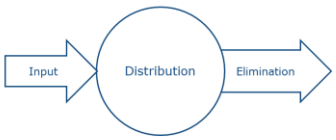
Slide 1	**Absorption Processes & Model Evaluation** **Guangda Ma** **Auckland Pharmacometrics Group** Department of Pharmacology & Clinical Pharmacology The University of Auckland MEDSCI 719 2020	
Slide 2	**Recommended Reading** • Chapter 4 (Drug Absorption and Bioavailability) in Principles of Clinical Pharmacology. ISBN: 9780123854711 • Chapter 1 (The Art of Modelling) in Pharmacokinetic-Pharmacodynamic Modeling and Simulation. ISBN 978-1-4419-9485-1 • Holford N. Absorption and Half-Life. Transl Clin Pharmacol. 2016 Dec;24(4):157-160. • Holford NHG, Ambros R, Stoeckel K. Models for describing absorption rate and estimating extent of bioavailability: Application to cefetemet pivoxil. J Pharmacokin Biopharm. 1992;20:421-42. • Savic RM, Jonker DM, Kerbusch T, Karlsson MO. Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies. J Pharmacokinet Pharmacodyn. 2007 Oct;34(5):711-26. • Mould DR, Upton RN. Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development. CPT Pharmacometrics Syst Pharmacol. 2012 Sep; 1(9): e6. • Model Evaluation Group of the International Society of Pharmacometrics (ISoP) Best Practice Committee. Model Evaluation of Continuous Data Pharmacometric Models: Metrics and Graphics. CPT Pharmacometrics Syst Pharmacol. 2017 Feb; 6(2): 87–109. ©G Ma, 2020, all rights reserved. 2	Chapter 4 (Drug Absorption and Bioavailability) in Principles of Clinical Pharmacology. ISBN: 9780123854711 Holford N. Absorption and Half-Life. Transl Clin Pharmacol. 2016 Dec;24(4):157-160. Holford NHG, Ambros R, Stoeckel K. Models for describing absorption rate and estimating extent of bioavailability: Application to cefetemet pivoxil. J Pharmacokin Biopharm. 1992;20:421-42. Savic RM, Jonker DM, Kerbusch T, Karlsson MO. Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies. J Pharmacokinet Pharmacodyn. 2007 Oct;34(5):711-26. Mould DR, Upton RN. Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development. CPT Pharmacometrics Syst Pharmacol. 2012 Sep; 1(9): e6. The following readings are more advanced. Model Evaluation Group of the International Society of Pharmacometrics (ISoP) Best Practice Committee. Model Evaluation of Continuous Data Pharmacometric Models: Metrics and Graphics. CPT Pharmacometrics Syst Pharmacol. 2017 Feb; 6(2): 87–109. Chapter 1 (The Art of Modelling) in Pharmacokinetic-Pharmacodynamic Modeling and Simulation. ISBN 978-1-4419-9485-1
Slide 3	**Objectives** • Define common models of absorption using closed form solutions and differential equations. • Find out how to compare the fit of models to the same data. ©G Ma, 2020, all rights reserved. 3	

Slide 4	**Revision**
	• A compartment model has three main components
	• Input
	  • Zero-Order
	  • First-Order
	• Distribution
	• Elimination
	  • First-Order
	  • Mixed-Order
	 
	
	4
		Models provide a means to describe observed phenomena. Compartment models are a simplification of drug pharmacokinetics.
		
		A compartment model requires description of three components. Input (rate in), distribution, and output (rate out).

Slide 5	**Revision**
	• Recall in the last workshop we described the amount of drug in the central compartment
	• Using a differential equation:
	`init(Gut)=Dose` `d/dt(Gut)= - Gut*Ka`
	`init(Conc)=0` `d/dt(Conc)=(Gut*Ka - CL*Conc)/V`
	`init(Ce)=0` `d/dt(Ce) = Keq*(Conc - Ce)`
	• Using a closed form (explicit) equation:
	`Conc=Dose*Ka/V/(Ka-CL/V)*(EXP(-CL/V*Time)-EXP(-Ka*Time))`
	• Today we focus on how we characterise absorption processes
	
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		In the last workshop, the amount of drug in the central compartment was described using differential and closed form equations.
		
		The differential equations describe the mass of drug in the gut compartment, central compartment, and (hypothetical) effect compartment.
		
		The focus of today's lecture is to discuss how we can characterise absorption processes.
		
		A quick note on the initial condition. The closed form equation is derived by integrating the differential equation, however, integration will result in a constant. For example say dy/dt=x, then by integration $y=x^2/2 + c$, where c is the integration constant. In order to determine c, then we need to know a value of x and y. The initial condition allows the constant to be fixed.

Slide 6	**Absorption**
	• Absorption describes the journey of a medicine travelling from the site of administration to site of action/site of measurement.
	• This process determines how much of an administered drug enters the body.
	• Two distinct factors describe drug absorption:
	  • **Extent**
	  • This reflects the total amount of drug entering the body
	  • Units of mass (e.g. mg)
	  • **Rate**
	  • This reflects how quickly the drug enters the body
	  • Units of mass per unit time (e.g. mg/h)
	
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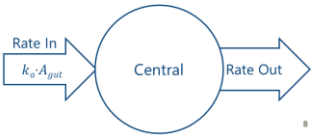
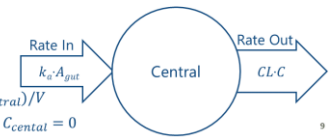
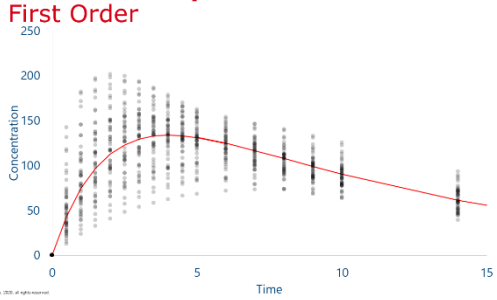
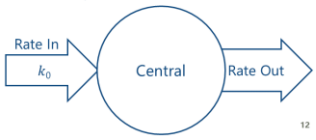
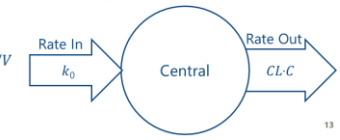
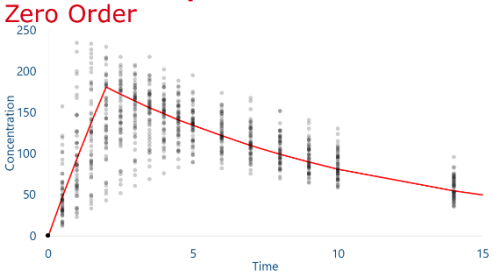
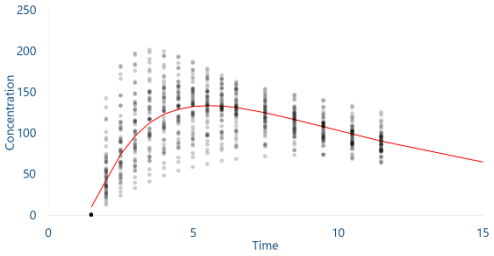
		Absorption describes the journey of a medicine (transfer of mass) from the site of administration across biological barriers to site of action/site of measurement.
		
		Absorption can be described using two factors, extent, and rate.
		Extent describes the total amount of drug entering the body. This is independent of time so the units here are of mass.
		Rate describes how quickly the drug enters the body. The units here units have a time quality

Slide 7	**Extent of Absorption (F)** • Fraction Absorbed (f) • into portal vein from gut • physicochemistry • metabolism/transport • First Pass Extraction (ER) • drug removed while passing through liver • organ clearance and blood flow **F = f · (1 - ER)** e.g. morphine F= 1 · (1 - 0.6) = 40% 7	The extent of oral absorption can be considered in 2 parts. The first part is the fraction of drug absorbed across the gut wall (f). This describes how much drug gets into the portal vein from the gut. Physicochemical properties of the medicine can impact the fraction absorbed. Small, unionized molecules (e.g. theophylline) are almost completely absorbed across the gut wall. Large, ionized molecules (e.g. gentamicin) cross membranes with difficulty and only a small fraction is absorbed across the gut wall. Fraction absorbed may be influence by metabolism of drug in the gut wall (e.g simvastatin by CYP3A4) or transporters which move drug back into the gut lumen (e.g. P-glycoprotein on digoxin). The second influence on extent is first pass extraction. Some of the drug may be extracted by hepatic enzymes. This is influenced by organ clearance as well as blood flow. The extent of absorption is therefore the amount of an oral dose that crosses into the portal vein, and which survives first pass extraction.
Slide 8	**Rate of Absorption** First Order • The rate of drug absorption can be described as: • **First-Order** • Dependant on concentration • Constant **proportion** of drug is absorbed per unit time • *e.g. Intra-muscular injection*  8	Absorption may also be described in terms of rate. We can describe processes as first order if they are dependent upon concentration. If absorption follows a first-order process, then a constant proportion of drug is absorbed per unit time. This one-compartment model describes first order absorption and first-order elimination. Therefore the rate in is proportional to the amount of drug in the gut, and the rate out is proportional to the amount of drug in the central compartment. First order processes can be used to describe diffusion across the intestinal membrane that is concentration dependent. The rate of diffusion is related to the concentration, therefore a higher rate can be observed at a higher concentration.
Slide 9	**Rate of Absorption** First Order • The rate of drug absorption can be described as: • **First-Order** • Dependant on concentration • Constant **proportion** of drug is absorbed per unit time • *e.g. Intra-muscular injection* $\frac{dA_{gut}}{dt} = -k_a \cdot A_{gut}$ $\frac{dC_{central}}{dt} = (k_a \cdot A_{gut} - CL \cdot C_{central})/V$ $when\ t = 0,\ A_{gut} = Dose,\ C_{cental} = 0$  9	The amount of drug in the gut compartment (A_{gut}) is proportional to the first-order absorption constant (k_a). Note that the rate of change in A_{gut} is negative as drug is moving out of the gut compartment into the central compartment, whereas the rate in here is positive. The rate out of the central compartment is also described using first-order kinetics here, and is related to clearance (CL) and the amount of drug in the central compartment (C). We can therefore use a set of differential equations to describe mass of drug in the gut and concentration of drug in the central compartments. Note that the initial condition needs to be specified in order to solve the differential equation. Also note that the equation for the central compartment describes the gut compartment in terms of amount (A; units of mass), whereas the central compartment is described in terms of concentration (C; mass divided by volume).

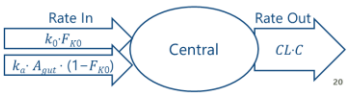
Slide 10	**Rate of Absorption** First Order • The rate of drug absorption can be described as: • **First-Order** • Dependant on concentration • Constant **proportion** of drug is absorbed per unit time • *e.g. Intra-muscular injection* $\frac{dA_{gut}}{dt} = -k_a \cdot A_{gut}$ $\frac{dC_{central}}{dt} = (k_a \cdot A_{gut} - CL \cdot C_{central})/V$ $when\ t = 0,\ A_{gut} = Dose,\ C_{central} = 0$ $C(t) = \frac{Dose \cdot k_a}{V \cdot \left(k_a - \frac{CL}{V}\right)} \cdot \left(e^{-\frac{CL}{V}t} - e^{-k_a \cdot t}\right)$ 10	The differential equation can be solved so that we can use a closed form equation to express concentration in the central compartment as a function of time. Differential equations provide an intuitive means to describe drug kinetics particularly when there is more than one compartment.
Slide 11	**Rate of Absorption** First Order  11	Some simulated data with a one compartment model with first-order absorption and elimination. When absorption or elimination is described using first-order kinetics, it is more intuitive to use half-lives rather than absorption or elimination rate constants.
Slide 12	**Rate of Absorption** Zero Order • The rate of drug absorption can be described as: • **Zero-Order** • Independent of concentration • Constant **amount** is absorbed per unit time. • *e.g. Constant rate intra-venous infusion; bolus intra-venous injection*  12	We can also describe the rate of absorption as a zero-order process. This process is independent of concentration, thus a constant amount is being absorbed per unit time. As an example this may be a constant rate intraveinous infusion (e.g. rate in as 5mg/hour). We can describe this rate in using the zero-order absorption constant (k_0)

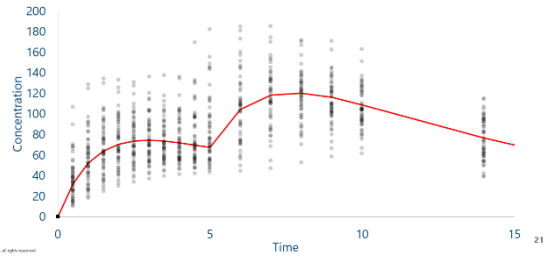
Slide 13	**Rate of Absorption** Zero Order • The rate of drug absorption can be described as: • **Zero-Order** • Independent of concentration • Constant **amount** is absorbed per unit time. • *e.g. Constant rate intra-venous infusion; bolus intra-venous injection* $\frac{dC_{central}}{dt} = (k_0 - CL \cdot C_{central})/V$ $when\ t = 0,\ C_{central} = 0$  13	Here we describe a zero-order input into a one-compartment model with first-order elimination. The concentration in the central compartment is determined by the rate in (k_0) and rate out (-CL·C). Note that the differential equation describes the rate of change of concentration, therefore the right hand side is divided by volume.
Slide 14	**Rate of Absorption** Zero Order • The rate of drug absorption can be described as: • **Zero-Order** • Independent of concentration • Constant **amount** is absorbed per unit time. • *e.g. Constant rate intra-venous infusion; bolus intra-venous injection* $\frac{dC_{central}}{dt} = (k_0 - CL \cdot C_{central})/V$ $when\ t = 0,\ C_{central} = 0$ $C(t) = \frac{k_0}{CL}\left(1 - e^{-\frac{CL}{V}t}\right)$ 14	We can integrate the differential equation, and solve for the integration constant using the initial condition to derive the closed form equation. Some medicines may be administered as an intravenous bolus. This means that the drug reaches the systemic circulation almost instantaneously.
Slide 15	**Rate of Absorption** Zero Order  15	This graph of zero order absorption highlights the constant rate in of a zero order process. A zero-order process may describe a formulation which releases drug at a controlled rate. Stomach emptying time that occurs at a steady rate can be described as a zero-order process.

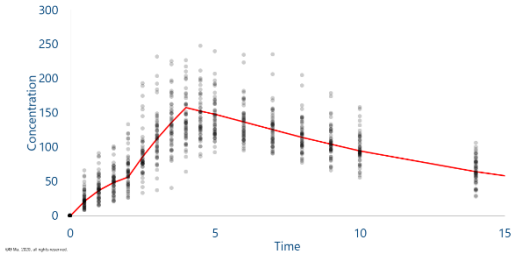
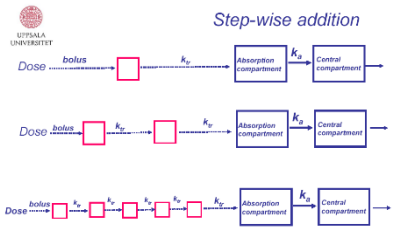
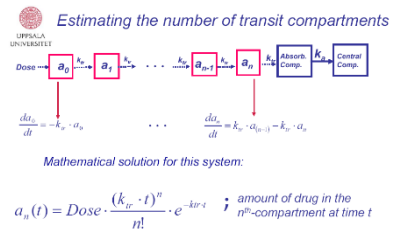
Slide 16	**Oral Absorption**
	• Absorption following an oral dose is dependant upon:
	• Medicine Specific Variables
	  • physicochemical properties of the medicine (pKa, solubility, lipophilicity)
	  • formulation characteristics (particle size, surface area, dosage form)
	  • site of absorption
	• Patient Specific Variables
	  • age, sex, co-morbidities etc.
	  • concomitant food, medications
	16
		The majority of drugs are administered orally, rather than via a parenteral route (eg, intravenous, intramuscular). The rate and extent of oral absorption can be influenced by the physicochemical factors of the medicine, and physiological factors of the patient.
		
		Following oral administration, the drug must disintegrate and dissolve in solution before it can cross the gut membrane, furthermore, in order to cross the membrane, the drug must be soluble in the lipid material of the membrane as well as the aqueous phase. Most medicines will not be absorbed in the stomach and require passage to the small intestine (where there is a large surface area) before diffusion into the circulation.
		
		Stomach emptying time can influence acid degradation and delay absorption. A fatty meal or cold food can slow stomach emptying rate. Concomitant medications can decrease (eg, morphine) or increase (eg, metoclopramide) stomach emptying rate.
		
		Note the difference between rate and extent of absorption. A delay in gastric emptying may mean a decrease in the rate of absorption but the extent of absorption may remain unchanged if the medicine does not degrade in the acidic environment of the stomach.

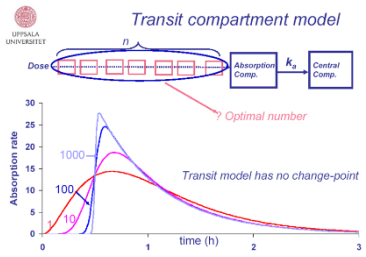
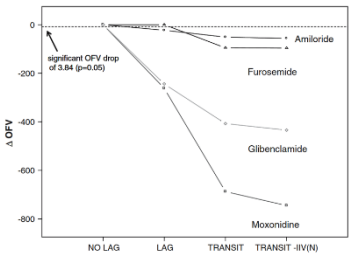
Slide 17	**Lag Time** • Absorption delay describes the phenomena where there a time delay between administration of dose and commencement of absorption. • One approach may be to shift the time at which absorption begins so it appears that the dose was given at a later time. $if\ t < t_{lag},\quad C(t) = 0$ $if\ t \geq t_{lag},\quad C(t) = \frac{Dose \cdot k_a}{V \cdot \left(k_a - \frac{CL}{V}\right)} \cdot \left(e^{-\frac{CL}{V} \cdot (t - t_{lag})} - e^{-k_a \cdot (t - t_{lag})}\right)$ 17	In earlier slides, we have described the time course of concentration with absorption beginning at the time of administration. This assumption requires further refinement. Disintegration and dissolution, transit to absorption site(s) and transfer across the absorption site are all factors that can contribute to absorption delay. A lag time allows quantification of the time delay between administration of dose and commencement of absorption. A simple approach is to shift the curve using a lag time, so absorption begins at after administration. Lag time may then be another parameter that we wish to estimate, thus each individual patient may have a different lag time. At any time prior to t_{lag} concentration in the central compartment is equal to zero. At any time after t_{lag} concentration can be described as a function of time; here a closed form equation is used to describe concentration in a one compartment model with first-order absorption and elimination. Note the shift in time using $t\text{-}t_{lag}$.
Slide 18	**Lag Time**  18	This graph shows simulated concentration time course following the implementation of a lag time, note the shift in the curve such that absorption does not begin immediately following dose administration.

Slide 19	**Two Part Rate Models**
	• We may observe more than one peak following oral administration.
	• This may be due to :
	  • Different sites of absorption
	  • Variable gastric emptying rate
	  • Formulation
		Using a compartment model, a variety of absorption processes may be described. Previously we have described a single zero order, or first order absorption process. Sometimes we may observe more than a single peak after drug administration, thus our model may have sequential or simultaneous absorption from one or more sites.

Slide 20	**Two Part Rate Models**
	• Mixed (first-order and zero-order) absorption model
	  • Combination of first-order and zero-order processes
	• Simultaneous absorption model
	  • Both absorption process starts at the same time
	• Sequential absorption model
	  • One absorption process beings before another
	 
	20
		Rather than describing input rate using a single process, two processes may be used. The two processes may use a mix of absorption rates (eg, first and zero-order) or use the same rate (eg, two first order). We may consider the two processes to be independent of each other or linked.
		
		Parallel (simultaneous) absorption processes can be used if we believe both absorption processes begin at the same time. This is shown in the figure above, one fraction of the dose (F_{K0}) is absorbed by a zero-order process and the remaining fraction ($1-F_{K0}$) absorbed by a first-order process, with both processes beginning at the same time.
		
		We may use a sequential absorption process if we believe one process starts before another. For example, a sequential linked zero-order then first-order model can be interpreted in a mechanistic way if the concentration in the gut is initially at the solubility limit for the drug. As drug is absorbed and the concentration falls below the solubility limit then the process converts from a zero-order input to a first-order input.
		
		See Holford NHG, Ambros R, Stoeckel K. Models for describing absorption rate and estimating extent of bioavailability: Application to cefetemet pivoxil. J Pharmacokin Biopharm. 1992;20:421-42.

Slide 21	Two Part Rate Models **Sequential First Order Input**  21	This plot is generated using sequential first order input (into a one compartment model with first order elimination). Note the first absorption process does not have a lag time, while the second process contains a lag time.

Slide 22	Two Part Rate Models **Sequential First-Order Zero-Order Input**  22	This plot is generated using sequential first order, then zero order input (into a one compartment model with first order elimination).
Slide 23	**Transit Compartment Models**  23	Absorption delay is influenced by many factors. A lag time is a very empirical approach to the delay between administration and measurable concentration. Instead of using a fixed time as the lag time, a more mechanistic description of the physiology that contributes to the delay is to describe absorption as a multi-step process. This model describes absorption delay as the passage of drug through a chain of transit compartments. Note that each compartment here is hypothetical and does not have a physical meaning. A single transfer rate constant (k_{tr}) is used regardless of the number of transit compartments. The final compartment of the transit chain is linked to the central compartment by a first-order absorption process (k_a). The transfer rate constant is related to the mean transit time (MTT; average time spent by drug molecules traveling from the first transit compartment to the absorption compartment); $k_{tr} = (n+1)/MTT$. The use of transit compartment models to describe delays in onset of absorption was developed by Radojka Savic at Uppsala. The following set of slides is taken from her work. See also Savic et al. J Pharmacokinet Pharmacodyn . 2007 Oct;34(5):711-26 and https://www.page-meeting.org/page/page2004/Savic.pdf
Slide 24	**Transit Compartment Models**  24	A mathematical solution can be used to estimate the optimal number of transit compartments

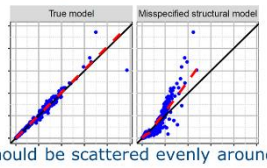
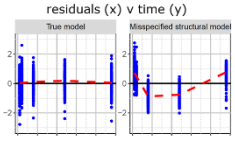
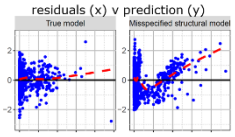
Slide 25	**Transit Compartment Models**  25	The absorption rate will thus look different depending upon the number of compartments. In contrast to a lag time model with is discontinuous about t=t_{lag}, this is not the case in a transit compartment model. Therefore the transit model will have a gradual (rather than abrupt) change in the absorption rate.
Slide 26	**Transit Compartment Models**  Savic et al. J Pharmacokinet Pharmacodyn. 2007 Oct;34(5):711-26.	We can compare the improvement in fit of (nested) models by comparing the change in objective function value (ΔOFV). As described in a later slide, the OFV is a measure of how well a particular model fits the data. When models are built in a stepwise fashion, and if there is one parameter difference between a full and reduced model, then a reduction in the OFV by at least 3.84 indicates that the addition of the parameter improves the fit of the model. In this plot we are comparing models for four different drugs (amiloride, furosemide, glibenclamide and moxonidine). The model without lag time is set as our baseline. Fitting a model with lag time results in a significant reduction in the OFV for all except furosemide. Fitting a model with a transit compartment results in a significant reduction in the OFV for all four drugs.

Slide 27	**Hands On**
	• Simulation
	  • Berkeley Madonna will be used to simulate closed form and differential equation for the ka1 absorption model
	  • Excel will be used to simulate three datasets which will be used for estimation.
	• Estimation
	  • Monolix will be used to fit models to the three simulated datasets.
	27	

Slide 28	**Assignment** • Discuss methods of comparing models for goodness of fit. • Find out what the log-likelihood, AIC and BIC are (displayed in pop_parameters.txt in the results folder for each Monolix model). • Write up the results of parameter estimation using Monolix. • Compare the results of fitting the 3 sets of data (ka1, ka1L, k01L) using each of the 3 models. 28	

Slide 29	**Model Evaluation**
	• In model building we fit a models to a dataset.
	• In model evaluation we examine:
	  • Goodness-of-fit between the model and dataset
	  • The appropriateness of the underlying model assumptions
	• Numerical Diagnostics
	  • Fit statistics
	  • Parameter estimates & Imprecision estimates
	• Graphical Diagnostics
	  • Prediction based (pred v obs)
	  • Residual based
	  • Simulation based (visual predictive checks)
	29
		Once a model is built we want to assess how good the model is, or compare one model to another.
		
		Approaches to model diagnostics can be classed as numerical or graphical.

Slide 30	**Fit Statistics**
	• Objective Function Value
	  • When fitting the model to the data, many software packages minimise the -2 log likelihood (-2LL). This is called the objective function value in NONMEM.
	  • The likelihood describes the likelihood of the observations being observed given the current parameters and model.
	$L = \prod_{i=1}^{n} \frac{1}{\sqrt{2\pi\sigma_i^2}} e^{\frac{-(Y_i-\hat{Y}_i)^2}{2\sigma_i^2}}$
	  • The OFV (-2LL) provides an overall summary of how a model with a given set of parameter values fit the data.
	  • The model with the lowest OFV is of best fit.
	• Information Criteria (AIC & BIC)
	30
		Objective functions are statistical criterions applied to nonlinear regression models as an objective measure of the differences between the observed and predicted values of parameters and the dependent variable. The objective function minimized in NONMEM is the -2 log likelihood.
		
		The likelihood (L) describes the likelihood of all the observations under the current model, structural and variance parameters. There are two parts to this equation. First is the likelihood of an observation, here we describe this as the i^{th} observation; this is related to the observed value (Y_i), the model predicted value ($\hat{Y}_i$) and the variance of the model (σ_i). Second, the likelihood n observations is the product of the individual observations, thus we multiply the probability of the first (i=1) to the n^{th} (last) observation.
		
		Rather than use the likelihood, which requires multiplication of n probabilities, we may take the log of both sides of the equation, as well as multiply this by -2. This results in the -2 log likelihood. When fitting the model to the data, we wish to find the structural model, and parameter values which minimise the -2LL, thus maximises the likelihood.
		
		Note that OFV is dependent on the method of parameter estimation and the data set, thus should not be used for comparison across data sets.
		
		Increasing the number of parameters in a model increases the degrees of freedom and can artificially inflate goodness of fit. The Akaike information criterion (AIC) and Bayesian information criterion (BIC) can be used to rank the goodness of fit of models taking into account improved model fit due to increased model complexity.
		
		See Mould & Upton. CPT Pharmacometrics Syst Pharmacol. 2013 Apr; 2(4): e38.

Slide 31	**Prediction Based Diagnostics** • The plot shows observations (y) v individual predictions (y) for a correct and misspecified model.  • Data points should be scattered evenly around the identity line. • Trends suggest possible misspecification in the underlying model 31	CPT Pharmacometrics Syst Pharmacol. 2017 Feb; 6(2): 87–109.
Slide 32	**Residual Based Diagnostics** • Residuals are the difference between the observations and the model predictions. residuals (x) v time (y)  residuals (x) v prediction (y)  • Data points should be scattered evenly around the identity line. • Trends suggest possible misspecification in the underlying model 32	CPT Pharmacometrics Syst Pharmacol. 2017 Feb; 6(2): 87–109.