todays speaker is dr diane mold in 9

chemistry and chemical biology at

stevens institute of technology she then

earned a phd in pharmaceutical and

pharmaceutical chemistry at the ohio

state university in 99

for years dr mold was a

pharmacokineticist in the industry where

she specialized in population

pharmacokinetic and pharmacodynamic

modeling

she was also an associate research

professor at georgetown university

currently dr mold is the president of

projection research inc a consulting

company offering pk and pd services

please enjoy todays lecture

hi my name is dr diane muld im

president of projections research

and im from phoenixville pennsylvania

im here to talk to you today about

disease progression models

so there are a lot of motivations for

developing such models primarily to

visualize the time course of disease

both in a treated and an untreated

condition

and we use these models to try to

simulate the future course of the

disease

to understand and simulate various

disease interventions and also to help

develop more informative clinical trials

also disease progression models are

supported by the food and drug

administration and can form a framework

for regulatory submissions

so there are new objectives for clinical

trials in most confirmatory clinical

trials the purpose of the trial is to

test the null hypothesis which basically

is looking at whether or not the drug

and the placebo are effectively the same

and theyre focused on testing that

because frankly thats a very easy thing

to test and theres always a hope that

you have an alternative model that can

be accepted in place of that

but testing that is easy is an easy

question to answer

but it actually isnt actually focusing

on the right question which is maybe

there are subsets of patients who would

benefit from different therapies or

different dosing regimens

so as tukey said its far better to

approximate an answer to the right

question which is often vague than to

come up with an exact answer to the

wrong question which can always be made

precise

so basically what were doing with these

disease progression models is trying to

develop an exposure response surface and

thats not an easy question to answer

but maybe its the right question to ask

however in developing these things we

have to make assumptions which can

weaken the robustness of the answers

assumptions can reduce the inferential

certainty because if our assumptions are

wrong

then the conclusions that we make based

on that model may also be wrong

however its the quality of the

assumptions and not their existence that

is really the issue

so typically when we develop these we
develop them as part of a team so that
we can get input for example from
clinicians and from other healthcare
providers who actually have a good
understanding of the progression of the
disease
also a summary of the surface function
such as an average over the response
surface can still provide robust answers
to the simpler questions essentially
what we can do then still is address the
null hypothesis question which is does
this drug work better than placebo or
standard of care or does it not
so during drug development patients can
have different responses to drugs and
theres a lot of different factors that
can contribute to the variability in the
outcomes of the study
its impossible to study all
combinations of treatments in different
doses by different patient types so
typically when were developing this we
may get some data for example from
elderly patients from younger patients

from pediatrics and were trying to

develop a dose response surface without

data from every type of patient given

every different dose and and duration of

therapy

also the time course of the disease in

the untreated state is also variable so

we want to characterize both the

untreated state and also allow for a

placebo response to better understand

the drug effect

in addition clinical markers are

inherently variable as well so for

example in certain areas where its a

very subjective assessment such as

depression and the hamilton depression

score the error thats associated in

other words the variability from

measurement to measurement that you see

in a hamilton depression score can be

quite notable

so we typically do repeated measures

because were more able to evaluate the

central tendency of that patients

response rather than focusing on a

single

assessment so model based evaluations

can provide a basis for developing an

exposure response by making

scientifically valid assumptions but

again it usually requires input for

multiple people during this development

models actually can help increase the

amount of information recovered from a

clinical trial

people that work in pharmaceutical

industry im sure are familiar with the

fact we have data that didnt quite

reach the p value

and thats because information thats

obtained from any scientific study is

detected based on the ratio of signal to

noise and in any study the information

that we gather is the total variation in

the data and the signal is the variation

due to identifiable causes in other

words did this patient receive therapy

or did they not receive therapy the

noise is the unexplained variation in

the data by building such models and

identifying factors for example patient

sex patient age other concomitant

medications or comorbidities we can

actually begin to reduce the noise and

improve the signal

and by doing that we can actually

improve the amount of information that

you can get from a clinical trial and

oftentimes see a signal of a drug effect

where under traditional assessments you

may not be able to see it

so clinical pharmacology if we think of

it as an equation and im a

pharmacometrician so i think of

everything as an equation

we look at it as the sum of disease

progression plus drug action

it also follows the drug action is

actually a combination of a drug effect

and a placebo effect so understanding

how the drug works involves

understanding the progression of the

disease

and a potential placebo effect as well

as the effect of administering a new

test drug

to do this we look at a variety of

different models including

pharmacokinetic and dynamic models and
these are fairly straightforward and
most people are familiar with them where
we look at kinetic models where we look
at the dose and the concentration we
look at how the drug is is handled in
different individuals and patients we
look at the effects of disease state
such as renal and impairment renal and
hepatic impairment
hemodialysis which can also affect drug
concentrations other things like
concomitant medications
and genetic influences
and then we also look at
pharmacodynamics so
now were looking at other measured
effects either through biomarkers or
surrogate endpoints or clinical effects
and endpoints now surrogate endpoints
are a fairly uncommon form of dynamic
assessment these are endpoints that have
been validated as correlating with an
actual clinical endpoint
so disease progression model accounts
for the time course of a disease in a

particular patient and in the literature

youll see this usually marked as s of t

meaning the status at some time t

and were measuring things like symptoms

or signs and symptoms are usually a

measure of how a patient feels or

functions and the signs could be

physiological or biochemical markers of

disease activity and again we can look

at surrogate endpoints or outcomes where

the endpoints can be validated markers

that are associated with an outcome and

then the outcome itself which may be a

measure of global disease status or it

could be a time to predefine disease

progression or a patients death

so many of you have seen some of the

other

lectures in this series may be familiar

with the emax model thats often used

in pharmacodynamic assessments and here

were looking at the

e of t

and basically that would be the effect

at some time t but if we think of it as

a status at some time t

and then we can have the e naught which

is a baseline

disease progression

and then a drug effect which comes from

the e max

function on the on the other side of the

equation

this is actually the simplest form of

disease progression model and in fact is

often one thats implemented in clinical

trial designs

basically what were assuming is that

the patients disease will not progress

during the course of the study

unfortunately thats not often an

appropriate assumption to make for

example patients with cancer often

progress in their disease during the

course of a trial

other patients who have for example

depression may have a seasonal component

to their disease and it may oscillate up

and down during the course of the study

but this is actually the simplest form

of a disease progression model

well start looking at some new ones

but the components of a disease

progression model then would be a

baseline some function describing the

natural history of the disease

a placebo

effect model and then the active

treatment response that youre seeing

so placebo response is something that

people talk about a lot its the change

in disease

based on patients who have been

randomized to receive placebo and its

usually seen as a transient improvement

in clinical status followed by a relapse

to the prestudy status so in depression

trials for example patients often feel

better just because theyre in a new

situation they have new health care

providers and theyre often being

assessed more frequently which actually

does have a beneficial effect

placebo response can be variable both in

magnitude and duration but its often

more notable when clinical status is

evaluated subjectively

so placebo response is a real issue

there was a publication some years ago

called the powerful placebo which was

subsequently debunked but

actually nonetheless

patients do have a measurable response

to placebo treatment

this is an ad that i found on a online

journal and its an ad for a

an approval of a new drug which is

called sucrosa its actually a placebo

that in this this humorous article was

being allegedly approved

for a variety of indications and there

were a number of side effects associated

with it as well including

potential for developing cavities

but the idea is that the concept of

placebo response is very well

known

even by people who dont work in

healthcare and the pharmaceutical

industry

so as i mentioned earlier when were

building these things we actually dont

work in isolation its always best to

have a group of people that are familiar

with the disease

and

also the treatment of that disease so i

usually recommend speaking with a

disease specialist

what i typically do is draw pictures of

the time course of disease and then try

to translate that into a disease

progression model

ill explain what the model and

parameter is to the specialist and try

to ask them for advice on factors that

may influence patients symptoms or

progression

we then translate the models with

appropriate parameters and covariates

and begin to evaluate the data in order

to get a sense about how that works

lets take a look at the construction of

a disease model

so for example if were looking at

patients undergoing solid organ

transplant in the normal trial setting

were going to look at whether or not

the patient was administered drug or

placebo

and then were going to see whether or

not that patient had any acute rejection

but a disease progression model goes

into the clinical situation a little bit

more thoroughly

so instead we actually go and ask is

this a catavaric donor is it a matched

or unmatched and is that for example

patients first transplant because

theyre less likely to have a rejection

on the first transplant than if theyve

had multiple transplants

then for example

for many renal transplant patients they

have an up regulation of cd positive t

cells which usually means that their

immune system is actually a little

hyperactive and that can actually be a

factor contributing to rejection

so we can measure those

and then we can look at whether theyve

got an immune or inflammatory response

by actually looking at markers of

inflammation il tnf alpha are also

very common assessments

and then we can link that to cell death

that may

preprecede an acute rejection

and then look at the effect of the

administration of drug and placebo

somewhere on this much longer pathway

and by accounting for all of these

factors we can see the drug effect a

little bit more clearly than simply

asking did the patient have a rejection

or not have a rejection

so this is the next most simple disease

progression model

were looking at the patients status at

some time of t

and we say at the initial time that the

patient enters this study their status

at baseline is s sub naught

and that we have a slope thats

occurring over time alpha

and so based on this very simple linear

disease progression model we can draw a

line and say over time this patients

status will follow this linear

trajectory now youll notice on the

xaxis that the time does not actually

have units but simply by looking at the

numbers you may guess that this could be

something like weeks

and thats because in many cases

diseases progress relatively slowly so

for example people with osteoarthritis

may start with just mild twinges and it

may take years before you really see a

major clinical issue so one of the

components of actually doing disease

progression modeling is often the need

to collect data over an extended period

of time in patients

so

there are a number of different ways of

describing the effect of drugs so if we

again go back to our very simple

linear effect and now were adding a

drug effect

which is the red line that you see

rising above that where this drug

actually offers some symptomatic

improvement

so that basically what were doing is

were simply adding a drug effect and

saying that at any given point in time

that patients status will be improved

by an average of a certain number of

status point metrics

and typically well use these looking at

any number of things either looking at

the plasma concentration but more

commonly what we use is something called

an effect site model because typically

when people begin taking a therapy it

may take a few days to even a few weeks

before you really can see a measurable

clinical effect and so as ill show you

in a minute we use these effect site

compartment concentrations as a way of

allowing for a lag between the start of

therapy and actually being able to

detect a clinical response

so basically we can either use measured

concentrations or as i mentioned we can

use this link model

and because of that lag we can actually

account for the fact that the patient

may have been taking drug for several

days to several weeks before we really

see an observed effect

so the effect compartment allows us to

infer from the plasma concentration time

profile

that we have some concentration at an

effect site it could be something for

example like receptor occupancy

or in diseases such as inflammatory

bowel disease we need to suppress immune

response for a certain period of time

before we can actually see mucosal

healing but

the original effect compartment models

attributed the

the transfer from the plasma compartment

to an effect compartment to diffusion

but in this particular case were

actually attributing it to the need for

something to occur before we actually

see a measured effect

so if we take a look at the

effect of eptistigmine on the trajectory

of alzheimers disease now this isnt

even actually a disease progression

model

but we can look at the um

the score for these patients and you can

see that patients that have

historically their

adas cog scores will decay over time but

the administration of eptistigmine does

provide some symptomatic benefit

but you can see that the annual

worsening is actually relatively slow of

about 0 points on the s cog score so

simply capturing information over a very

short period of time like three to six

months you may not really be able to

actually estimate the slope of the

untreated patient

if you remember from your

pharmacokinetics lectures where you

needed data over two to three halflives

in order to be able to accurately

estimate a halflife for a drug

you similarly

similarly need data over the same period

of time in order to be able to

accurately estimate the slope

and then you can see that you can make

an assessment as to whether or not your

drug is providing some form of benefit

this is some work that was done by mark

sales

looking at the effect of azt on cd

counts for patients with hiv

and you can see that theres a placebo

response where theres a transient

slight improvement followed by a decay

in cd count

where azt actually again increases the

cd count so this again is an example of

a symptomatic benefit thats provided by

the drug to help alleviate the symptoms

of the disease

tachrin which is often used to treat

alzheimers disease

has also been modeled as a disease

progression model

so we have the same basic function with

a baseline disease status of s naught

we have a linear natural history and in

this particular case we accounted for a

placebo response and also an active

treatment response and this is work that

was produced by nick halford and carl

peace

so lets take a look at that function

and as you can see the disease

progression scores the light line thats

the historical score and then you have

the placebo response which is

represented by the dotted line and so

you have a transient dip in that

followed by a return to baseline

and then you have a drug effect which is

the heavy dash line

the net effect is a total difference it

looks like a simple shift and a

symptomatic benefit but this also

provides some useful information because

basically the placebo response is still

fairly high

even two months after initiation of the

study which would suggest that if youre

trying to make a shortterm

proofofconcept study with this

particular disease a placebo effect may

confound your ability to be able to tell

if a disease if a drug is working in a

particular disease so characterizing a

placebo effect can actually help you

understand data from proof of concept

studies which may not be long enough to

accurately capture the full benefit of

the drug effect

but by understanding that a placebo

response may still be active while

youre actually looking at data

can help you separate a placebo response

from an actual drug response and make a

better assessment even from

proofofconcept studies as to whether

or not the drug has any potential and

should be carried forward for

longerterm clinical trials

this is some work that was done in 99

by griggs looking at young boys with

muscular dystrophy and he was measuring

muscle strength and you can see a

natural history line and hes testing

the effect of prednisone at two

different doses plus placebo

and you can see as mentioned earlier

even in this data which is not modeled

but simply plotted that you do have a

transient improvement even for patients

who are on placebo

but nonetheless the prednisone at 0

megs per gig shows what appears to be a

symptomatic benefit

at a higher dose 0 we see that the

slope of the line for the 0 mig per

gig dose

actually is now different from the

natural

course of the disease

suggesting that there may actually be

something additional going on aside from

a simple symptomatic improvement so how

do we deal with that

we start to alter our disease

progression model

so now instead of separating the

effect from the slope we actually put

the drug effect in with the slope and

multiply it by time

and that allows the disease

the effect of the drug on the disease to

alter the slope

and so we can have

patients with differing slopes

as a consequence of therapy and this

suggests that you have a disease

modifying activity of the drug

so for example if we look at the nepazil

on on alzheimers disease we can see

again the natural history is the solid

black line with the dinapazil showing

some difference from the slope of the

the natural history of the disease

suggesting again a potential impact on

the disease progression itself

similarly we can have various

combinations and permutations where we

can combine either a symptomatic or a

disease progression modifying disease or

one that characterizes both

so these different models can be changed

in different ways to try to reflect what

appears to be going on with the data

that you have at hand

so how do we tell these apart

well the easiest way to tell whether or

not youve got a disease modifying drug

or a symptomatic drug is to actually

stop the therapy

so if we look at the panel on the left

we can see that the disease progression

is the black solid line when we add the

drug therapy

we see a decrease in the progression and

then after we stop therapy it returns to

baseline

and on the right panel we can see that

when we stop therapy the red line which

is representing the patients that have

been treated is not actually returning

to baseline and thats a very good

indication that the drug is actually

modifying the disease progression

studies like this are actually very

difficult to

consider particularly for patients who

are clearly benefiting and so are not

always considered ethical

an appropriate workaround is something

called the staggered start model where

for example you instead of randomizing

patients 0 0 to placebo or therapy we

might randomize only a third of the

patients to start active therapy right

away

and then later in the study well

randomize another third to cross over to

active now why would that make a

difference or why would that tell us

that one is disease modifying and one is

symptomatic

if the drug is actually symptomatic

regardless of when the patient was

randomized to receive active treatment
they should still reach the same effect
of improvement however if you have a
true disease modifying drug what will
happen is that the patients who received
the active therapy earliest will have
lower scores than patients who were
later randomized and so youll actually
effectively end up with three different
groups the placebo arm the patients who
were randomized late therapy
and the patients who were randomized
early to therapy and this is a way of
ethically discerning whether or not you
have a symptomatic drug or a true
disease modifying effect
now im going to be giving an awful lot
of functions and really the point of
this entire talk isnt so much to
memorize or completely understand all of
the math but to understand that there
are a variety of different functions out
there and that you can utilize functions
like this
with or without colleagues to actually
help develop models and so there are a

host of different functions that can be

applied depending on what kind of metric

youre using to make a determination

about the disease status

so this next set of functions are

asymptotic progression models and these

are typically used when the disease

progression has a natural limit where it

either falls to zero or goes to some top

steady state value

so the zero asymptote would be

indicative if you have someone had

spontaneous recovery so for example a

patient who has the flu

will eventually recover whether or not

theyre treated

and theres multiple functions that can

be used to describe that

a nonzero asymptote might be for

example with

patients with parkinsons where they

reach a maximal score on the updrs and

they simply cannot actually progress any

further so it would be progression to

some maximal or in this case what we

would refer to as a burned out state

and there again several functions that

can be used to describe that kind of

time course

so the zero asymptote model is shown

here where youve got a symptomatic the

natural history is the black line and

you can have both symptomatic and

protective effects so the symptomatic

would offer a very rapid drop

where the protective effect or a

combination of both has a slower drop

now people have often felt that disease

modifying drugs actually

have a you know better quality of

therapy but thats not always the case

if we were looking at status as

something like a pain score for a

patient whos recently had a wisdom

tooth extracted a zero asymptote model

would certainly apply to that setting

which is sooner or later the healing

will occur and

the incision or the where the tooth was

removed will not be as painful

but for patients like that a symptomatic

improvement that

sets on very quickly

is actually preferred to something

thats got a an alteration in the

progression which as you can see in this

picture would take quite a bit longer so

the

type of drug that you may be looking for

is often dependent very much on what

exact indication youre in and what kind

of benefit the patient would need the

most

so we can look at a variety of different

study designs here as well and so heres

some of ours

zero asymptote functions and here weve

got a simple exponential function and

one of the ways again to tell whether or

not the drug has got symptomatic or

disease modifying effects is by

administering a second dose

as you can see in the top panel when

that second dose is administered theres

another drop

in the score for the patient whereas if

you have a disease modifying effect it

tends to be a smoother transition

so these models can actually be used to

simulate different

study designs that may help you decide

or determine whether or not your drug

has a disease modifying activity or

asymptomatic

the

emax functions can be used the same way

and as you can see this is a simple emax

function but we have a decay where it

actually speeds up over time and again

we can see the discerning between the

symptomatic and disease modifying in

this setting can actually be looked at

by administering a second dose and we

can see that we have an additional drop

in the upper panel indicating that weve

got a symptomatic benefit whereas

administering a second dose as you see

in the lower panel actually just

accelerates the improvement a little bit

so

again simulation

can be a very useful tool in planning a

more informative studies and such models

actually are very very useful for trying

to decide what study design would best

tell you how your drug is working

and what additional things should be

done to help you differentiate and

identify

dosing regimens and understand what the

likely outcome of that study is going to

be

so we have also the possibilities i

mentioned earlier of the socalled

nonzero asymptote model where the

patients status will actually worsen

until it reaches some maximum state

and as we saw before weve got the same

kinds of things that can go on so our

black line here

is natural history and then for the red

line we can have a symptomatic benefit

which is you see

at the time eight point where weve

stopped therapy the patient will

actually return to their untreated

status

but because we have a more complicated

model the drug can actually now even if

its a disease modifying drug

can actually work in different places

one where we lower the maximum response

thats the

protective steady state so in other

words these patients will not progress

to this

maximum score or we can have some kind

of a product protective model where it

actually slows the progression

so

the more complicated disease progression

models offer a lot of different areas

where a disease effect can actually be

assessed and tested in order to

understand better exactly how this drug

is working in the patient population

so again as was shown before weve got a

fairly elaborate function here where the

patients

disease is progressing over time at some

rate of k progression

and we have a steady state value and

were looking at a drug effect here

where again weve just added a second

dose and we can see that the patients

score is actually drops weve got a step

score going on there

versus whether or not the drug effect

has still got a smooth effect on the

improvement in patient scores so with

all of these models the same kind of

evaluations can be done

these are data that were taken from the

parkinsons study group psg from a study

called data top where they were looking

at patients with parkinsons disease and

they were looking at what the impact of

administering ldopa was to these

patients

so the panel on the upper left is all of

the data and the score you can see how

incredibly variable the data are but

when we look at the patients one at a

time we can see

that the orange triangles those are the

individual updrs scores that were taken

over time

and the sudden change which you see in

particular in patient one where the

score has gone up and then suddenly

drops

thats where ldopa was administered

patient two didnt have quite as much of
a response patient three we can see a
substantial drop again about year two
where eldopa was administered but you
can actually see that in this particular
patient these scores are actually
declining back to a more normal score
and you can see that the impact on these
different patients is quite variable so
in addition to a very strong indication
of a symptomatic benefit from ldopa you
can see that in many of these patients
the progression which would be the slope
thats occurring after treatment is
initiated is actually often different
than it was before treatment was
initiated
if we look for example at patient seven
up to year two we can see that patient
was progressing fairly rapidly after
year two where this patients ldopa
therapy was initiated we can see that
the slope that goes from two to six
years appears to be a lot shallower than
it was prior to the administration of
ldopa

so youve got in this particular case

indication of both

symptomatic benefit but as well disease

modifying benefit so what does that

really mean in terms of patient care

basically for drugs that are used to

treat chronic diseases that progress

typically

you want to try to

slow the progression down as quickly as

possible and oftentimes that would

suggest if the drug truly does have

disease progression modifying activity

thats often better to start the therapy

earlier rather than later so that the

patient doesnt have a chance to

progress very far before therapy is

initiated so these kinds of models can

actually be used to try to inform not

only how much drug to give and how often

to give it but when to initiate therapy

in order to provide the most benefit for

patients who are taking the

drug now this is something called an

inverse bateman function

and again for those of you who may

remember your pharmacokinetics lecture

in this course series uh if we remember

the one compartment oral model where we

had first order input and first order

output and it forms kind of a little

camels hump thats called abatement

function

this is flipped upside down hence the

term info inverse abatement function

so what we see and what were trying to

describe here is through the hamilton

depression score where patients

typically with depression are often at

their greatest

degree of depression during the winter

months and so theres a seasonal

component that we see

and so typically in the summer their

scores are better in the winter their

scores are worse and this is without

treatment now why is it important to

capture or characterize that variability

in the underlying score

its because during these clinical

trials because enrollment may take over

a year sometimes longer to enroll a

study youll have patients that are

starting therapy at different times in

the year so its important to understand

for example a patient who enrolled at

their uh worst possible score which

would be in the winter and finished at

the summer at their best possible score

that that is oftentimes just due to the

uh cyclical component of their disease

and should be captured in order to fully

understand whether or not its your drug

or its just a change of the seasons

thats improved that patients status

so what we can see here is a symptomatic

drug

the

lines there the dotted lines are the

administration of the drug and we can

see that this particular drug is

improving the hamilton depression score

but again when drug is stopped it will

return back to its original time course

so all of these other models were fairly

empiric and in fact most disease

progression models are somewhat empiric

in nature because in many cases all of

the underlying pathophysiology of

diseases is not terribly well known but

there are diseases for which we can

develop physiological models of disease

progression and those are usually the

preferred models to do

so if we for example look at

baseline status and we have

also

a rate of something coming in and a rate

of something coming out so for example

the level of a particular enzyme or

protein in the body in the normal status

we have a rate of formation which is our

case in

and we have a rate of loss which is k

loss

for a patient for example that has a

disease

their casein and kdeg

may be altered

and so basically that can affect the

overall

for example enzyme level or protein

level so if a patient has a compromised

synthesis of a particular enzyme then

their status or their concentration of

that enzyme will be low and the disease

will be

manifest as a consequence of a low

enzyme

or if their loss is very high similarly

theyll have a low level

i think of these models as being sort of

analogous to a faucet pouring water into

a sink and then we have a drain coming

out

at steady state the water level in the

sink will be a constant level thats

related to the rate of how much water is

coming into the sink

versus how much water is going out

through the drain

if for example we were to turn down the

tap so that the water flowing into the

sink is reduced the water level in the

sink will drop

alternatively if we were to expand the

drain so that the loss from the sink is

actually increased will lower the water

level

conversely if we turn up the tap the

water level will rise or if we block off

part of the drain the water level will

rise

so the case in is analogous to the

faucet and the k loss is analogous to

the drain

so each of these can change with time

and thats what produces our disease

progression

so this would be an example of some

physiological disease mechanism where

weve got again some marker that were

following

kdi where were looking at a synthesis

and a k loss and a symptom and we can

actually add a drug effect into that and

again we can use the same delay function

such as an effect compartment if for

example adding drug or adding enzyme or

protein

takes some time before you actually see

the symptoms begin to resolve

so for example

if we look at disease progression due to

decreased synthesis so the now the lower

red line which has fallen off to a very

low level might be in the untreated

state

adding drug by inhibiting the loss or

stimulating the expression can actually

reduce the

issue with regard to the disease by

bringing their status back up to a

normal value

now because these are

models that actually move over time we

cannot instantly say ah

our slopes are different therefore this

must be a disease modifying drug the

reason is in this particular case if we

take the drug away the patient will

still return to baseline so again

simulation and different study designs

is often needed to make a determination

in these more complex settings as to

whether or not youve got a disease

modifying drug or youve got a

symptomatic drug

similarly if we have an increased loss

of something for example bone mineral

we can have a fall off where by altering

the rate of loss or

changing the synthesis of something we

can actually bring that patient back up

to a normal value

and thats reflected in some work that

was done on raloxafin which is used to

treat patients with osteoporosis

and you can see here the red line the

bone mineral density is actually falling

over time and these are also three

different doses of relaxant and we can

see

an improvement in the bone mineral

density over time

youll notice that we actually have some

projection out for future years

so again these models can be used to

simulate what we would expect to see

over multiple years of treatment with

these drugs but of course whenever you

do such simulations you have to have the

caveat that you are extrapolating so

those values are much more questionable

than ones where you actually have data

to support that

another physiologic model would be the

use of what we call transit models and

here we use a string of compartments to

implement a delay in response to drug

and these are analogous for modeling

things like anemia neutropenia and other

chronic progressive diseases

so if we look at the top here

if were looking at for example

hemoglobin and administration of epo

we can see the pulses or the

administration of the drug and we can

see

an improvement in hematocrit over time

and if you remove the drug of course the

hematocrit will go back to its original

value

now one of the interesting things about

these salt transit models is that they

have something called schedule

dependence meaning that if you

administer

very large doses you can actually

saturate the system

and so the plot on the bottom is

actually the same drug the same total

amount of drug just being administered

at a different schedule in the lower

pale line you see there

were administering a very large dose

but were giving it

weekly if you look at the next line

were giving it several times a week and

if you look at the upper red line were

giving the same drug

every day

so why are we getting such a huge

response with daily administration when

were getting a much lower response with

the once weekly and the reason for that

is that when you administer this large

dose youve actually saturated all the

receptors that the drug can work on and

much of the drug thats been

administered

actually has absolutely no ability to

act

so were giving a bigger dose but were

not actually getting everything that we

possibly could out of it

so why isnt epo administered on a daily

basis

heres where we have to look at the

balance between patient compliance and

preference versus clinical activity so

in many cases its better to go to a

less frequent dosing even if we have to

give drug that we know is probably not

going to produce a real clinical benefit

in order to spare the patient from

having to inject themselves on a daily

basis

so cell transit models and in fact many

of these physiologically based models

have this kind of property and you can

actually explore things like dosing

frequency to see which may be optimal in

response but also what may be necessary

in terms of the clinical situation

so models describing growth are actually

very common these are semiphysiologic

models and they can look at things like

antimicrobial growth viral growth and

also tumor growth and here were looking

at the change in response over time

where we have a k growth which is the

rate of growth and then a rate of death

and then theres a drug effect on that

so basically

what weve got is a circular rate so

that in other words if were looking at

a tumor cell as you know a small tumor

initially wont appear to have grown in

diameter very much but as it gets bigger

and bigger itll appear to grow more and

more quickly

youll see more and more metastases so

basically whats happening is it sort of

feeds on itself

and then we have

a loss or death of the tumor cells for

example

and our drug can actually work on

increasing the rate of tumor cell death

so it would be a stimulatory function to

try to reduce cell counts

models like this as i also mentioned can

be used for looking at antimicrobials or

viral agents as well

remember the effective drug is to

stimulate the loss of response here

which would be the tumor cell size or

the cell count for

microbes or viral count

so these growth functions basically show

that you have a growth going on over

time and then as you administer

treatment you would expect that whatever

it is youre measuring would decrease

but when you stop therapy youll see

that there is in fact

a beginning of the return to baseline

but again this is not a

symptomatic ben this is not a disease

modifying benefit because you havent

completely removed the thing that was

growing in the first place so despite

the fact that the slopes in these cases

are different this is not a disease

modifying its simply a symptomatic

improvement gompers functions are

somewhat more elaborate growth models

and here we actually can do a somewhat

better job as im sure uh people that

have done research in cancer are aware

that theres often a group of tumor

cells that are senescent or are

resistant and here we have two different

populations the sensitive which is rs

and the resistant which is rr

and cells can actually transit back and

forth between a sensitive state and a

resistance state and we can imply the

drug effect the emax

function to the growth rate of the

sensitive cells

so basically drug effect is delayed via

a link model or limited to an emax

model but cells that are in the

senescent or resistance state will not

be affected by the drug effect and so

what that allows you to do

is understand

relapse that can occur so if we look

here for an untreated low and high dose

the untreated is the blue line and we

can see that the tumor will grow to a

certain maximum value

in the red line we can see a low dose

where weve reduced tumor size but again

on cessation of therapy you would have

regrowth of the tumor

but at a very high dose we can barely

see anything

but because we have that resistant

population we can later see regrowth and

this would explain in cancer

chemotherapy for example why a patient

can appear to be disease free sometimes

for two or five or more years before

evidencing

a relapse of their original

cancer another form of analyses that we

do is looking at something called a

survival function and we use those to

describe disease progression as well so

these are empiric means of evaluating

the relationship between drug effect and

the time course of disease progression

so we can link these very fancy

pharmacodynamic models

to a measurement of outcome

so our survival functions basically we

look at the survival at some time of t

as being the probability that something

will occur at

that is before the end of the study

and these are monotone decreasing

functions so survival is one at time

zero but zero as time approaches

infinity

and the rate of decline varies according

to the risk of experiencing an event

so basically this the survival at time t

is an exponential of a hazard function

over time

um to think about it in more simple

terms i like to think about this as like

a game of musical chairs where you have

a number of chairs and one plus the

number of chairs children circling the

chairs when the music stops everybody

scrambles to get on a chair and one one

student or child actually is eliminated

from the game they remove a chair and

they do the same thing so everybodys at

the same risk

while theyre circulating the chairs but

when the music stops its time to see

whos still in the game and whos not

and thats actually a very effective way

of looking at a survival function

so the hazard function defines the rate

of occurrence whether its an

instantaneous progression in many cases

here well use the pkpd model to act on

the hazard function so in other words

can it reduce the hazard of something

occurring

cumulative hazard is the integral of the

hazard over a predefined period of time

and usually thats the duration that the

study is ongoing and that describes the

risk of an event occurring so this

translates these very fancy mathematical

pharmacodynamic models into a useful

measure of outcome

so for example if i were to administer

gcsf to a patient whos receiving

chemotherapy i would expect to reduce

the risk of that patient actually

developing febrile neutropenia

so we can look at the benefit or adverse

events and compare them with existing

therapy fairly easy

so we define t as a time to some

specified event and if were again

talking about gcsf we could be things

like fever infection or sepsis following

chemotherapy

t is continuous thats our time and its

characterized by the hazard or the rate

of occurrence of the event the

cumulative hazard or risk and the

probability of the event not occurring

before time equals little t which as i

said is usually the end of the study

we assume the hazard is a continuous

function and it can be a function of

biomarkers and there are a number of

transit models for example which you

just saw earlier that can describe

neutrophil count over time after

patients have received

chemotherapy the hazard functions can be

adapted from any clinical endpoint

and the hazard function then is

integrated over time to yield a

cumulative probability of experiencing

an event by some specified time

so what does that all mean

if we define a hazard is constant rate

and the cumulative hazard then is h of t

is equal to k

then we can see that the survival if we

go through all the math over there is an

exponential of negative k times t

and this may look somewhat familiar to

you

and if it does i say that would be

absolutely excellent because it looks a

lot like a one compartment iv bolus

falloff so basically if we think of this

in terms of for example molecules of

drug after youre administered an iv

bolus of

drug you have a constant hazard of being

cleared over time and thats the lower

line along the bottom

and the actual survival of the drugs is

measured by that exponential fall off

and then the cumulative hazard is the

amount of drug thats been eliminated

over time

so these all link back to functions that

you should be familiar with or may have

heard about before

and essentially should help make it a

little bit more familiar to you

so if we think about our neutropenia

situation again here were looking at

white cell count over time

and what was applied here was the simple

hazard function where we assume that

once the cell count falls below a

certain level

that patient is at an increased rate our

risk of developing neutropenia uh

febrile neutropenia infections sepsis

that sort of thing

so the the period of time that were at

great risk is that those that

represented by that red line

and the um survival uh which is the

patients that are not developing these

adverse events

is represented by the green line and

then the overall cumulative hazard which

is the yellow line actually as you can

see increases over time

so the longer that patients neutrophil

counts are at this low level the greater

their cumulative hazard and the less

likely it is that theyre going to not

have one of these problems occurring

this sort of thing can actually be used

to compare to new forms of therapy that

may help ameliorate the

neutropenia

and were showing here

our functions

so if we add another molecule you can

see what its doing is not only reducing

the nader that is occurring in this

experimental molecule its also reducing

the duration of time

that this patient is at risk of

developing febrile neutropenia or

infections

and thats represented by the so you

would have a better survival which is

represented by that very light green

line and that the cumulative hazard is

also quite a bit lower

so what does that really mean for us

it means that we have a better survival

so in order to be able to understand

valuations of the importance or the

improvement that were seeing in terms

of clinical benefit we can apply this

kind of analysis to

studies of patients that are receiving

either gcsf or for example this new

hypothetical gcsf

and

on with a much shorter study duration

make a determination as to what patient

risks are being

improved simply by shortening the

duration of time that the patients at

risk for developing severe complications

of neutropenia

so disease progression models have been

developed for a variety of different

diseases

including alzheimers disease diabetic

neuropathy parkinsons disease and

osteoporosis

in fact theres a lot of them that have

been developed by the fda as well and i

certainly recommend that you actually

evaluate their

publications on that

for alzheimers disease its typically a

linear function and the drugs effects

have generally been identified as being

symptomatic

for diabetic neuropathy again generally

a linear function but there are some

indications with some of these newer

molecules that there may actually be

both a

symptomatic and also potentially

modifying impact

for parkinsons disease because that

does have a maximum score asymptotic

models are typically used

and for osteoporosis for example as you

saw earlier inhibition of bone loss has

been

a common marker in most cases as i

mentioned earlier the functions that we

use to describe these disease markers

are empirical but whenever possible its

best to use mechanistic models that

should be used for most

of these agents usually because the

complete disease mechanism isnt always

fully understood

so in summary accounting for the disease

progression is a very important

uh component of understanding how the

drug is actually working

by having that youre better able to

discern the true effect of the drug

and it improves your reliability when

youre doing simulation work

particularly in designing new trials

that can be more informative and better

powered and can also

increase the signal to noise so that you

can better see whether your drug is

working or not and more importantly on

which patients is working best in which

patients receiving much less benefit

so its very useful during the

development of new drug candidates it

helps you visualize ways of using the

drug better

and it helps convert data into

understanding

there are issues that are associated

with building disease progression models

particularly a lack of available data

for untreated patients

however there are different ways of

actually getting such data

the nih actually does have

some databases that they can make

available on older data older studies

also as you

saw earlier in some cases you have to

collect data over very long periods of

time so

at least when youre building these

initially you may require a lot of

time to collect this data

for people working in the pharmaceutical

industry its often helpful to go back

to older studies and take the placebo

arms of studies in related diseases in

order to begin developing these disease

progression model

and also because some of these markers

are quite variable as you saw earlier

the hamilton depression score can have a

lot of variability in it

you often need data from a large number

of subjects to determine parameters

accurately so again going back to larger

available databases that are available

to scientists or in the pharmaceutical

industry historical studies is often a

good place to start in order to be able

to get data thats of sufficient quality

enough patience and over sufficient

period of time that you can begin to

build a very robust model

thank you very much i hope you found

that this information was useful

and if you have any questions please

contact the program coordinator