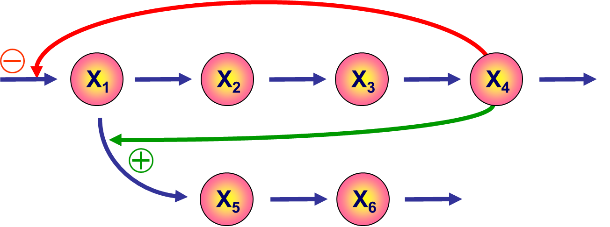
**Projects with PLAS**

**1. Branched Pathway with feedback** (30 mins)

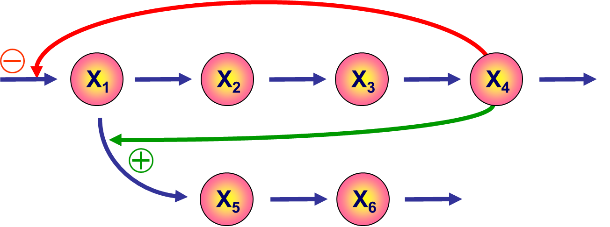
Download from t-square a model for the pathway on p. 33. It was uploaded as PLAS file *Branch\_Pathway.plc*.



* + Check the model structure; identify the components of the PLAS file
  + Start with the given parameter values and solve the system numerically
  + Change initial values and check what happens.
  + Change parameter values, in particular those representing the strengths of activation and/or inhibition, but also change others; check the impact of each change
* Practice model design by adding a variable that receives material from *X*6.

**2. Monte Carlo Simulation**

Reconsider the model from last week, representing the pathway



It was implemented in the PLAS file *Branch\_Pathway.plc*. We saw that different values for parameters representing the strengths of inhibition and activation, *g* and *h*, respectively, led to rather different responses. The question we want to answer now is: Which combination of values for *g* and *h* give us the highest / lowest values of *X*1, *X*5, or *X*6?

To answer the question, download *Branch\_Pathway\_MCS.plc*, which allows you to execute simple Monte Carlo simulations with the system. The way the file is set up, the commands g = -1 and h = 2 are enabled and g = rand[2] - 2 and h = rand[4] are disabled. Run the system and record the final values of *X*1, *X*5, and *X*6. Now interpret the commands g = rand[2] - 2 and h = rand[4]. What do they entail? Enable them and disable the simple settings for *g* and *h*. Run the system several times and look at the responses. To see just the graphs of *X*1, *X*5, and *X*6, disable reporting the values of *g* and *h* by using

!! X1 X5 X6

..!! X1 X5 X6 g h

If necessary, double-click graphical output and disable the legend. To see the graphs as well as the table of results, including *g* and *h*, use

..!! X1 X5 X6

!! X1 X5 X6 g h

Study the results (including *g* and *h*) in the “Message Board.” Close this board after every simulation, unless you want to accumulate results.

Copy the results of one simulation into Excel and custom-sort them by *X*1, *X*5, or *X*6 to see which combinations of *g* and *h* tend to lead to low or high output values.

Adjust the file to study which combinations lead to the highest overshoot in *X*1.

**3. Blue Sky Catastrophe (40 mins)**

Implement the Blue Sky Catastrophe on p. 31

x' = y

y' = x - x^3 - 0.25 y + A \* sin[t]

(note: in PLAS, time needs to be defined explicitly, *e.g.*, as *t*’ = 1, *t* = 0; why?)

Use *A* ≈ .264 as a default. Explore how the trajectories change with (i) small / large changes in *A*; (ii) small / large changes in initial values. Predict what the phase-plane plot will look like. Check in PLAS. Create a pseudo-3-d plot where *t* is the additional variable.

**4. Approximation**

Write a PLAS program that “automatically” computes a power-law approximation (PLA) of the Michaelis-Menten function (MM). Here, “automatic” means that, for given *KM* and *Vmax*, one inputs the operating point and the PLAS code computes MM and PLA as functions of substrate *S*.

**5. Limit Cycle**

Implement in PLAS the system from the first week’s lecture:



Make sure you can recreate the output shown (the slides actually have output prettified in PowerPoint). Fix a1=1 and vary other parameters, such as the exponents or the rates of 1 in order to see whether you can find cases where slight changes lead to qualitatively different behavior (e.g., damped oscillation becomes persistent). In each case, look under the tab and select the values of X1 and X2 as start values for your simulation. For instance, for a1 = 0.9 and h = 0.2 you should see X1 = 0.8256663, X2 = 0.3837274.

**6. Lotka-Volterra Chaos**

Implement the LV model from the book as PLAS file. Explore responses to slight changes in parameter values or initial conditions.

**7. Stability**

Simulate the S-system

4

for different initial values. Compute all steady states. Analyze the stability of its non-trivial steady state in terms of eigenvalues and also with respect to the type of approach of the steady state (as in Book Fig. 4.16).

**8. Approach of Steady State**

Study the approach toward a stable steady state in the system d**x**/dt = **A** **x**, where **A** is a 2 × 2 matrix. Begin with

and superimpose in PLAS several phase-plane plots starting from different initial values. Compute the determinant, trace, and discriminant of the matrix and identify the location of the system in Book Figure 4.16.

Trace:  *tr*(**A**) = *A*11+*A*22

Determinant:  *det*(**A**) = *A*11 *A*22 – *A*12 *A*21

Discriminant:  *d*(**A**) = *tr*(**A**)2 – 4 *det*(**A**)

Change elements in **A** and repeat the analysis. For instance, use

.

**9. Fermentation**

9.1. Consider the following microbial fermentation system, in which the growth of bacteria is driven by the availability of substrate (glucose, G) and inhibition by product (ethanol, E):



Assuming constant glucose, explore the following dynamics for bacteria and end product generation:

*B'* = *max* (*G*/(*K1* + *G*)) \* *K*2 / (*K*2 + *E*) *B* – *a B2* // some bacterial death or loss through outflow

*E'* = *b B* – *c E*  // some evaporation or loss through outflow

The system is implemented in PLAS file “Fermentation System” on t-square. Download the system and get a feel for it by changing initial values, parameter values, etc. Investigate how much you can increase end product by increasing glucose input. Explain the results. Study which parameters are most influential.

9.2. Compute the power-law approximation of the fermentation system at its steady state. Implement this system in the same file as before (Fermentation System), but use different names, such as GG, BB and EE. Compare the responses of the original system with the approximating power-law system. For instance, start at the steady state and add a bolus of glucose.

**10. Linearization**

Linearize a system like Eq. (4.22), where and , and *n* is 1, 2, or 4, and the *ci* are positive parameters. Give a possible interpretation for these equations in terms of a metabolic or cellular system. Compute the functions and their approximations for different sets of parameter values. Consider different operating points.

**11. Simplified MAPK cascade**

11.1. Design a diagram of a simplified MAPK system, in which each level only contains a single phosphorylation step.

11.2. Formulate appropriate equations.

11.3. Select parameters and implement the system in PLAS. Run simulations and refine the parameter values.

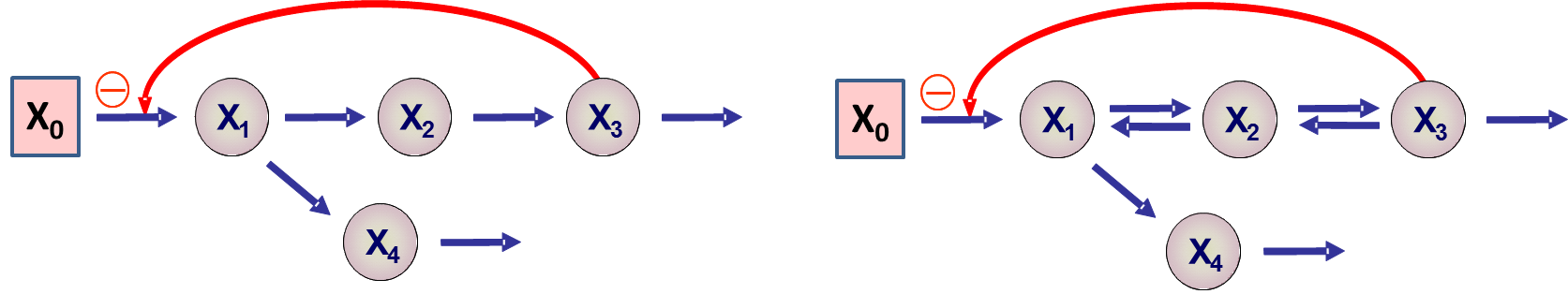
**12. Reversibility**

12.1. Download the power-law (GMA) model for the pathway system (file *Reverse.plc*). Identify parameters that differ for the two variants of the pathway. Also identify parameters that represent the inhibition effect and the degradation of *X*3. Run a few simulations to get a feel for the system.

12.2. For easy comparisons of the two pathways, copy all equations containing X into Word, replace all X with Y, and copy the result back into the PLAS file. Confirm that the differing parameters equal 0 for pathway on the left and are positive for the pathway on the right. Change the strength of inhibition by *X*3. Predict and simulate steady-state and dynamic features and record them. Which features are particularly interesting?

12.3. Increase the parameter values characterizing the reverse reactions and the inhibition effect, one at a time or together, beginning with very low fluxes and weak inhibition. Before executing the simulations, predict in detail what will happen. Increase flux rates, explain what happens, and report your findings.

12.4. Select parameter values from the study in 12.3 that you like and keep them fixed for the following. Change the degradation rate of *X*3. Predict, study, and report the effects.



**13. Mono-stability, bi-stability, hysteresis**

13.1. Consider the equations below, where *S* is an independent variable representing a signal. Sketch an interaction diagram that could be described by these equations.





13.2. Implement the equations in PLAS with initial settings *X* = 15, *Y* = 10, *S* = 5. Determine whether the system is bistable.

13.3. Determine whether the system exhibits hysteresis. If so, create a plot similar to Figure 9.15 of the book.

**14. Exact Michaelis-Menten Mechanism**

Formulate ODEs for the Michaelis-Menten mechanism. Choose parameter values and solve the system in PLAS. Compare the appropriate results with the typically seen Michaelis-Menten rate law. Study different parameter values and assess to what degree the quasi-steady-state assumption is reasonable.

**15. Predator-prey system**

15.1. In a typical formulation of this system, prey grows exponentially, and the only cause of death is predation by the predator. Furthermore, the only source of food for the predator is the particular prey of the system, and death is modeled as an exponential decay function.

Formulate equations and implement them in PLAS such that the number of prey is much higher than that of predators (why?) and the peaks in prey abundance precede those of the predators.

Check simulations (are they realistic?) and eigenvalues (interpret their real and imaginary parts). Display results in the phase plane.

15.2. Explore perturbations like

@ 10 P = 5 or @ 5 N = 2

for different time points and magnitudes. Interpret results.

15.3. Test what happens if the predators have a second, constant food source.

15.4. Without actually doing it, consider what happens if the prey has an additional “natural” cause of death.

15.5. In the logistic growth function, the death term is modeled with an exponent of 2 (why?). Check what happens if you implement this for the predators. Use different rate constants, including very small ones. Interpret results.

15.6. Test the consequences of hunting the prey with a small constant rate.

15.7. Test the consequences of hunting the predator with a small constant rate.

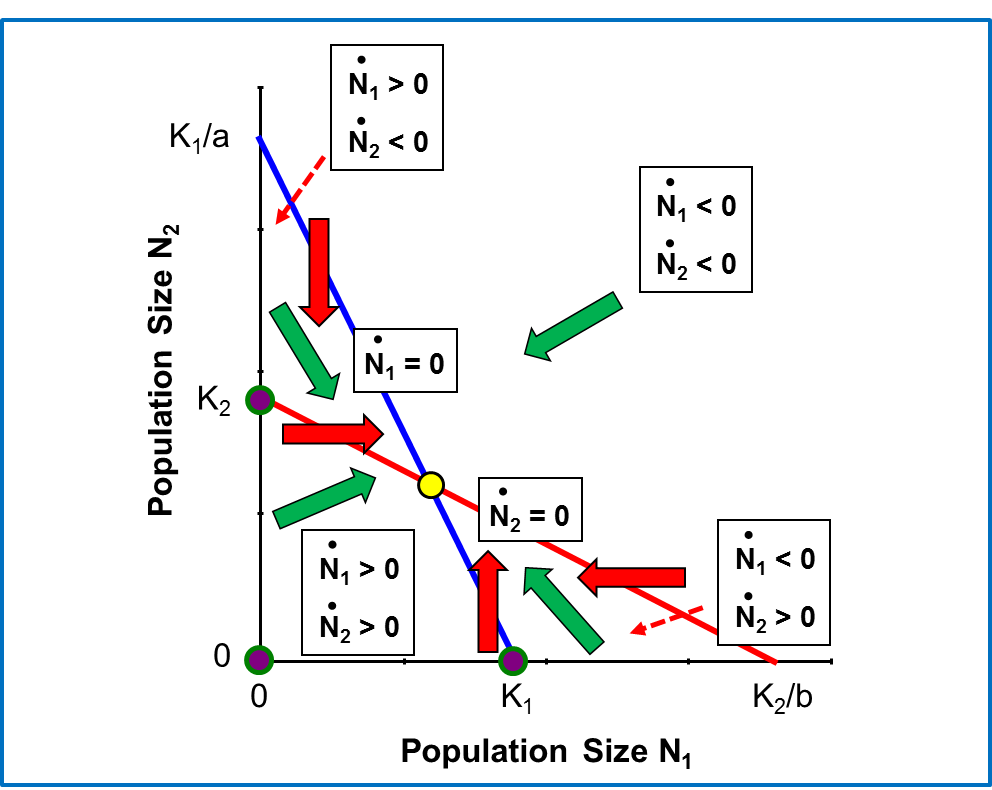
**16. Phase-plane analysis**

Review details of Phase-Plane Analysis









What do the various arrows mean? Where do they come from? How general is this representation? How do the steady states differ?

16.1. Download file *Pop1.plc*. Use the equations above to confirm that the system corresponds to the figure above. Determine all steady states. Start with different initial values and display time course and phase-plane plots. Save each result under a different name with extension *.res*. Open all *.res* files and use the *Merge* option to superimpose them. Compare with figure above.

16.2. Download file *Monte Carlo Pops.plc* and run. Plot as time course and 2-d phase plane.

16.3. Download file *Vectorfield Pops.plc* and run. Use phase-plane representation.

16.4. Change *b* to 0.75. Discuss the consequences. Run simulation and explain.

**17. Personalized Medicine and Drug Development**

17. Consider the simple two-compartment model of Figure 13.17 in the book. The model is implemented as *TwoComp.plc* for a bolus of 10, administered at 8 o’clock for 0.1 time units.

17.1. Download the model and test responses to boluses IN that differ in length and amount.

17.2. Assume that a treatment is required that elevates the concentration of a drug in L persistently to a value between 2 and 4. The concentration should remain within these limits for an extended period of time (several days). Your task is to develop an administration regimen for IN. Keep in mind that patients want to take pills as few times a day as possible (not every two hours, for instance). In addition, assume that you have the power to vary one, several or all rate parameters within a five-fold range (that is, within [0.2, 5] times the original value). Design a treatment that succeeds in terms of the required liver concentration, keeps the blood concentration relatively low most of the time, and requires as few dosing times as possible. Be aware that there may be many different solutions.

**18. Purine Metabolism**

Consider the simplified purine pathway in the diagram. The corresponding equations are:



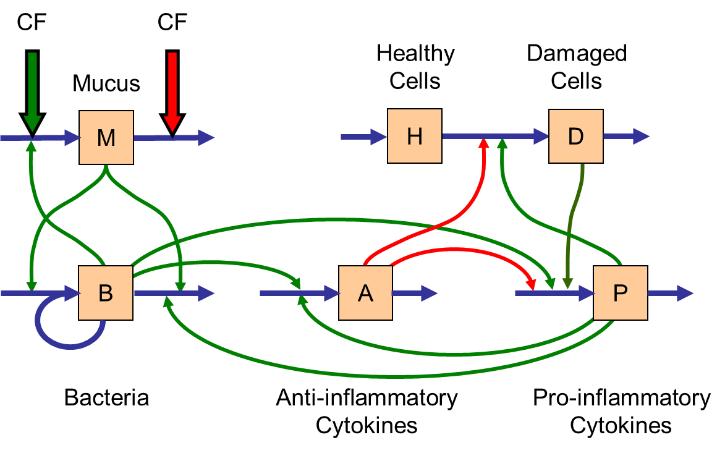
The system is implemented as *Purine\_simple.plc* with initial values (*P*, *I*, *G*, *H*, *X*, *U*) = (5, 100, 400, 10, 5, 100), which more or less correspond to the steady state.

18.1. Download file *Purine\_simple.plc*. Confirm that the system corresponds to the diagram in the figure. Start with the given initial values and with other values and confirm that the system indeed reaches the steady state. Now reduce the enzyme activity of the process (vPHI) by 10%, 20%, 50%, 80%, and 90%. A reduction in activity of this enzyme can lead to the devastating Lesch-Nyhan disease (look it up!). Check the uric acid concentration. Also look at concentrations of other intermediates. Which variables are affected most (in terms of percent changes)? Change other enzyme activities.

18.2. Now we focus on inter-personal variations. Suppose that every rate *k* in the system can vary within the population by up to +20%. The question is how much some of the steady-state values (say, P, I, H, and U) can vary within the population as a consequence of this variability. Set up a Monte-Carlo simulation where each *k* is randomly selected from within +20% around its nominal value. Use the MC simulation of populations (from last week) as an inspiration for setting up the PLAS code. Before you run the simulations, make predictions regarding the expected ranges of P, I, H, and U. Export results to Excel to study the ranges.

**19. Cystic Fibrosis**

The diagram below shows a very simplified model of cystic fibrosis. Study this diagram and interpret its features, arrow by arrow. Download the model *CF model.plc*, run it as it is and try to understand the output by looking at the PLAS code and the diagram. Interpret D, LF, PH, and AB, and explain the strange output trend.



The following options are available for treating CF.

(1) Antibiotics may be given to kill bacteria.

(2) A chest vest can be used to loosen (and remove) mucus.

(3) Anti-inflammatory drugs may be given to reduce pro-inflammatory cytokines.

(4) Of course, (1) – (3) may be combined.

Devise and implement a treatment that counteracts “acute pulmonary exacerbations,” which correspond to the down-steps in the original output.