Compartmental Model Tutorial.

General Overview:

This "tutorial" is divided into 6 sections. Each is arranged with progressive development of ideas and of the technology of the modeling. Each has a focus on a topic area. All of the models here can be downloaded and run on your own computer (Windows, Linux, Apple) under JSim, which can be downloaded and installed in about a minute. The JSim Simulation system is free. The code is human-readable written in standard equation format except that a derivative dx/dt is written x:t. This tutorial provides an introduction to the use of simple equations and how to write them so numerical solutions can be obtained. The computer is used as a "mind expander": making extreme changes in the parameter values can't hurt the computer, and can test for errors in numerical methods.

All models are wrong! Compartmental models = stirred tank approximations = instantaneously mixed chambers with internally uniform concentrations, as if diffusion is infinitely fast. They misrepresent or oversimplify the biology in other ways too. These models should be mathematically correct, have mass balance, and have balanced units in all of the equations. Please report any errors or point of confusion that you encounter. Please send comments to us about inadequacies in the models or the explanations. If you correct our models or write new ones you may wish to have them archived on the Physiome Model website at www.physiome.org; we would be pleased to work with you to accomplish that. If you use the same general format of these models it will be easy for us to work with you to archive your successes on the Physiome site. See www.physiome.org/Models for other models and tutorials.

For this compartmental tutorial:
Start at the top of the list and grind your way through. Each model is on the website www.physiome.org. Download JSim. These models can all be run on the website, but it is useful to download so that you can revise them, add notes or comments. Download model 1 to get going. The goal is to "own" each one of

them.

Make sure you understand the first one: the code, the language, and the physical meaning of the phenomena described. These models, the whole lot, are based on the untenable assumption that each compartment is an instantaneously mixed chamber. Reflect on how good or bad that assumption might be under varied circumstances. If mixing were not complete, instant by instant, what would that do to the responses of the system. How would you observe such inconsistencies with the basic assumption?

Then go to model 2. Figure it out and then go to Model 3. It'll get faster after the first one. When you arrive at an osmotic model you should be able to understand it: the language, the coding, the physical meaning, the limitations imposed by the assumptions and so on.

Each model has also a note section, opened by clicking on Note at the bottom of the control page. Read the Notes page in every model as you go through them. These notes sometimes raise questions, sometimes offer additional tests.

Each model is very simple, step by step. But they are not at all trivial, and real understanding requires a combination of a thoughtful, skeptical approach, and exploration of the model behavior so that the physical or chemical events are understood.

Try to do a model each day. You'll be learning JSim at the same time. Make new versions of models. Duplicate and revise ad lib. And have fun.

Overview of the Six Sections of the Compartmental Tutorial.

(1) Comp1 (single stirred tank) models (7 of them) are all elementary, using ordinary differential equations. They provide an introduction to modeling in general. Simple as they are, there is material to provoke thought. The "Notes" section of each ".proj" explains some things in more detail and raises questions, makes suggestions. Four of these are accompanied by the same model in a different .proj file with "Plus" appended to the name. These versions elaborate on the model and use it to illustrate important general ideas. I recommend going through all of the elementary ones first, and then come back to take a look at the "Plus"

versions.

(2) Comp2 (two tank) models (8 models) take a step toward the real physiology. Each of these includes a membrane, and therefore must consider compartment-to-compartment exchange and the mechanisms for the exchange. (The movement of ionic species across a charged membrane is postponed for a later tutorial.) Passive diffusional flux across the membrane is the simplest. Facilitated saturable transport is considered next, first using the Michaelis-Menten approximation (imitating its use for enzyme kinetics) and demonstrating some of its inconsistencies and internal contradictions, and finally resolving these with models of kinetically self-consistent transporters (the "Transp." models.

(3) The Osm or osmotic models (4 models) are just 2-compartment models with the focus on the interactions between solute fluxes and solvent water fluxes across the membrane. The "OsmUncoupled" models have no solute-water interactions and serve as references for the "OsmCoupled" models. The Pore model illustrates the relationships between solute size and pore size (in this case assuming a theoretical ideal, a spherical molecule passing through a cylindrical pore). The Kedem and Katchalsky equations for the interactions (Coupled) are also idealized, but illustrate the basic phenomenology of the irreversible thermodynamics of coupled water and solute flows. It's irreversible because viscous drag represents dissipation of energy into heat, raising entropy.

(4) Higher Order Models (7 models) illustrate slightly more advanced applications. The CTEX models, composed of N-stirred tanks in series, are an introduction to approximating spatially distributed systems such as a capillary with gradients in concentrations between inflow and outflow. These allow for diminutions in concentrations of substances like oxygen being consumed in the tissue and for increases in concentrations along the capillary as for CO2 being released from the tissue. This is particularly important when both O2 and CO2 compete in binding to hemoglobin. The last of these, CTEX20.5path illustrates a technique for a good approximation of model solutions for

multipath systems with heterogeneous flows in parallel paths, giving great efficiency of computation.

(5) PHARM or pharmaceutical models (9 models) serve as the briefest of introductions to pharmacokinetic/pharmacodynamic modeling (PKPD) and to biochemical modeling. The "ThreeExpDecay" is an often used descriptor to parameterize a washout or decay process, and though it formally represents three independent processes in parallel, it can represent a real multicomponent system. The "Propofol" and "Aspirin" analyze experimental data and introduce some approaches to using automated optimization to find the best fitting set of parameters to fit the data. The succession of "Progress3" models start with uncatalyzed reactions, then use Michaelis-Menten reaction kinetics and finally a full, but still simple, enzymatic catalysis for the reaction A -> B -> C. All of these can be reversible reactions leading to equilibria.

(6) "Tracers.Comp.vs.PDE_Tutorial" is a more advanced treatment on the use of tracer-labeled reactants in studies of capillary-tissue exchange processes, with the take home message that compartmental systems are generally speaking not adequate to unravel the nature of capillary-tissue exchange processes. Even where the compartmental models fit the data they tend to give large errors in estimates of the parameters for exchange.

Section I. One-compartmental Models:

The Comp models are a set of stirred tank or compartmental models. Any material within the compartment is instantaneously uniformly dispersed within it. When the inflow concentration is spread over some time, the material entering into the compartment is mixed instantaneously and completely with any material already present, as if there were a discontinuity at the entrance, like a hose into a bucket. In a flowing compartmental model the concentration at the outflow is identical to the uniform concentration within the tank.

When there is removal of material either by a constant flow or by

a constant rate of reaction, then the process is first order, i.e., the decay in concentration (when there is no further input) is a constant fraction per unit time. This is an exponential decay process. A semilog plot of concentration versus time gives a straight line.

The assumption of instantaneous mixing is not appropriate when diffusion distances are so large that concentration gradients take significant time to dissipate. It is inappropriate for systems of intracellular reactions, unless the volumes are so small and the concentrations of reactants so high that diffusion from one reaction site to the next is infinitely fast. This assumption fails for example when calcium is released inside a cardiomyocyte by an excitatory stimulus: the Ca++ must diffuse from release sites to binding sites within myofilament bundles, and since the diffusion coefficient is very low, gradients exist transiently.

Also, compare a stirred tank to a capillary-tissue exchange unit. With the tank, it is as if the inflowing artery dropped its fluid and solute content into a marvelously rapidly stirred bucket, so that there is a sudden drop in concentration at the point where the artery empties into the capillary. At the venous end, the outflow concentration is identical to the concentration within. The failure of the compartment as a model for circulatory studies is the discontinuity in concentration at the entrance, and the uniformity of concentration within.

The assumption fails also when cellular concentrations for a particular reactant are exceedingly low. One then thinks no longer in terms of concentration, an averaging concept, but thinks in integer terms, how many molecules there are and where are they located relative to the sites where reactions occur. For example the number of copies of a gene regulatory protein is likely very small, less than 10 for example. This is a situation that requiring using stochastic simulation in order to recognize the discrete nature of molecule-to-molecule interactions rather than using continuous system simulation.

In general, the models are solved numerically; in several cases the numerical results are compared with analytic solutions.

One-Compartment models illustrate basic compartmental responses to different inputs and conditions. Start by exploring one of the simple one compartment models, Comp1. Most of the project files, model.proj, provide further detail in the NOTES (button on bottom line when JSim is in Run Time mode). Browse through these for questions, some answers, and additional tests.

1. Comp1Decay: One compartment with decay of substance, a first order process.

A compartment model has a volume and a concentration of a substance. The product of the volume and the concentration is a quantity of material. The change in the quantity is described by mass balance equations. This can be solved analytically as well, so providing a check on the accuracy of the numeric solution. Also see Comp1DecayPlus.

2. Comp1Flow: Flow through a single tank:

As set up, this is a stirred tank with a single inflow, a single outflow and a constant volume. Load parameter set 'ExternCin' which has an input function, Cin(t), set up to use a function generator, fgen_1, accessed by clicking on the circle containing the ~ at the bottom of the list of "Model Inputs".

A single stirred tank operator is also known as a "lag operator", equivalent to a first order lag filter. (An operator deforms or operates on an input to produce a delayed and deformed output.) This can be shown by using a Gaussian probability density function as an input and observing that the output function is know right skewed, as well as being delayed. Also see Comp1FlowPlus.

3. Comp1FlowDecay: Models single compartment with inflowing and outflowing concentration of a single substance which undergoes decay.

A Flow carries an inflow concentration, Cin, into a one compartment model with a given Volume. Cin is constantly and instantaneously well mixed becoming C, the concentration in the compartment. C empties out of the compartment and is designated Cout. G is a clearance rate. For a constant concentration of inflowing material the analytic solution is given. Also see Comp1FlowDecayPhysiologicalVersion for a version with physiological units, and an expanded version in Comp1FlowDecayPlus.

4. Comp1Reaction: Reaction within a stirred tank:

In this model there is no flow, merely a reversible reaction from C to D at rate Gc2d and the reverse at rate Gd2c. (G is used to denote consumption or gulosity, the rationale for choosing the letter G was that C (which might be consumption) is used for Concentration, M for metabolism is used in Molar.)

5. OneEnzReversible: An enzymatically facilitated reaction within a stirred tank.

The critical difference between this and Comp1Reaction is that the substrate binds with the enzyme to form a complex. The forward reaction to form a product frees up the enzyme, making it available to bind another substrate or product molecule. The binding of substrate or product to enzyme lowers the concentration of free sollutes and of free enzyme, and accounts for a part of the total mass of material.

6. Comp1FlowReaction: A single compartment with flow, where substrates C and D convert to each other using an equilibrium constraint.

This one compartment model has one input, two outputs. F is flow, Cin is inflow concentration, Cout and Dout are outflow concentrations, V is volume, kc2d is the rate at which substance C is converted to substance D, and kd2c is the rate at which substance D is converted to substance C. C0 and D0 are the initial concentrations of C and D respectively. The amount of material in the compartment is calculated by multiplying the volume by the sum of the concentrations and also by integrating the flow multiplying the difference of what flows in minus what flows out.

7. Comp1FlowReactions2: Single Compartment with flow and irreversible conversion of C to D and D to E.

This one compartment model is for exploring the effects of reaction on concentrations as conversions occur: F is flow, Cin is inflow concentration, Cout, Dout, and Eout are outflow concentrations, V is volume, Gc2d is the rate at which substance C is converted to substance D, andGd2e is the rate at which substance D is converted to substance E. The reactions are irreversible. C0, D0, and E0 are the initial concentrations of C, D, and E respectively. The irreversibility precludes reaching an

equilibrium; for equilibrating reactions see the "Three State Models" under the section of compartmental models under "Pharmacology"

Section II. Two Compartmental Models:

Models in this section concern transport across a membrane, either between two stirred tanks or between a stirred tank with flow through it and a stirred constant volume non-flowing tank. Having a reaction as well can complicate the situation. Transp2solComp2 is a transporter model for two solutes; it is set up as a PUZZLE since the result (Concentration B higher on the opposite side of the membrane from where it is produced) looks to be thermodynamically impossible, but it isn't! Try to figure it out from the shapes of the curves and the parameters of the model as provided.

1. Comp2Exchange.proj: Models two compartments with a single substance passively exchanging between the two compartments.

2. Comp2ExchangeReact.proj: Two compartment model with two substances, irreversibly converting A to B.

3. Comp2FlowExchange.proj: Two compartments, plasma and interstitial fluid (ISF), with flow and exchange using physiological names and units for parameters and variables. The model is optimized to fit a data set.

4. Comp2FlowExchangeReaction: Model with two species A and B, with flow in a plasma compartment and exchange with an interstitial fluid compartment with A converting to B reversibly.

5. Comp2Flow.MMExchange.proj: Adds a Michaelis-Menten type facilitating transporter to replace the passive transport PS. There is also a reversible reaction (the G) for A <--> B in the extravascular region.

6. Comp2FlowMRIContrast: Model for analysis of NMR contrast agents from MRI signal from an organ region of interest (ROI).

7. CortisolSecrete: A biological 2 compartment model for analysis of cortisol secretion, with feedback control of precursor to cortisol and its adrenal secretion.

8. Transp1solComp2: A two compartment one solute facilitated transporter kinetic model including binding steps and transmembrane flip rates for free and occupied transporter.

9. Transp2sol.Comp2: Facilitating Transporter for 2 competing solutes in two compartments, including binding steps. Shows countertransport facilitation/inhibition with enzymatic conversion in the second compartment.

III. Osmotic Models:

While previous models have exemplified situations where the solute free (unbound) concentrations are the driving forces for transport across a membrane, in this section there is both solute and water movement across the membrane, and the forces involve hydrostatic and osmotic pressures and concentration differences.

1. OsmUncoupled1: Independent pathways for water and for solute across the membrane. There is no carriage of solute by the water transport, as if water went through selective pores driven by the sum of osmotic and hydrostatic pressures while solute traverses the membrane by an independent permeative (diffusional) mechanism driven by the concentration difference. Volume changes cause pressure changes as the chamber walls are considered elastic.

2. OsmUncoupled2 is the same as OsmUncoupled1, except that the chamber wall are considered stiff and a change in volume changes the heights in two fluid columns venting the chambers, so that hydrostatic pressure across the membrane is represented by the difference in column heights.

3. PorousTransp: The model is for the permeation of hard spheres (molecules) through cylindrical water filled pores. The viscous drag effects of water on solute motion, and the viscous drag of the pore walls on the flow of water (filtration) are related to the ratio of molecular radius to pore radius.

4. Osm1solCoupledKK: The kinetics of solute water in an idealized porous membrane are expressed as by Kedem and Katchalsky (1958) characterizing the solute water interactions. The fundamental premise is that water and solute both have to pass through the same uniform sized pores and therefore must interact. The thermodynamic irreversibility is due to the dissipation of energy through viscous (frictional) interactions and energy is

lost to produce heat.

IV. Higher order, Multi-compartment Models:

1. Comp3Flow.proj: Three compartments, a flowing capillary and two stagnant regions orthoganal to the flow, representing interstitial flow and the cells of an organ for example, with passive permeation between the adjacent tanks. Later capillary-tissue exchange models will account for the extended length of capillaries e.g the CTEX20 series that follows. so this is like a 3-region model but with only one segment axially (and stirred instantaneously so that it fails to account for axial gradients in concentration).

2. Comp2x2.Recirc.proj: Two units, each composed of 2 paired tanks as in comp2.Flow.proj, are arranged to recirculate. No consumption. Provides residual quantities in each pair. Extensive "Notes".

3. Comp6Recirc.proj: Three pairs of tanks, the first pair in tandem, the second and third pairs in series. With PS in first pair = 0, this model becomes merely 5 tanks in series and is a 5th order Poisson process.

4. CTEX10: Models a capillary consisting of N compartments flowing in series. Explores sensitivity analysis and optimization.

5. CTEX20: Computes N serial two region capillary-ISF model.

6. CTEX20b: Capillary-tissue unit using serial stirred tanks with passive exchange via both passive linear transport and permeation via a saturable transporter.

7. CTEX20_5path: Multipath Capillary-tissue exchange unit accounting for intra-organ flow heterogeneity. The basis is that for linear exchange processes, the concentration-time curve at a point halfway along the capillary is identical to that emerging from an identical capillary-tissue unit with twice the flow. On that basis the curves of C(t) in a transient at many points along the same capillary can be weighted to account for the transport function across and intact organ with heterogeneous flow.

V. PHARM:

These models are introduced briefly in the General Introduction. Individual models have extensive descriptions and discussions on the Website, in JSim's MML code and in the "Notes" section of the Project files, so they are simply listed and linked here.

OPTIMIZATION of parameters to get the best fitting of model solutions to data is emphasized in the first three pharmacological type models.

1. Three summed exponential decay reactions (fit to data)
2. Six Compartment: Propofol Kinetics (i.v. → tissue)
3. Asprin Clearance (Saturation kinetics of metabolism)
4. Indocyanine Clearance in the Liver
5. Biochemical Reactions
    1. One reversible enzymatic reaction
    2. PG Isomerase
    3. Four sequential enzymatic reactions
6. Three state, two progressive reactions (Reactions in series, no enzyme)
7. Three state, two progressive MM reactions (Michaelis-Menten reactions in series)
8. Three state, two progressive Enzymatic reactions (Enzymatic reaction in series)

VI. Tracers:Comp.vs.PDE_Tutorial and Anderson08.pdf.

In Tracers modeling, the contrast between lumped compartmental modeling and distributive modeling (accounting for spatial variation in concentrations) illustrates that compartmental models fail to represent some of the physiological mechanisms. In some situations, if enough compartments are used one can get good representation of spatially distributed systems. The lesson is that it is usually computationally cheaper to use the better representation as partial differential equations, rather than the compartments. See Anderson08.pdf.

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