not going to be very precise

like in this case for example if I

sample only at hour and say nine or 0

hours then Im missing all the behavior

that is in between and in this case Im

going to overestimate my area under the

curve because Im actually getting a lot

more area than the actual data would

have given me had I been able to sample

it so as the number of samples the blood

sample goes down from dense to sparse

sampling schedule then interpolation

even interpolation may not be accurate

it depends on the shape of the curve and

there are considerations of experimental

design that help us um make a

uh an educated guess as to how to

optimally place these samples right and

thats another fi that has been evolved

in quite a bit in the last few years and

like I mentioned earlier because these

areas are um needed for infinite time

for the formulas to work once we take

the last measurement we need a way to to

extrapolate beyond the end of the

experiment and so uh most often the the

terminal portion of the curve where I

havent measured is assumed to be a

nonexponential function a single

exponential starting from the the last

Point onwards and so it has an exponent

and and a a rate of Decay and of course

I can also estimate from there the

terminal halflife the half life of

terminal Decay which is another

important component of noncompartmental

analysis and is often reported in these

in these kind of analysis so so the half

life of terminal concentration is is as

simple as log two divided by the

exponent of terminal Decay which can be

calculated from data without having a

more complex model than just a singal

going down with time and so oops so in

like in this case you know from the last

data point I can essentially extrapolate

with a single exponential here is that

portion of the curve that um that starts

at the last yellow diamond and thats

basically all things that I havent

measured but I can extrapolate and that

gives my

can give rise to to an estimate of half

life which is essentially the terminal

half life of the particular

curve now this extrapolating function is

crucial uh if for example I didnt do a

you know a a good job uh in experimental

design maybe I stopped sampling too

early and now I have a little bit of an

ambiguity which curve is the right one

is it the green or the red right they

both fit data L up to the last point but

the long term the the the estimation of

of the area under the curve that is

under the green line as opposed to the

red line uh you know theyre theyre

quite different and so the choice of extrapolating functions is crucial to get an accurate or realistic estimate of very end of the curve and there are techniques that we use in terms of including a optimal number of data points along the curve to choose what function may be better but of course it is a source of potential error because if if I leave the extrapolation too ambiguous then my my estimate can be wrong and just to to remind you you know why do we use for example the end of the curve is to provide us with an estimate of clearance so if my Au is wrong my clearance is going to be wrong and so I may make the wrong conclusion in terms of how the drug behaves in a uh in a biolog system and so uh like I said earlier very briefly when we um estimate the required integrals we just sum up the individual components so we sum up the part of the integral that is from trapezoidal integration and then the last element in the sum is the

extrapolated time time concentration curve which then completes my area under the curve and area under the moment curve calculation and then I can use these now to calculate my non complemental parameters including like for example clearance mean residence time and so on and then half life was also a byproduct of this from the extrapolation I can get an estimate of half life and the beauty of this calculation you know is that um extrapolation is done automatically as part of the fitting and one can have statistical information for all the parameters and despite the Simplicity of this approach there is a natural connection with the solution of constant coefficient comparment knowledge if youre interested and software is widely available for for those of you that dont want to deal with the intricacy the intricacies of model building but they prefer essentially to have you know a a reproducible compartmental Sy or computer system calculate this for

you but um despite the Beauty and the
Elegance of the approach there were some
assumptions and so if I if you remember
the key assumption that we made based on
non compartmental analysis was that
every molecule that leaves accessible
pool has to come back uh except when
its irreversibly cleared from the
accessible pool itself so depending on
the particular drug at the particular
biological system this assumption can be
met or not but if it is not met then
there are the the estimates will be
incorrect you know to a varying degree
and also the the last item that we
mention is that if um there are
nonlinearities in the system like the
the time varying rates that we saw
earlier in the compartmental case where
we have a m rate of elimination the the
non compartmental approach cannot handle
those very canot handle those properly
and so uh that means that in this case
no comp cannot be applied because the
estimates may be
misleading so the advantages of

compartmental models in general are that
they can handle nineties morle they
provide a way to State hypothesis that
we may have about the system structure
and the arrangement of these
compartmental units can a in
experimental design and can support
translational research but the non
compartmental the non compartmental
method has has an advantage that is very
easy to calculate it can provide very
useful parameters if the assumptions are
met um there are the the biases that can
be introduced by non complemental
analysis have been described previously
um and these essentially boil down to
viol
of the single sync and the single Source
hypothesis and these have been described
in the literature but is to say that if
the Assumption on the right is not met
then some of these estimates may be
erroneous or or misleading so one
instance for example where nonmental
analysis can be misleading is that of
biologic uh or monal antibody from

cinetics often and I think you will see

it in other modules of this course but

often antibodies exhibit whats called

Target mediated disposition which is

basically um the receptor the target

receptor itself impacting the

disposition of the antibody at the

Target site and essentially the target

if it turns over quickly and is present

in a large a large abundance can

actually uh turn into an additional sync

for the antibody meaning that the the

clearance of the antibody will

uh will be impacted will increase

because of of of disposition that occurs

through Target binding so the

elimination of the of the antibody drug

can occur as sites that are remote from

plasma due to binding and

internalization processes and so this is

basically balls down to a violation of

noncompartmental analysis because when

drug elimination is influenced by

binding to the Target the Assumption may

not be met and parameter estimates may

be misleading and moreover such a system

doesnt necessarily meet um linearity

and timing variance but but that being

said you know we can still use

noncompartmental analysis to figure out

that something is going on like in this

example we have if we plot uh

noncompartmental Au uh volume clearance

and halflife as a function of those we

see that the system doesnt behave

linearly with respect to those and so

this is a um a a signal or or evidence

that no compartmental analysis

assumptions cannot be met and the A and

clearance and volume at any given dose

are not a complete representation of the

disposition of the of the drug in this

case and so one has to resort to more um

complex modeling approaches where the p

of the antibody is uh uh includes not

only Administration and distribution but

also binding to the compartment are to

the to the

pharmacological Target receptor and the

and the resulting elimination that

occurs from there but again

noncompartmental approaches can be

helpful to help us understand that

something is going on and a more

sophisticated method of analysis may be

required in this case so um theres a

theres a

a lot of literature on these ideas and

and theres a lot of um of writings they

want can go to to understand this a

little better I put them some of them in

the lecture but maybe if there is a take

home message here is that to estimate

key useful PK parameters either approach

compartmental

noncompartmental uh is probably

adequate you know when the sampling

schedule is dense or Rich provided that

all assumptions that are required for

either analysis no compartmental

especially are meant if the sample

schedule is sparse and the disposition

of the drug is nonlinear uh then the

these are challenges for

noncompartmental analysis and then when

it comes to noncompartmental methods uh

maybe the last point is that they cannot

be predictive they cannot be used to

scale from one system to another or from

one species to another like

compartmental models can do under s

circumstances and pbpk models do very

elegantly and so they have limitations

in that sense so so the best strategy I

would say is probably a blend so its

perfectly okay to

start data analysis with the very simple

noncompartmental approach and see what

the numbers are and then see what the

behaviors are if there is evidence for

no linearity or saturation and so on

then one can switch to other um

approaches always being careful about

the key

assumptions so I think we got to the end

of this particular module so thank you

very much for listening so far and Id

like to acknowledge Again David Foster

my former colleague who was the one that

developed these methods when back when

the course was actually started so thank

you very much and uh good luck to the

rest of the

course