PharmacoLearn

MPH203T Computer Aided Drug Delivery System, M.Pharm Semester 2

Unit 2: Computational Modeling of Drug Disposition

Free notes at pharmacolearn.fyi

2.1 Introduction: why disposition is modeled

Disposition is what happens to a drug after it reaches the body: absorption into the circulation, distribution to the tissues, and excretion or metabolism out of them (the ADME sequence, with metabolism usually counted alongside). Every step can lose the drug, delay it or concentrate it in the wrong place, and historically each was discovered experimentally, late and expensively, in animal studies or in failed clinical trials. Computational modeling of drug disposition exists to move that discovery earlier and cheaper: to predict, from chemical structure and a modest set of laboratory measurements, how a molecule will be absorbed, where it will go, how long it will stay and how it will leave, before large studies begin. The predictions prioritise which molecules deserve synthesis and testing, design the experiments that follow (doses, sampling times, species), and flag the liabilities, poor solubility, efflux by transporters, rapid clearance, that formulation scientists (MPH201T, MPH202T) will have to engineer around. The methods range from structure based statistical predictions that need nothing but the molecule's drawing, to full physiological simulations (Unit 4) that need measured data. This unit takes the modeling techniques step by step along the disposition pathway, and ends with the active transporters, the membrane proteins that the syllabus names individually because they defeat simple predictions and must be modeled explicitly.

2.2 Modeling techniques: the levels of modeling

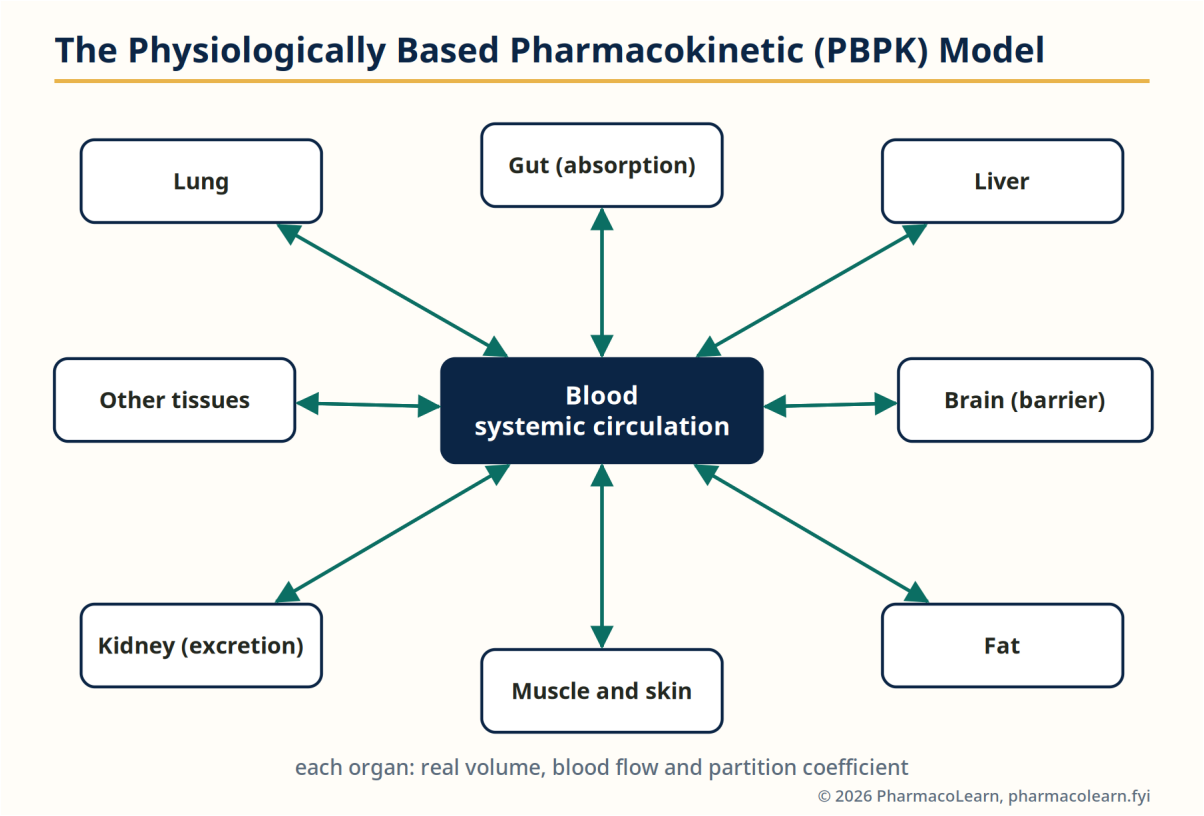

Figure: The physiologically based pharmacokinetic model. Organs are real compartments with volumes and blood flows, joined by the circulation; the drug's physicochemical and in vitro properties decide how it partitions into each.

Three families of technique cover the field. **Structure based (in silico) prediction** computes or correlates properties from the molecular structure itself: calculated descriptors such as molecular weight, partition coefficient (log P), polar surface area, hydrogen bond donors and acceptors, and rotatable bonds feed statistical (QSAR type) models trained on measured data for solubility, permeability and activity. Simple rule sets, of which the Lipinski criteria (molecular weight not above 500, log P not above 5, limited hydrogen bonding) are the famous example, act as early filters for oral drug likeness. **Compartmental modeling** treats the body as a small number of well mixed pools connected by first order transfers (MPH202T, Unit 3): empirical, data driven, excellent for describing and interpolating measured concentration profiles, weaker for predicting a new molecule. **Physiologically based pharmacokinetic (PBPK) modeling** builds the body from organs and tissues with real volumes and blood flows, and the drug's movement from its physicochemical and in vitro properties: mechanistic (section 1.3), more demanding, but able to predict a profile before any human data exist and to extrapolate across doses, populations and formulations. Modern disposition modeling chains the three: structure based predictions feed the PBPK model, the PBPK model predicts the profile, and compartmental or population analysis (section 1.9) refines parameters once data arrive.

2.3 Modeling drug absorption

Absorption modeling predicts the rate and extent to which an oral dose reaches the portal blood. A complete absorption model multiplies two chances: the drug must dissolve in the gut fluids, and the dissolved drug must cross the intestinal wall, while both processes race against transit out of the absorbing region. Inputs are the drug's solubility (section 2.4), its permeability (section 2.5), dose and particle or formulation properties, and gut physiology: regional pH, fluid volumes, transit times and surface areas. Models range from simple classifications, the biopharmaceutics classification system (BCS) sorting drugs by solubility and permeability into four classes that predict whether dissolution or permeation limits absorption, to the full gastrointestinal simulation of Unit 4, which follows the dose compartment by compartment. Outputs are the fraction absorbed, and with distribution and clearance added, the predicted plasma profile including Cmax and Tmax. The formulator uses the same model in reverse: if dissolution limits absorption, particle size reduction or a solubility enhancing formulation is the fix; if permeation limits it, no amount of dissolution improvement will help, which is precisely the kind of decision the modeling exists to support.

2.4 Modeling solubility

Solubility decides how much drug can be in solution at once, and so caps the absorption rate. Computational work addresses two quantities. **Intrinsic solubility** is the solubility of the unionised molecule, predictable in silico from structure by models trained on measured values, using descriptors that capture crystal packing (melting point is a practical surrogate: a high melting, strongly crystalline solid is usually a poorly soluble one) and solvation. **pH dependent solubility** follows from the intrinsic value and the pKa by the Henderson-Hasselbalch relations worked in MPH202T: solubility rises as ionisation rises, steeply for strong acids and bases, so a weak base may be freely soluble in the stomach and nearly insoluble in the intestine, with the risk of precipitation on transit, a phenomenon the Unit 4 simulation tracks explicitly. Measured solubility in biorelevant media (simulated gastric and intestinal fluids, including bile salt media for the fed state) anchors the models, and the modelling of solubility is also where salt selection, polymorph screening and amorphous strategies are compared on paper before they are compared in the laboratory. The honest limit is accuracy: in silico solubility predictions are commonly within about half to one log unit of measurement, good enough to rank compounds, not good enough to replace measuring the candidates that matter.

2.5 Modeling intestinal permeation

Permeation is the crossing of the intestinal wall by dissolved drug. Experimentally it is measured in cell monolayers, the Caco-2 human intestinal cell line above all, and in artificial membrane systems (PAMPA) that isolate passive diffusion, and the modeling task is to predict the human effective permeability from such data or from structure. In silico models use the same descriptor family as solubility models: lipophilicity raises passive permeation, while size, charge and hydrogen bonding capacity lower it, so permeation and solubility pull in opposite directions on lipophilicity, which is why drug design is a compromise. Permeation models must also decide whether the molecule merely diffuses or is carried: uptake and efflux transporters (sections 2.8 to 2.13) make measured permeability direction dependent, with an efflux ratio between the two directions across a cell layer as the standard experimental signal that a transporter is involved. A modeled permeability then enters the absorption model of section 2.3 and the gastrointestinal simulation of Unit 4, where it competes with dissolution and transit to set the fraction absorbed.

2.6 Modeling drug distribution

Distribution modeling predicts where the drug goes after absorption: the volume of distribution at its simplest, and in PBPK work a concentration in each tissue. The governing idea is partitioning: drug moves between blood and tissue until the unbound concentrations equalise, so tissue levels are set by tissue composition (water, lipid, protein) and the drug's binding and lipophilicity. PBPK models compute tissue to plasma partition coefficients from composition based equations using the drug's log P, pKa, fraction unbound in plasma and blood to plasma ratio, all measurable or predictable in vitro. Plasma protein binding is itself modeled and measured, because only unbound drug distributes, acts and is cleared, and binding displacement is a classic interaction mechanism (MPH202T, Unit 3). Distribution modeling also handles the barriers: the blood brain barrier as a distribution problem with tight junctions and efflux transporters (section 2.13), the placenta, and sanctuaries such as the eye.

2.7 Modeling drug excretion

Excretion removes drug, unchanged or as metabolites, through the kidney and the bile. Renal excretion modeling starts from the three kidney processes: glomerular filtration, which passes unbound drug and is predicted well from the fraction unbound and the glomerular filtration rate; active tubular secretion, carried by transporters (section 2.12) and much harder to predict; and tubular reabsorption, which returns lipophilic unionised drug to the blood and is therefore pH and urine flow dependent, the basis of urine alkalinisation in salicylate poisoning. Biliary excretion moves drug from hepatocytes into bile through canalicular efflux transporters, favoured by larger, amphiphilic molecules, and connects to the enterohepatic recycling of section 2.11 when the excreted drug or its conjugate is reabsorbed from the gut. In PBPK practice, total clearance is assembled from such organ clearances plus metabolism, and excretion modeling is what allows predictions for patients with renal impairment, a population in which doses must fall with filtration, and for transporter mediated interactions at the kidney and liver.

2.8 Active transport: the transporters as gatekeepers

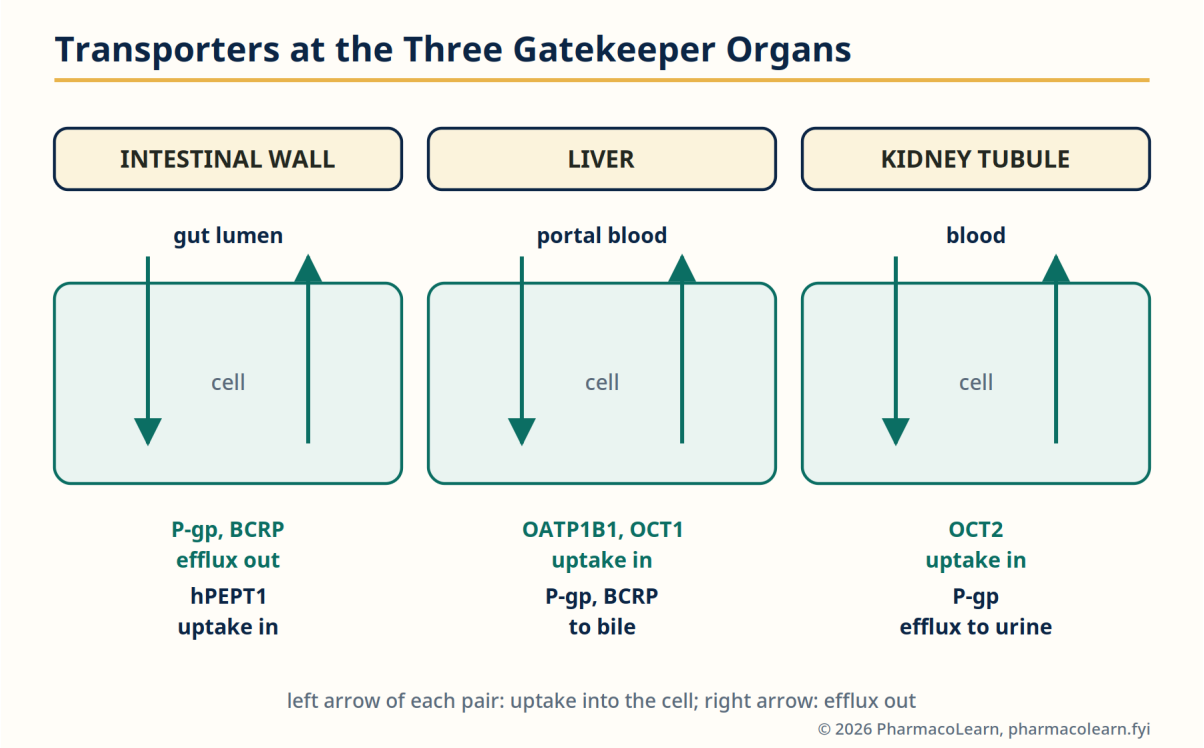

Figure: Uptake and efflux transporters at the three gatekeeper organs. Disposition at each barrier is the balance of the two directions, which is why transporters are modeled explicitly.

Passive diffusion is only half the membrane story. Membrane transporter proteins move specific substrates across cell membranes, uphill if necessary, and organs place them exactly where disposition is decided: the intestinal wall, the liver, the kidney tubule and the blood brain barrier. Transporters divide by direction of effect. **Efflux transporters** of the ATP binding cassette (ABC) family, powered by ATP, pump substrates out of cells: into the gut lumen, into bile, into urine, or back into blood at the brain. **Uptake transporters** of the solute carrier (SLC) family carry substrates into cells: from gut lumen into enterocyte, from blood into hepatocyte, from filtrate back into blood. A drug that is a substrate of an efflux transporter may be poorly absorbed and excluded from the brain however good its passive permeability; a drug needing an uptake transporter to enter the liver may fail to be cleared, or to act, when that transporter is inhibited or genetically deficient. Modeling disposition therefore includes a transporter layer: which transporters accept the drug, where they sit, how strongly they act, and what happens when another drug inhibits them, the machinery behind a large share of modern drug drug interaction prediction. The syllabus names the principal players; the next sections take them in turn.

Transporter	Family and direction	Main sites	Representative substrates or roles
P-gp (ABCB1)	ABC efflux	Gut wall, liver canaliculi, kidney, blood brain barrier	Digoxin, many anticancer drugs, ciclosporin
BCRP (ABCG2)	ABC efflux	Gut wall, liver, blood brain barrier, placenta	Rosuvastatin, sulfasalazine, topotecan
hPEPT1 (SLC15A1)	SLC uptake	Intestinal wall (apical)	Beta-lactam antibiotics, valaciclovir
Nucleoside transporters (CNT, ENT)	SLC uptake and equilibrative	Gut, liver, kidney, most tissues	Nucleoside analogue drugs: gemcitabine, zidovudine
ASBT (SLC10A2)	SLC uptake	Terminal ileum (apical)	Bile acids, enterohepatic recycling
OCT (SLC22A)	SLC uptake	Liver (OCT1), kidney (OCT2)	Metformin, cimetidine

Transporter	Family and direction	Main sites	Representative substrates or roles
OATP (SLCO)	SLC uptake	Liver (OATP1B1, OATP1B3), blood brain barrier	Statins, methotrexate, bilirubin
BBB choline transporter	SLC uptake	Blood brain barrier	Choline, for acetylcholine synthesis in brain

2.9 P-glycoprotein and BCRP: the efflux pumps

P-glycoprotein (P-gp, gene ABCB1) is the best studied efflux transporter: a broad specificity pump in the apical membrane of enterocytes that ejects absorbed drug back into the gut lumen, in the canalicular membrane of hepatocytes ejecting drug into bile, in kidney tubule cells into urine, and in the endothelial cells of the blood brain barrier ejecting drug back into blood. Its modelling significance is threefold. In absorption, P-gp works with the enzyme CYP3A4 in the gut wall as a combined barrier, the pump repeatedly presenting the drug to the enzyme. In distribution, P-gp at the blood brain barrier is the reason many peripherally intended drugs spare the brain, and why the classic substrate digoxin, normally excluded, becomes neurotoxic when P-gp is inhibited. In interactions, P-gp inhibitors raise, and inducers lower, the plasma levels of substrate drugs, an effect PBPK models now predict quantitatively. Breast cancer resistance protein (BCRP, gene ABCG2), named from its discovery in resistant tumour cells, is the second great efflux pump, sharing many sites with P-gp and adding the placenta and the lactating mammary gland; its standard probe substrate is the statin rosuvastatin, whose exposure rises markedly when BCRP is inhibited or genetically reduced.

2.10 hPEPT1 and the nucleoside transporters: uptake into the body

The intestinal peptide transporter hPEPT1 (gene SLC15A1) moves dipeptides and tripeptides from the diet across the apical membrane of the enterocyte, and its broad specificity is a gift to drug design: molecules built to look like peptides are carried with it. Beta-lactam antibiotics such as cephalexin are substrates, and the prodrug strategy that defines this transporter is valaciclovir, the valine ester of aciclovir, which hPEPT1 carries so efficiently that the oral bioavailability of aciclovir rises several fold. Absorption models for such drugs must include the carrier: uptake is saturable, so fraction absorbed can fall as dose rises, and subject to competition between substrates. The **nucleoside transporters** handle the building blocks of DNA and RNA and, unavoidably, nucleoside analogue drugs. The concentrative nucleoside transporters (CNT family) use the sodium gradient to move nucleosides uphill into cells; the equilibrative transporters (ENT family) let them move down their gradient in either direction. Antiviral and anticancer nucleoside analogues, zidovudine and gemcitabine among them, depend on these carriers for cell entry, gemcitabine uptake through hENT1 being a studied determinant of its activity, and transporter expression in a tissue can decide whether the analogue reaches its intracellular target at all.

2.11 ASBT and enterohepatic recycling

The apical sodium dependent bile acid transporter (ASBT, gene SLC10A2) sits in the terminal ileum and reclaims bile acids from the gut lumen into the enterocyte, from where they return through the portal blood to the liver, the enterohepatic circulation that recycles the bile acid pool many times a day. Its place in disposition modeling is that anything riding this circuit, bile acids themselves, drugs excreted into bile and their conjugates hydrolysed by gut bacteria, can be reabsorbed rather than lost, producing long apparent half lives and sometimes secondary peaks in the plasma profile. A model that ignores recycling will underpredict exposure and misread the profile shape. ASBT is also a drug target in its own right, inhibitors interrupting the circuit to lower cholesterol or treat bile acid diarrhoea, and a potential delivery route for bile

acid conjugated drugs aimed at the liver.

2.12 OCT and OATP: transporters of liver and kidney

The organic cation transporters (OCTs, gene family SLC22A) move small positively charged molecules into cells. OCT1 in the liver takes up cationic drugs from portal blood, and OCT2 in the kidney takes them up from blood into tubule cells for secretion into urine. Their textbook substrate is metformin: hepatic OCT1 governs its delivery to its site of action, renal OCT2 begins its dominant elimination route, and inhibitors such as cimetidine, itself an OCT2 substrate, raise metformin levels by blocking the renal step, a transporter interaction with no enzyme involved. The organic anion transporting polypeptides (OATPs, gene family SLCO) are uptake transporters of the liver above all: OATP1B1 and OATP1B3 sit on the blood facing membrane of hepatocytes and pull a wide range of anionic and neutral drugs, the statins prominently, out of blood into the liver for metabolism and biliary excretion. When OATP1B1 is inhibited, for example by ciclosporin, statin plasma levels climb and muscle toxicity risk follows; when its gene carries the reduced function variant common in the population, simvastatin exposure rises in carriers, one of the clearest pharmacogenetic findings in practice. PBPK models therefore carry OATP mediated hepatic uptake as an explicit, saturable, inhibitable step rather than burying it in a passive clearance term.

2.13 The BBB choline transporter

The blood brain barrier (BBB) is built to keep things out, tight junctions sealing its endothelium and efflux pumps (section 2.9) ejecting what diffuses in, yet the brain must import nutrients, and each nutrient carrier is a potential door for drugs. The BBB choline transporter carries choline, an essential nutrient, from blood into brain, where it is the precursor for the neurotransmitter acetylcholine and for membrane phospholipids. The transport is saturable and specific for the quaternary ammonium structure of choline, which makes it a studied target for delivering choline like drugs and drug conjugates into the central nervous system, and a factor in the disposition of cationic drugs generally. Its modeling role completes this unit's picture: disposition at a barrier organ is the sum of passive permeation, efflux and carrier mediated uptake, and a prediction that omits any of the three will be wrong for the molecules that use or suffer it. The same three way accounting, applied organ by organ, is what Unit 4's physiological simulations automate.

```
The in silico ADME funnel of Unit 2
Thousands of virtual structures
   |  structure based filters: descriptors, Lipinski type rules
   v
Hundreds of candidates
   |  predicted solubility, permeation, transporter liability
   v
Dozens measured in vitro
   |  Caco-2, PAMPA, binding, transporter assays
   v
PBPK prediction of the human profile
   |  absorption, distribution, excretion assembled
   v
A few compounds taken forward
```

More free M.Pharm notes and unit wise PDFs at pharmacolearn.fyi
Free video lectures on the PharmacoLearn YouTube channel