FINAL PROJECT

You can work alone, or in pairs. If you would like to work in a group of three, then perform the analysis for two drugs (e.g. comparing two drugs for the same disease). If you are not working alone, let me know the name of your partner(s).

Choose a drug to work on (not Artesunate!). The drug must be one that is taken repeatedly (repeated injections or repeated oral doses). A list of drugs employed in last year's projects is attached. Pick a drug for which at least some PK and PD information is available. I attach some papers that describe models of some drugs that you could choose to use, but you are not limited to these and you can base your project on any drug you choose. You will want to read through the rest of this project before you pick the drug. If in doubt, email me about the drug you are choosing.

Step 1 – Build the model – Build a combined PK-PD computational model of the drug. If a model has previously been published for the drug, that's fine, you can base it on that. Note that recreating someone else's model is not necessarily easier than building from scratch! Include in your report (a) a schematic of the model, including compartments and kinetic rates; (b) a table of parameters for the kinetic rates and other parameters (e.g. compartment volumes, molecular density/concentrations), which should include a citation to the source of each parameter. If there are unknown or uncertain parameters, give a reasonable estimate and describe how you arrived at that estimate; (c) the differential equations that govern the model; (d) the code for the model. The model should include a mass/mole balance in order to ensure that the model is working, and should be built in a functionalized form to enable analysis of the model. The PD component (i.e. the drug effect) depends on the specific drug you have chosen, and could mean (as examples): the effect that the drug has in activating or depleting its target; or the effect that the drug has in curbing tumor growth or viral infection; or the effect that the drug has in alleviating a particular symptom.

Step 2 – Analyze the model – Decide what you consider to be the key time-dependent PK and PD variables of the model – e.g. drug concentration in blood and/or target concentration in tissue – and give a list of those outputs and their units. This list does not have to be exhaustive – exercise your judgment to identify the 3 to 5 most important outputs. Run your model for a range of dose levels levels of the drug; plot graphs of how the key outputs change over time following drug delivery. In terms of time, it should cover at least 10 sequential treatments, or however many is necessary to get to a plateau of drug levels in the body.

Identify the key metrics of overall treatment efficacy – e.g. AUC and/or C_{trough} of drug concentration or target concentration. List these metrics and their units. For these metrics, run and graph a sensitivity analysis of the model parameters (including kinetic parameters, concentrations, dose size, volumes etc).

Step 3 – Population variability of response – Of the parameters involved in the PK/PD model, identify two for which there is likely to be variability among the population. Identify and

cite sources for values for these parameters. If they are indirect – e.g. volume of distribution varying with weight – then note how you calculate the distribution. Examples of variability for PD might include molecular expression variability; cell density/tumor burden; disease stage. You could use a distribution or a list of many individual patients if available. If you use a distribution, generate a random set of at least 100 individuals based on the distribution. Take care to note whether there is a difference between the disease population and the broader population. Show how the key metrics (step 5) are predicted to vary across the population. First, run for each of the two population-varying parameters individually; then, run for individuals with both parameters varying.

Step 4 – **Missed dose analysis.** Adherence to a drug regimen is often imperfect – people miss doses. Analyze the impact of a missed/skipped dose; what happens to the trough and peak concentrations and the AUC of the therapy? Is the magnitude of this effect different for different people (i.e. what is the distribution of the effect across the population)? And what is the effect of a 're-taken' dose? Medications will often say not to take two doses at the next timepoint if one forgets a dose. But what about if one remembers at some time in between? What is the impact on peak and trough concentrations of the dose being re-taken in between scheduled doses? Let's say the time between doses is *m* hours. Explore the effect (on peak and trough concentrations) of taking the missed dose at m/10, 2m/10, 3m/10, …, m hours after the scheduled time.

Step 5 – Interactive Visualization. Assignments 4 and 5 will introduce you to interactive visualization. For the final component of this project, develop an interactive visualization of your choice that allows us to explore at least one aspect of the model. The choice of visualization is up to you. There are some basic requirements: (a) you must create a Shiny app that incorporates at least two figure panels and one widget (e.g. slider, checkboxes); (b) at least one panel must use Plotly; (c) the interaction chosen should add value and/or clarity to the displayed data. Exercise creativity, and toy with different ideas as to how best to present the data and how interacting with the data makes it easier to understand, or clearer, or tells a story that static graphs cannot.

Final Report. Your final report will synthesize your work on this project in a coherent report form. The goal is to mimic a paper like those we've seen in class – Title + Authors; Introduction/Background; Methods/Model (including parameter tables); Results; Discussion; Bibliography. All figures should have figure legends that describe their contents. Finally, you should attach relevant codes as separate files. The codes should run! A good rule of thumb is to have one code for each (multi-panel) figure in the report – this makes it easier to understand the code.

Last year's projects. These drugs are fair game to use again; I show them here to indicate how many different drugs and classes it was possible to study.

- **Omeprazole** (Prilosec) (GERD)
- Pioglitazone (Actos) (DM2)
- Insulin detemir (Levemir) (DM2)
- **Atorvastatin** (Lipitor) (high cholesterol)
- **Rosuvastatin** (Crestor) (high cholesterol)
- Enoxaparin (Lovenox, LMW heparin) (anticoagulant)
- Lidocaine (anesthetic, antiarrhythmic)
- Celecoxib (Celebrex) (NSAID)
- Buprenorphine (Suboxone) (opioid)
- Vincristine (Oncovin) (chemotherapy)
- Lomustine (CeeNU) (chemotherapy)
- **Trastuzumab** (Herceptin) (mAb – cancer)
- Sunitinib (Sutent) (TKI – cancer)
- **Levothyroxine** (Synthroid) (TH deficiency)
- **Etanercept** (Enbrel) (autoimmune)
- Nicotine

Bold – top 10 drugs either by $ value or by # of prescriptions

Useful databases to capture the information: (active links on next page)

Table 1 Key knowledge bases and databases

Database or knowledge base	URL
SIDER (computer-readable side effect resource)	**http://sideeffects.embl.de**
DrugBank	**http://www.drugbank.ca**
Chemical Effects in Biological Systems (CEBS)	**http://cebs.niehs.nih.gov/**
NCBI Database of Genotypes and Phenotypes (dbGaP)	**http://www.ncbi.nlm.nih.gov/gap/**
Comparative Toxicogenomics Database	**http://ctd.mdibl.org/**
Genetic Association Database (archive of human genetic association studies of complex diseases and disorders)	**http://geneticassociationdb.nih.gov**
Kyoto Encyclopedia of Genes and Genomes (KEGG) (bioinformatics resource for linking genomics to life)	**http://www.genome.jp/kegg**
The Pharmacogenomics Knowledgebase (PharmGKB) (resource describing how variation in human genetics leads to variation in response to drugs)	**http://www.pharmgkb.org**
Gene Expression Omnibus (GEO) (database repository of high-throughput gene expression data and hybridization arrays, chips, and microarrays)	**http://www.ncbi.nlm.nih.gov/geo**
Connectivity Map (detailed map that links gene patterns associated with disease to corresponding patterns produced by drug candidates and a variety of genetic manipulations)	**http://www.broadinstitute.org/genome_bio/connectivitymap.html**
The Gene Ontology (GO) (standardized representation of gene and gene product attributes across species and databases)	**http://www.geneontology.org**
Tox21 (Computational Toxicology Research program)	**http://epa.gov/ncct/Tox21**
International HapMap Project (database of genes associated with human disease and response to pharmaceuticals)	**http://hapmap.ncbi.nlm.nih.gov**
Human Interactome Database (database of human binary protein-protein interaction networks)	**http://interactome.dfci.harvard.edu/H_sapiens**
European Bioinformatics Institute (EBI) ArrayExpress Archive	**http://www.ebi.ac.uk/microarray-as/ae/**
NCI-60 DTP Human Tumor Cell Line Screen	**http://dtp.nci.nih.gov/branches/btb/ivclsp.html**
Library of Integrated Network-Based Cellular Signatures (LINCS)	**http://commonfund.nih.gov/lincs/**
Reactome	**http://www.reactome.org/ReactomeGWT/entrypoint.html**
Online Mendelian Inheritance in Man®	**http://www.ncbi.nlm.nih.gov/omim**

Annu. Rev. Pharmacol. Toxicol. 2013. 53:451–73

Useful databases - links

SIDER	http://sideeffects.embl.de
DrugBank	http://www.drugbank.ca
Chemical Effects in Biological Systems (CEBS)	http://cebs.niehs.nih.gov/
NCBI Database of Genotypes and Phenotypes (dbGaP)	http://www.ncbi.nlm.nih.gov/gap/
Comparative Toxicogenomics Database	http://ctd.mdibl.org/
Genetic Association Database	http://geneticassociationdb.nih.gov
Kyoto Encyclopedia of Genes and Genomes (KEGG)	http://www.genome.jp/kegg
The Pharmacogenomics Knowledgebase (PharmGKB)	http://www.pharmgkb.org
Gene Expression Omnibus (GEO)	http://www.ncbi.nlm.nih.gov/geo
Connectivity Map	http://www.broadinstitute.org/genome_bio/connectivitymap.html
The Gene Ontology (GO)	http://www.geneontology.org
Tox21 (Computational Toxicology Research program)	http://epa.gov/ncct/Tox21
International HapMap Project	http://hapmap.ncbi.nlm.nih.gov
Human Interactome Database	http://interactome.dfci.harvard.edu/H_sapiens
European Bioinformatics Institute (EBI) ArrayExpress Archive	http://www.ebi.ac.uk/microarray-as/ae/
NCI-60 DTP Human Tumor Cell Line Screen	http://dtp.nci.nih.gov/branches/btb/ivclsp.html
Library of Integrated Network-Based Cellular Signatures (LINCS)	http://commonfund.nih.gov/lincs/
Reactome	http://www.reactome.org/ReactomeGWT/entrypoint.html
Online Mendelian Inheritance in Man	http://www.ncbi.nlm.nih.gov/omim