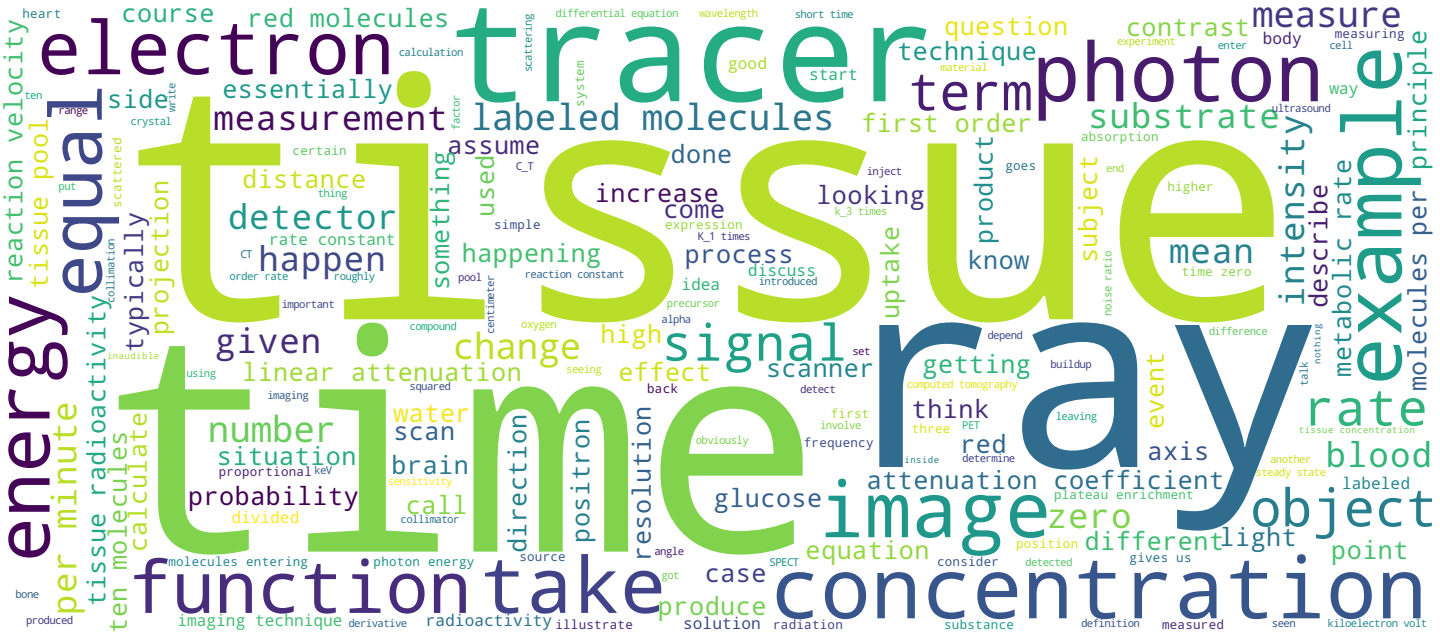
7.2 Tracer kinetics

Fundamentals of Biomedical Imaging

Prof. Rolf Gruetter



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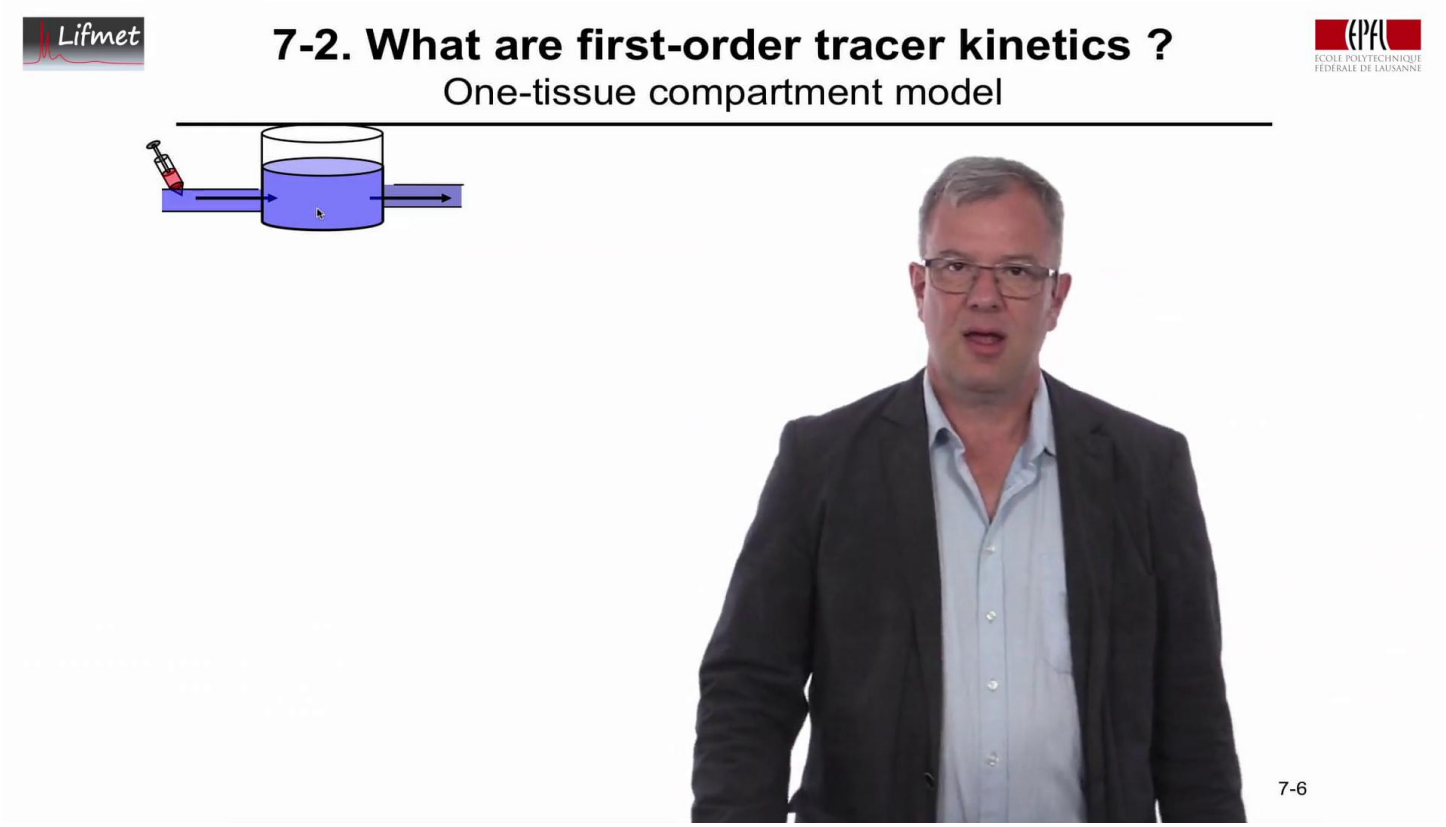
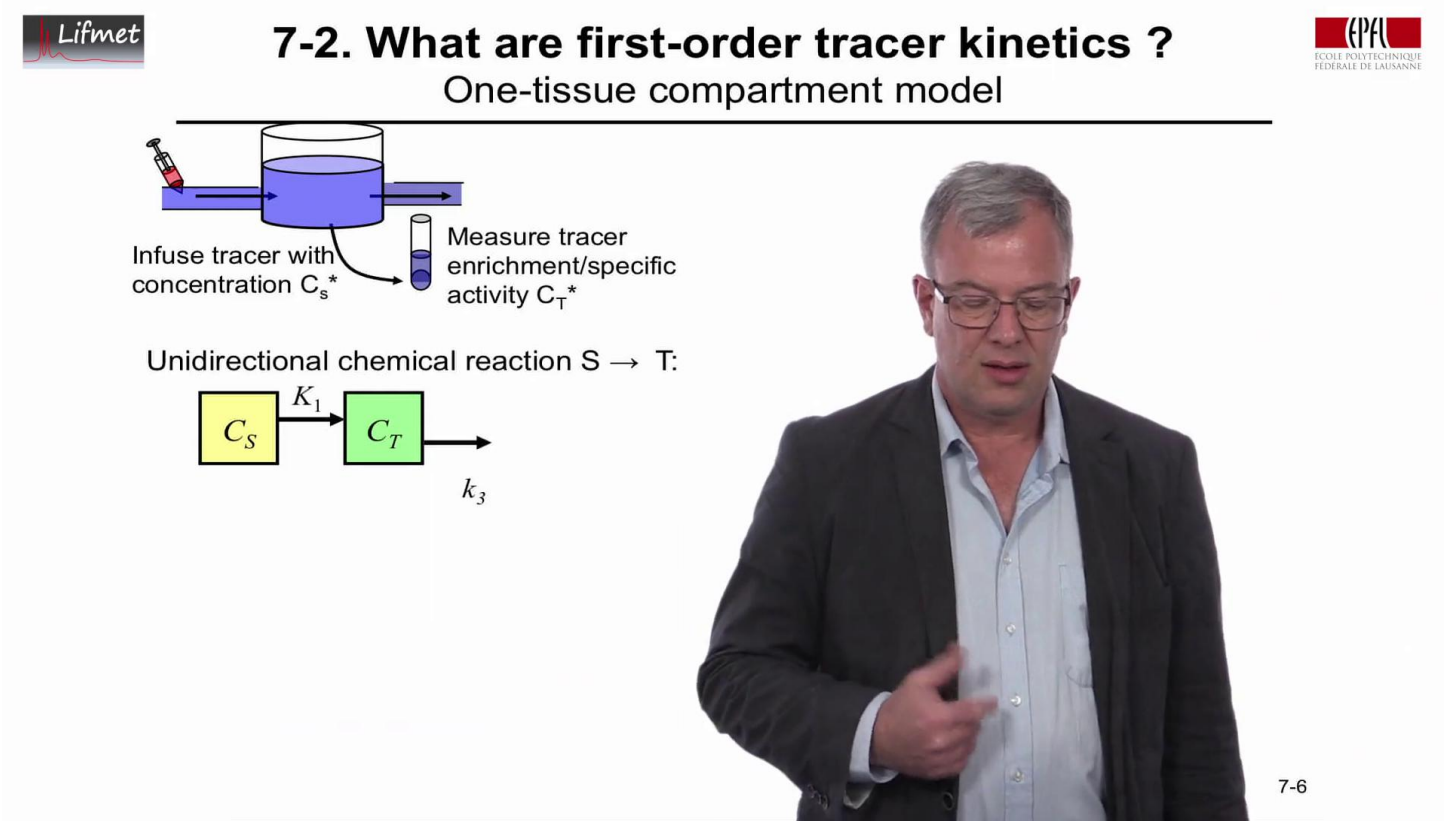


So now, how do we describe these tracer kinetics? That is, we're going to look at, as I've introduced, I've already stated that we can use first-order rate constants; I've introduced the concept of a tracer, and so now we want to see how these first-order tracer kinetics, how they can describe the process. So let's start with a situation here, that's be this our organ, it is mimicked by a beaker, full with a fluid. We have a supply tube. We have an exit tube, that's our blood circulation. There is a certain flow going in, and a certain flow going out. The water paint level here of this beaker does not change. The water content of our tissue doesn't change, or the content of the substance doesn't change. Then we will inject our marked molecules, our tracer. The tracer can be also-- you can think of it as colored molecules. You can think of it as a dye. You can think of this as a little river; this is a little lake; and this is the river, downstream from the lake, and you inject some water dye, and what we're measuring with imaging is what's happening to the color of the lake. And believe it or not, this is what environmental engineers do to understand, for example, lake dynamics, so it's the same principle there.

Notes

Summary

0m 04s

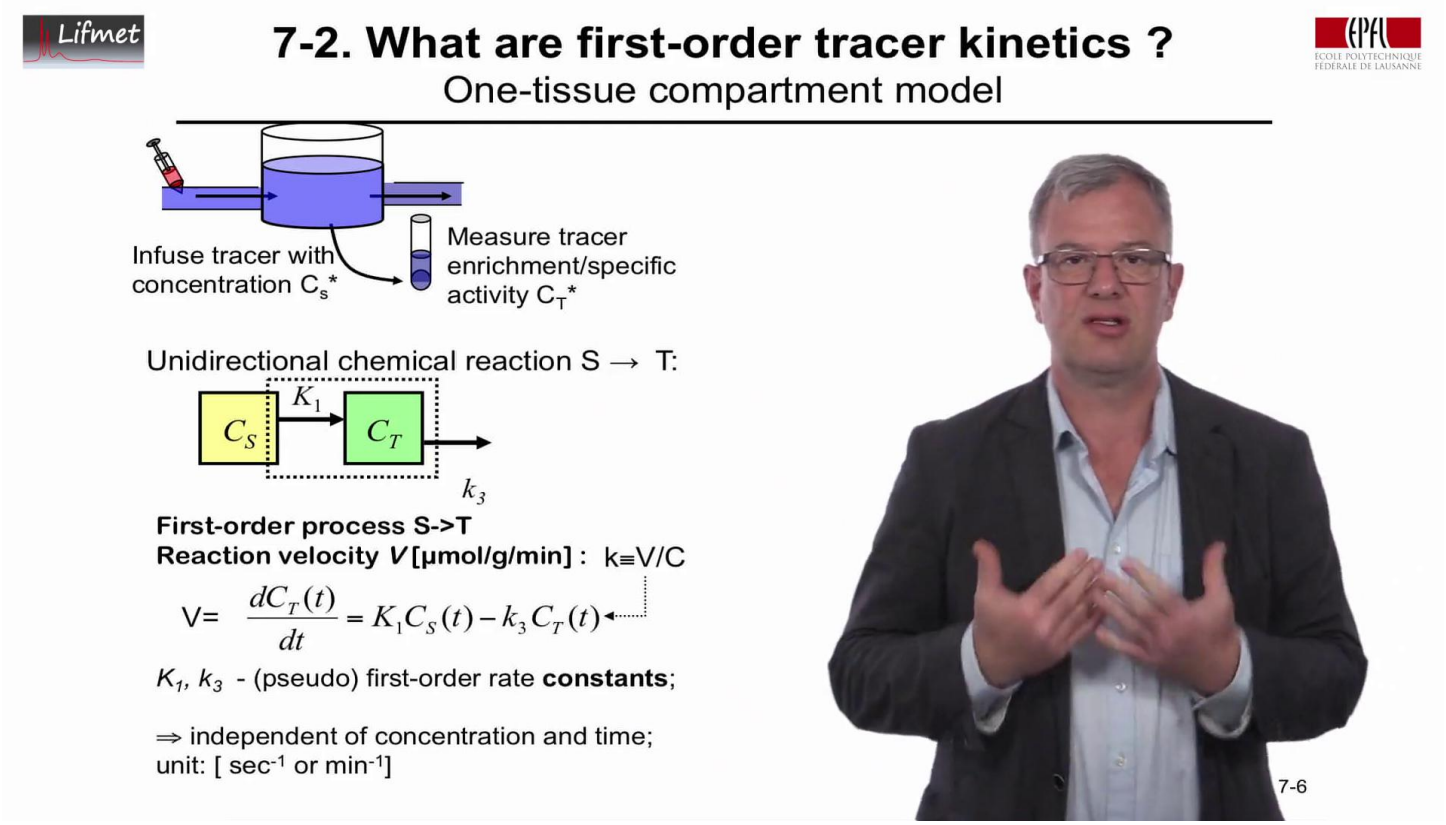


So what we'll do with the experiment is we'll infuse a tracer with concentration, C_s *, "*" means it's radioactive, "C" is the concentration, and "s" here is subscript for "substrate." That's our substrate. We measure from our beaker here, we measure the sample, and there we measure the tracer enrichment, or the specific activity in the tissue. Here "C" is, again, for the concentration, "T" for tissue, and "*" means the radioactivity. In the case of a lake, this means taking samples, doing the measurement there. In the case of our imaging techniques, this means taking an image and measuring the radioactivity spatially, using the imaging techniques that we've discussed the last two weeks. Now, let's look out when we have a unidirectional chemical reaction from substrate to product "T", so we have the concentration of the substrate, we have the concentration of the product, and we have a unidirectional reaction. This means we can only proceed in one direction. And hexokinase is a very good example of such a metabolic system. The product, then, is being metabolized further by another reaction, and we describe it here with a reaction called [Synth] k_3.

Notes

Summary

1m 26s



So what we are measuring is-- this is our compartment here; this is the measurement, the tissue reactivity; and now we'll look at a first-order process that converts S into T, and we'll look at the reaction velocity here. Now, reaction velocity is concentrations per mass per time, so it's micromoles per gram per minute. And now the reaction velocity is equal to the rate of change in concentration of the molecule in the tissue, C_T, and this is now given by, with first-order kinetics, is given by K_1 times the concentration of the substrate, minus k_3 times the concentration of the product. Here we have used the expression that the rate constant equals to the reaction velocity divided by the concentration, so if we put that back in here, then we can see this term is equal to V in, the velocity in, and this is equal to the velocity out, reaction velocity V out. So K_1 and k_3, in this context, they are the first-order rate constants. They are not true constants because they mimic the situation of the system in a particular state, they're not really true reaction constants. That's why one also often refers to them as pseudo first-order rate constants.

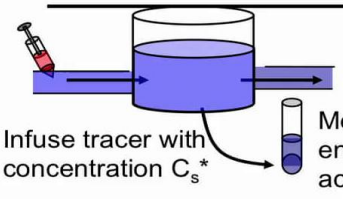
Notes

Summary

2m 44s

7-2. What are first-order tracer kinetics ?

One-tissue compartment model

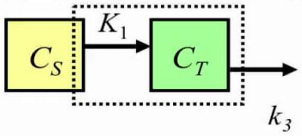


The rate of labeled molecules entering C_T

dC_T^*/dt = Metabolic flux V x probability of precursor C_S labeled

$$\frac{dC_T^*(t)}{dt} = V\frac{C_S^*}{C_S} = K_1 C_S^*(t)$$

Unidirectional chemical reaction S → T:



First-order process S->T

Reaction velocity *V* [µmol/g/min] : k≡V/C

$$V = \frac{dC_T(t)}{dt} = K_1 C_S(t) - k_3 C_T(t)$$

K_1, k_3 - (pseudo) first-order rate **constants**;

⇒ independent of concentration and time;
unit: [sec^{-1} or min^{-1}]

7-6

For our experiment now we'll assume that they are independent of concentration and time. The reaction constants have-- the unit typically is used per minute, but it can also be per second. So this is, if we have more molecules entering than leaving, we'll have buildup of the product here, and this will increase. If we have less molecules entering than leaving this system here, we have a reduction of the concentration of this tissue component. Now let's look at what's happening if we are supplying, in the substrate C_s, we are supplying radioactive molecules. And now we're interested in understanding how the rate of labeled molecules that enters the tissue pool, C_T, is calculated. Now the rate of radioactive molecules here in C_T-- just to be sure, it does not have to be radioactive, but we'll just call the term radioactive, or labeled molecules here, is equal to the metabolic flux; that is, the flux of the number of molecules per unit entering here into this pool, times the probability that one of those molecules is actually labeled. So what this means is we're saying we'll take this term, here. We have the rate of labeled molecules that appear here is equal to the reaction velocity times the probability they are labeled.

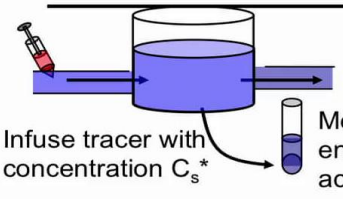
Notes

Summary

4m 17s

7-2. What are first-order tracer kinetics ?

One-tissue compartment model



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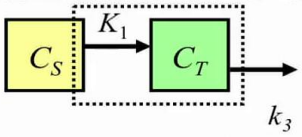

First-order process S->T

Reaction velocity *V* [µmol/g/min] : k≡V/C

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The rate of labeled molecules entering C_T
dC_T^*/dt = Metabolic flux V x probability of precursor C_S labeled

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How many labeled (red) molecules/per min ? (Assume the rate is V=10/min)

7-6

This is the number of labeled molecules, C_s *, divided by the total number of molecules. That's the probability that they're labeled, that is gives us the rate of molecules entering C_T, and if we [plug] this in here, with this definition here we'll find that this is equal to K_1 times the concentration of labeled molecules, in the substrate here, C_s. So, to give you an example here, we have a hypothetical situation. We have ten molecules, and now we'll say okay, these molecules are being supplied at a rate of ten molecules per minute. That's just an arbitrary number, to give us something we can easily calculate and we can visualize. So let's say we have ten molecules per minute that are being supplied, and now the question is how many of those are going to be producing, in the tissue here, the concentration, what is the rate of red molecules that are being produced, assuming that we are supplying, here, on this side, we're supplying a total of ten molecules? So how many molecules, if you have ten molecules coming here, how many red molecules are being produced here? Let's talk about the first situation-- we have no red molecules entering. Then the rate of product that is being produced is zero.

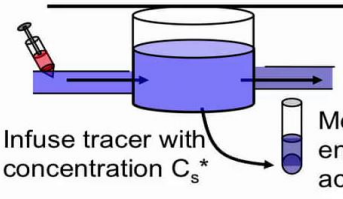
Notes

Summary

5m 53s

7-2. What are first-order tracer kinetics ?

One-tissue compartment model



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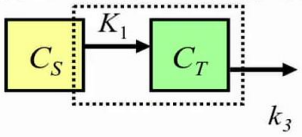

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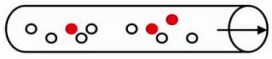


$$\frac{dC_T^*(t)}{dt} = ?$$

7-6

Now, you can use here *red* as a synonym for *labeled*, just to give an idea, and one of the problems that we have put together is a situation with colored cars between two cities. So the question is, what is the rate of buildup of labeled molecules? So we're going to have to look here in the calculation, we're going to have the reaction velocity, which is ten per minute, times the probability of a molecule being labeled, being red. So if we have one out of ten, what is the rate of red molecules appearing in this pool? How many molecules per minute? Well, we have ten that are coming in. One of the ten is red, so we'll have one per minute that is being synthesized, labeled molecules. If we have two, then we have-- again, the velocity is ten molecules per minute-- we have two out of the ten, so it's 1 over 5 molecules, 20%, that are red, and so the rate of labeled molecules that enters into the tissue pool is now two. And that's the last example here, so if we have three, then we have three red molecules entering, we have ten total, 30% of them are labeled, so we have three molecules per minute that enter into our pool.

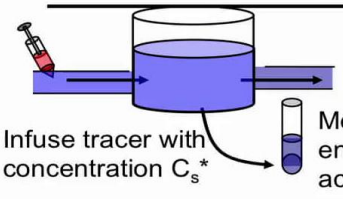
Notes

Summary

7m 21s

7-2. What are first-order tracer kinetics ?

One-tissue compartment model



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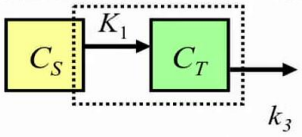

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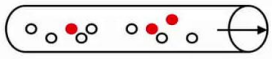
How many labeled (red) molecules/per min ? (Assume the rate is V=10/min)



$$\frac{dC_T^*(t)}{dt} = ?$$

Need to add efflux from C_T:

k_3: Metabolic efflux V x probability of molecule C_T being labeled

$$\frac{dC_T^*(t)}{dt} = K_1 C_S^*(t) - k_3 C_T^*(t)$$

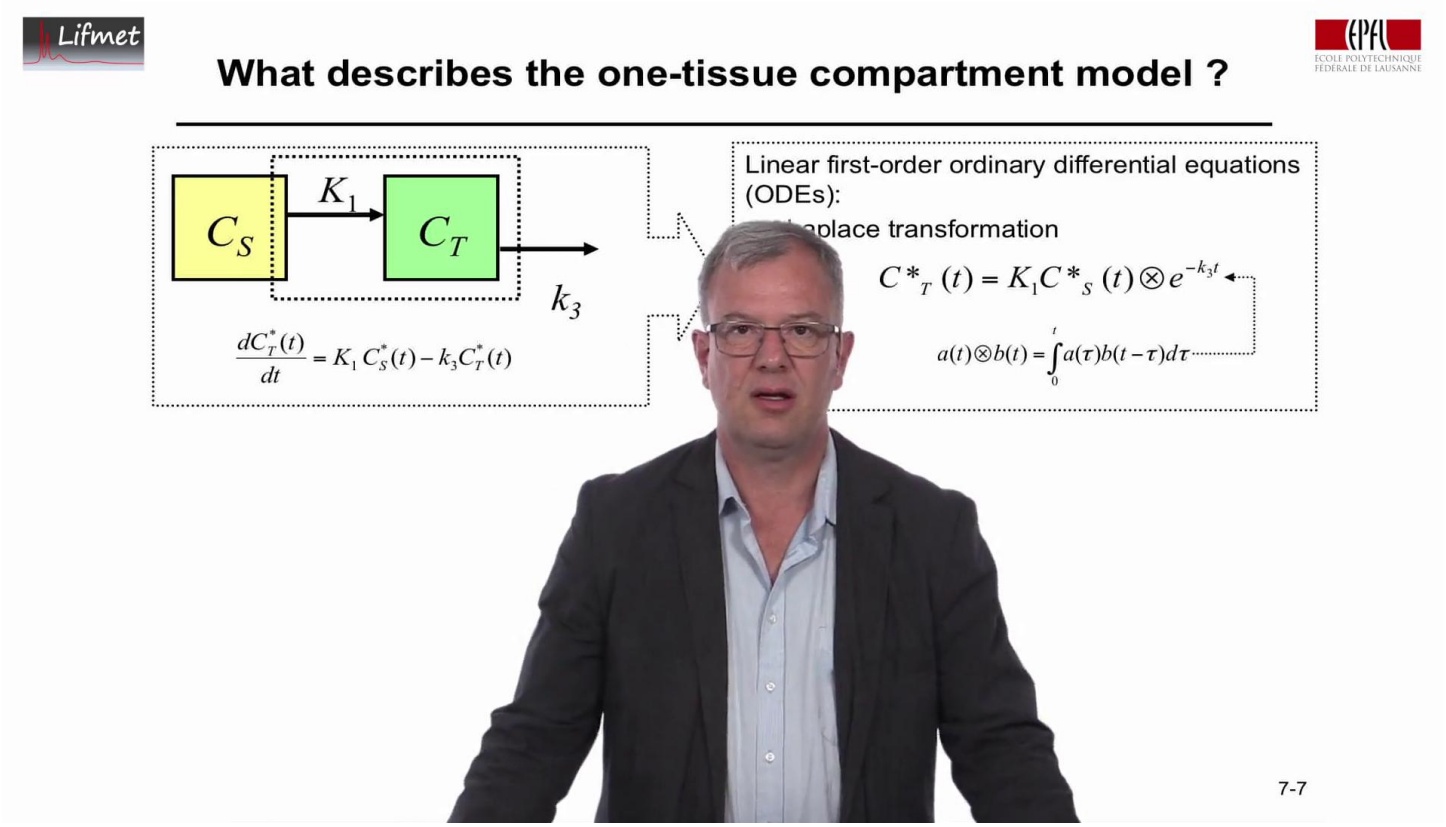
7-6

So I hope this example gives you an idea of how to understand how we calculate the buildup of tissue radioactivity-- it's velocity times probability. This turns out to be, with this definition, to be the rate, the pseudo first-order rate constant, times the concentration of the substrate radioactivity. Now what happens if we keep supplying labeled molecules? We obviously will increase the percentage of these molecules that are labeled, that are red, and at some point, they will no longer change. And at some point we'll have a significant number of red molecules that leave this pool, so we need to add this efflux, this reaction rate, to the calculations. Now, what is the percentage of red molecules that are leaving this pool here? It's equal to the metabolic flux times the probability of this molecule being labeled, so it's the flux, here, this is the flux, times this term here, now we just put C_T * over C_T, and so we get here by taking this, plus this, applied to this pool, we're now obtaining the efflux term, and that's -k_3 times the tissue activity of the tissue pool, as a function of time. And this is essentially the system of a linear differential equation that describes the rate of change of labeled molecules appearing in the tissue pool as a function of the radioactivity of the tracer in the substrate that is the blood pool.

Notes

Summary

8m 56s

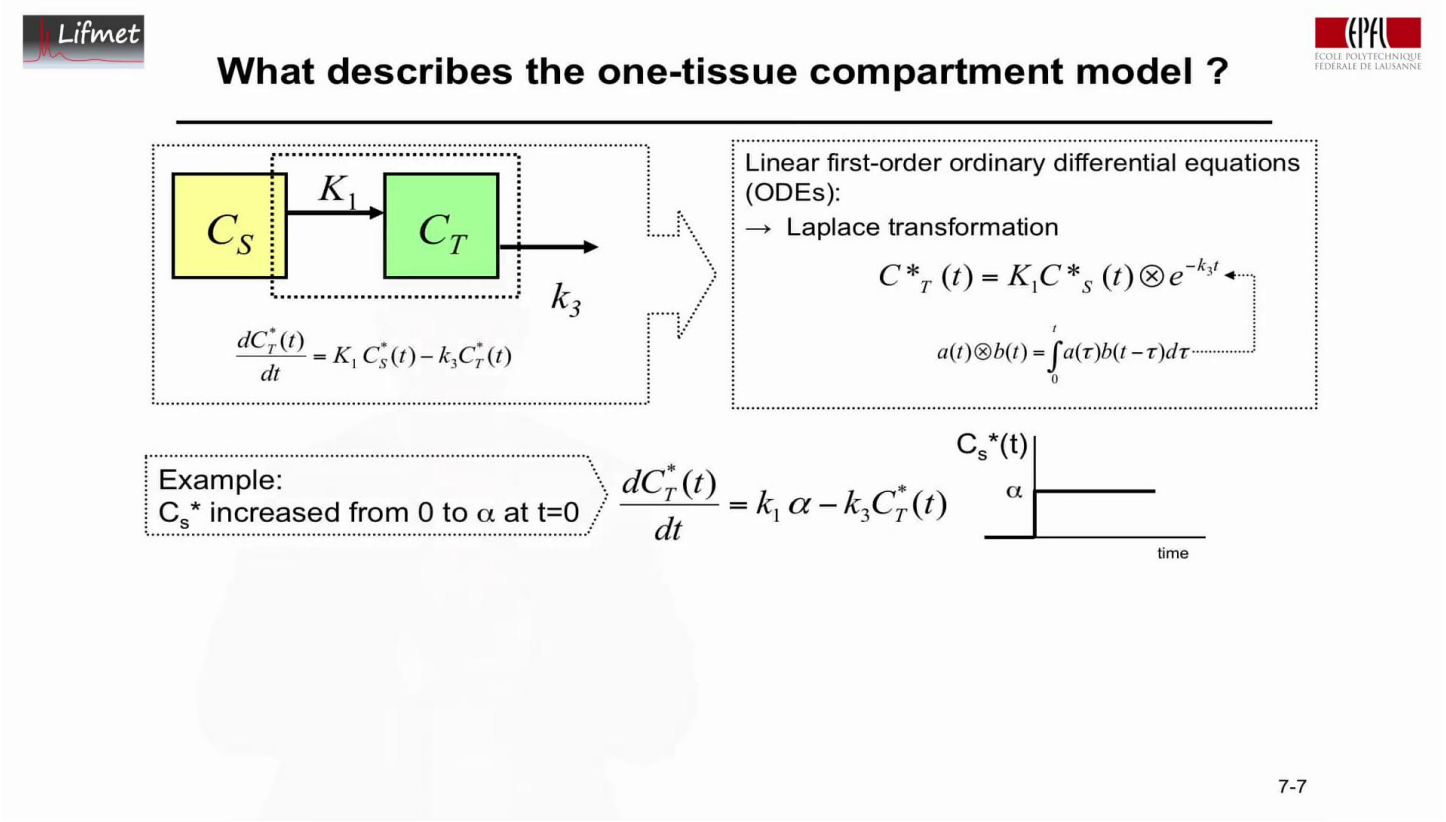


So now the question is how do we describe this one-tissue compartment model? What are some of the features? I'll recap here the model. We have the substrate. We have the influx reaction that's describing the reaction constant K_1. We have the efflux reaction describing the reaction constant k_3. We have the two concentrations in the tissue pool. And we just established the equation that describes the rate of change in labeled molecules in the tissue as a function of the change in labeled molecules in a substrate, for example, in the blood or the precursor. So this is a linear differential equation. It's a linear first-order ordinary differential equation, and this can be solved mathematically by using the Laplace transformation. The solution, then, is given by the tissue radioactivity, the tracer in the tissue is equal to K_1 times the precursor, the C_s * here, or the function of time convoluted with e to the -k_3 T. Mathematically, the convolution is this mathematical operation, and so this is, in principal, the solution that we can obtain, so mathematic. Now the Laplace transformation is not a very easy-- algorithmically, it's not very easy to handle.

Notes

Summary

10m 36s

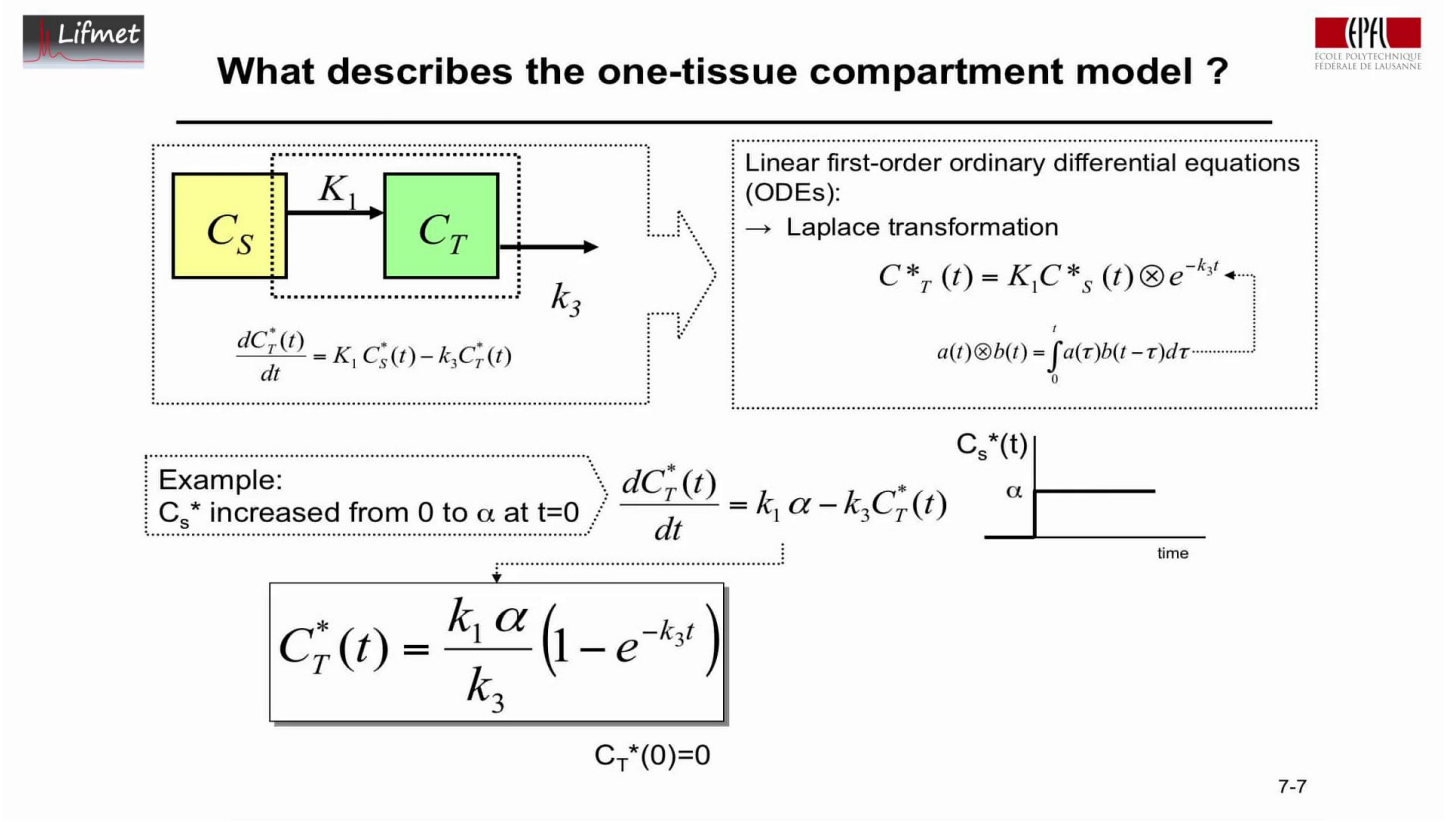


It is not very intuitive, and actually, in practice, it is hardly being used, although this is, strictly speaking, the mathematically strict solution. So instead I want to illustrate a simple example first. This example is very simple, because it also makes us understand a few important features. So we'll take this example, and we'll assume that we have done an experiment where we raised the activity, the tracer concentration, in the blood or the precursor, at time zero, from zero to a value alpha. We'll call it alpha. We can call it anything that we want. So, if we look at the concentration of C_s *, the labeled molecules, the tracer, at time zero, it goes from zero to alpha, and then [inaudible]. And then we assume it is constant. Now this is a very simple situation. Now we can write the above equation here, so we'll [inaudible] for this situation. We'll write the equation, and we'll see, at times zero or higher, what is happening is that the tissue concentration of the substrate of the tracer is equal to K_1 times alpha, because then we have set now this concentration to constant minus k_3 times the tissue concentration of the tracer. And this is something we can mathematically handle ourselves.

Notes

Summary

12m 04s

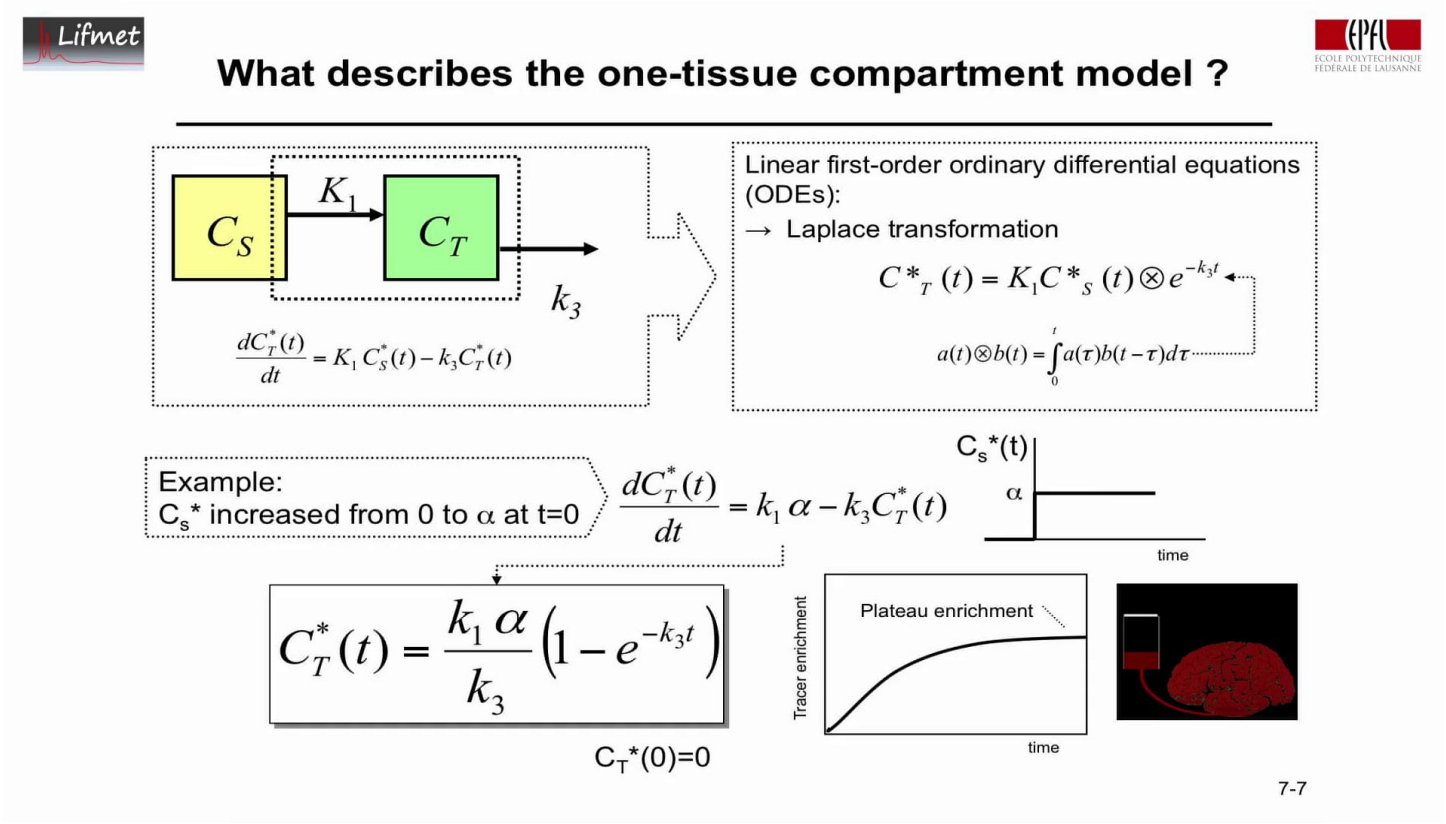


So on the left side we've got a variable, C_T*, that is the time derivative; and on the right side we've got the same variable, and typically when we have the derivative on one side of a function, and the function on the other side, well, this basically means we're looking at something where the derivative of the function is equal to the function times some constant, and the solution here involves, therefore, the exponent e to the minus something. And one can do the Ansatz-- I won't go into the mathematical details here, and I'll just give you the solution here. So, and this you can verify by plugging this expression that we have here into this differential equation, and solving and verifying that this is indeed a proper mathematical solution. Now, what does this imply? Well, if we take this function, and we have on the right the time zero, so we set T to zero, this term becomes zero, then the tissue radioactivity at time zero is zero. That makes sense, because we have said we start out with nothing, so there's nothing in the tissue, and at time zero we jump to alpha in the precursor-- that's this term here.

Notes

Summary

13m 31s

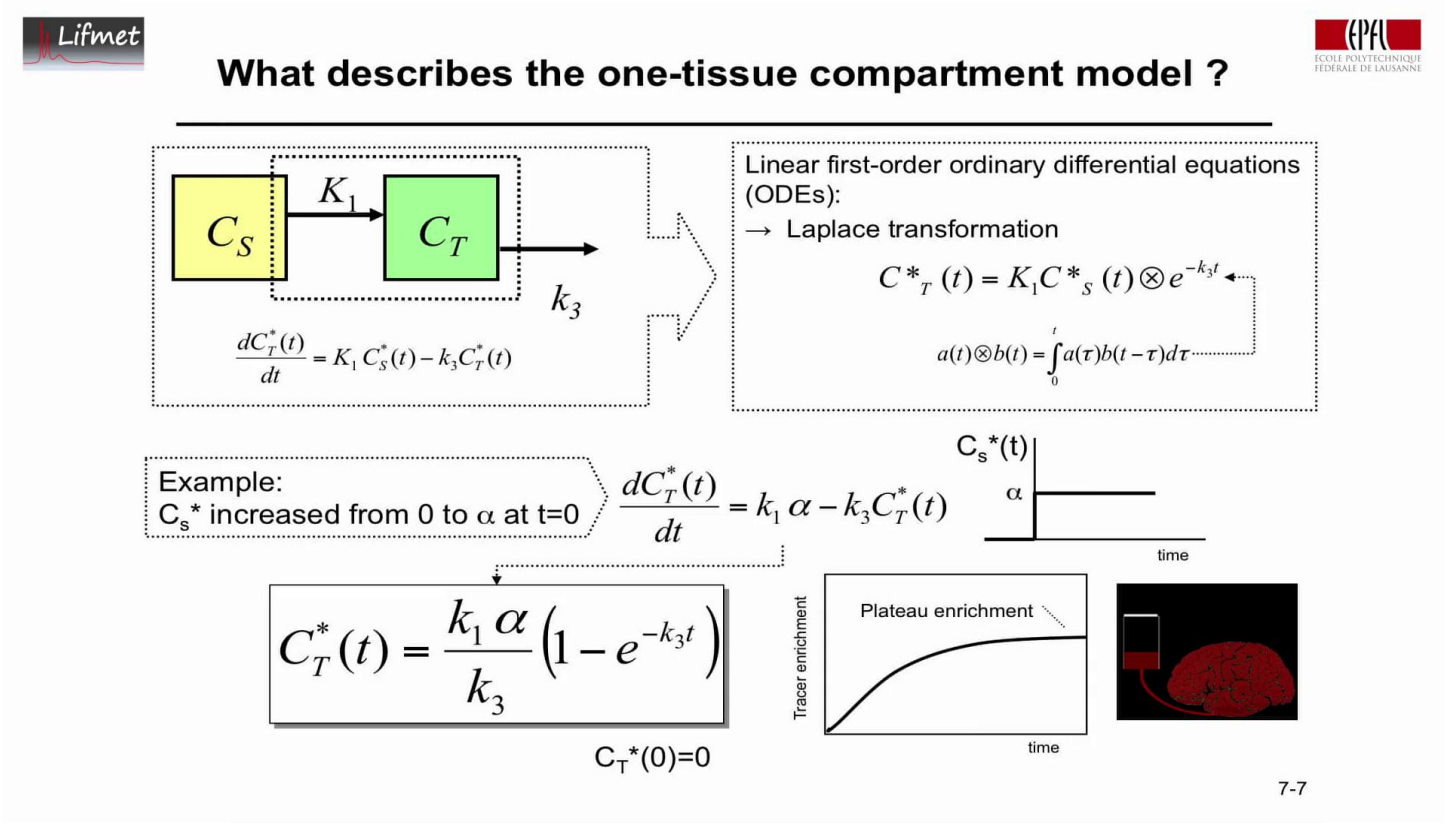


Now, what's happening at time infinity, the tissue radioactivity will, exponentially, approach a constant value, K_1 alpha over k_3, so we're getting an exponential increase, [or developed from your side], an exponential increase to a plateau level with time. So, I have schematically drawn this here. We have time on the x-axis, the tracer arrangement on the y-axis, and what we'll see, this function as an exponential increase with time. And we're getting the plateau enrichment. Or, to illustrate this here, we have an injection of a tracer, this is an illustration from a brain experiment, and the brain will change color as the tracer is appearing in the tissue, and labels the tissue concentration. Now, conceptually, what we need to get our metabolic rate, this is described by the parameter k_3, so we need to determine this parameter, k_3, here. And we might think that, for such a simple function, an exponentially increasing function, e to the minus asymptotically going to a steady state value, but this, mathematically, is very simple. It actually turns out this is not as simple in practice, and there are... one has to be a bit cautious here.

Notes

Summary

14m 37s



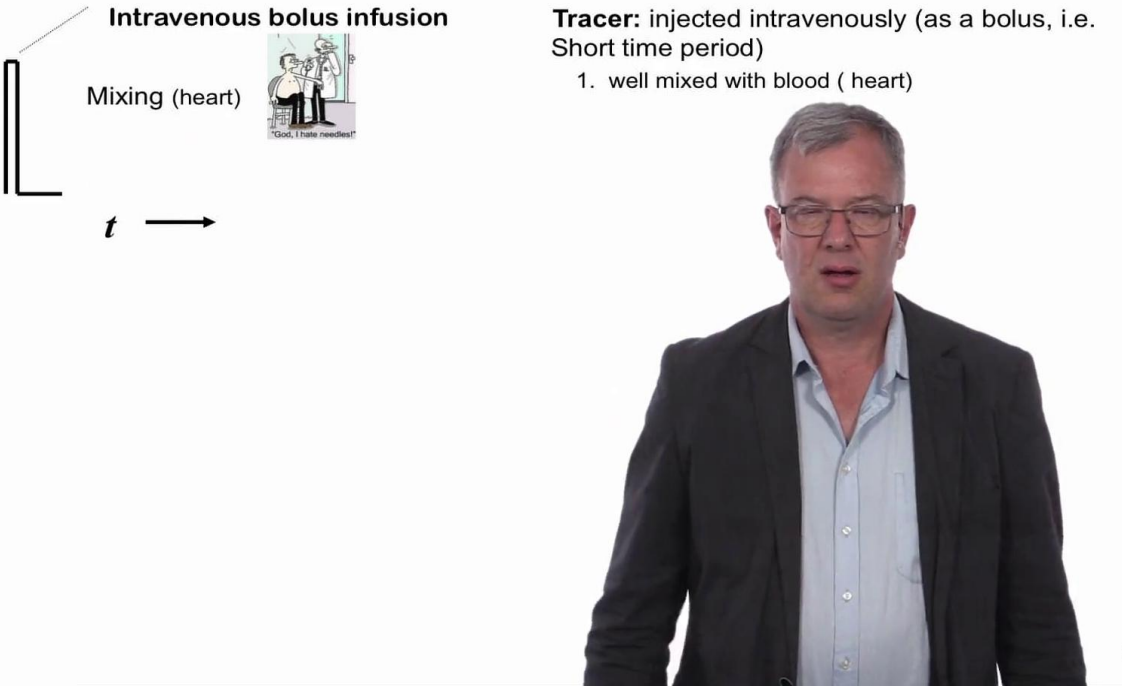
For one thing, to determine this time constant, one needs to know when the plateau enrichment is achieved. If we don't measure to the plateau enrichment, we don't have a good idea what a plateau enrichment is, and so this constant, k_3, is actually practically not very well determined. So it depends, strongly, on whether we know what this steady level is, so that we can estimate, from the fitting process, the rate at which the enrichment is achieved. If we have a fast metabolic rate, it happens like this; if we have a slow metabolic rate, it happens like that, but to get a fairly precise estimate, we need to have a good idea on the plateau enrichment, and this is, essentially, to any function that has this form is a mathematical feature there, that we have. This term, the steady state enrichment, and this term, the rate at which it achieves its steady state, mathematically, when you fit this to the time course, they are correlated, typically, with very negative correlation coefficients, so this is one of the difficulties, and we'll be seeing more of these equations in the second course on MRI.

Notes

Summary

16m 05s

What is the input function ?



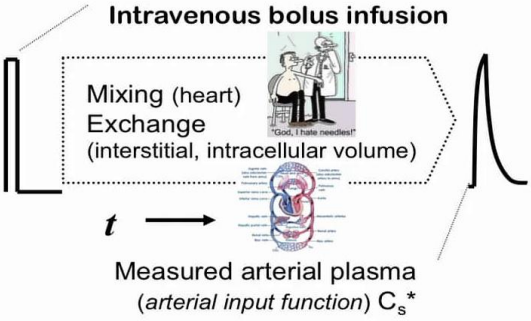
The measurement of metabolic rates depends on our knowledge of what's happening in the substrates, in the precursor pool, C_s, relative to the tissue pool, and we have just worked with a simple example where what is happening in the blood was assumed to be a state function, but let's now look at what is this input function, what's happening in the blood in reality. So we'll take an example, of a practical example-- We'll infuse the tracer with a so-called *intravenous bolus infusion*. This basically means we'll take the syringe, we'll inject the tracer into the bloodstream in a relatively short time, that's what the bolus means, intravenous, obviously, into the veins, so it's a very fast application. So, the tracer goes into the vasculature in a short time, as a bolus. Yes, and this does involve needles, so if you're queasy about needles, this is not the technique you want to expose yourself to. Then, what happens is this tracer that goes in in a very short time, we'll assume it's very short, undergoes mixing in the circulation. We'll assume here it's well mixed with the blood, so this involves the heart, then the substance can undergo exchange with, say, interstitial spaces or even intracellular volume, so this happens in the circulation.

Notes

Summary

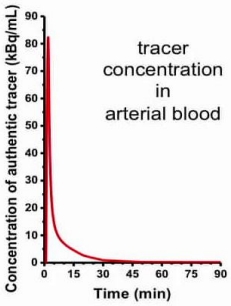
17m 21s

What is the input function ?



Tracer: injected intravenously (as a bolus, i.e. Short time period)

1. well mixed with blood (heart)
2. distributed to capillary bed→ exchange with tissue



tracer concentration in arterial blood

Uptake into tissue, e.g.
Perfusion
Endothelial permeability
Vascular volume fraction
Transport across cell membranes

Specific binding to receptors
Non-specific binding
Enzyme activity

7-8

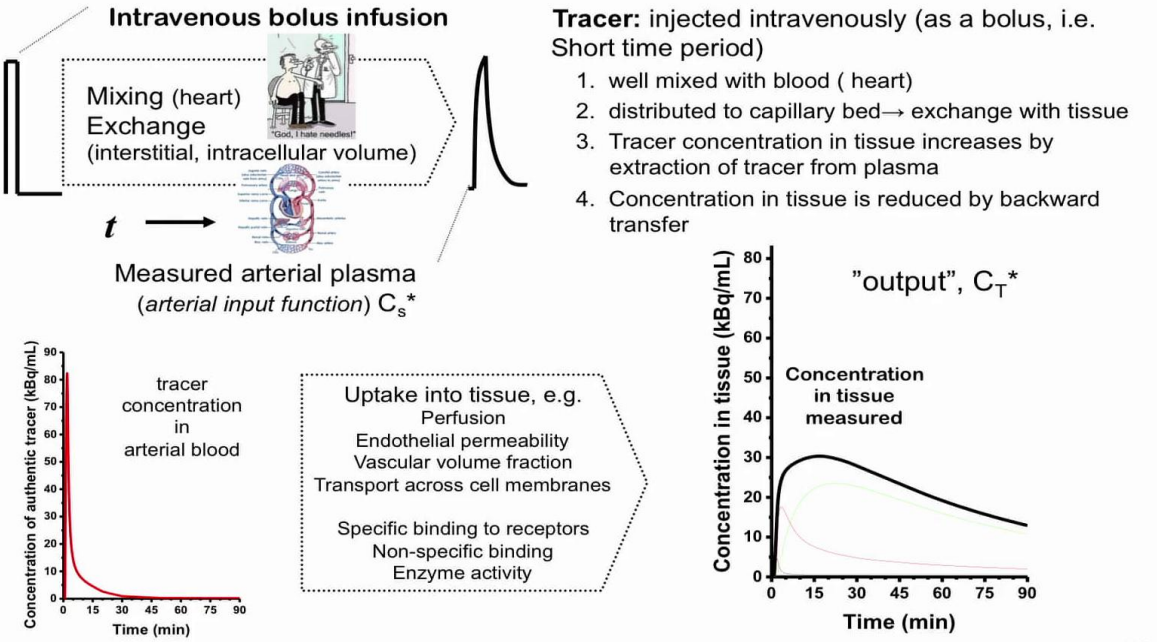
And as a result of this process, instead of getting a bolus where the tracer appears-- it's very high for a short time, and then again zero-- what we'll see in the blood is a rapid rise of the tracer, and then sort of a relatively slow decay, sort of dispersion, due to these mixing processes, and that's what is then measured. Typically in the artery it's the measurement of the tracer in the arterial plasma, and this is what we call the arterial input function, or C_s *. So if you look at the tracer in arterial blood, this is a typical tracer here, concentration, this is in decays per second per milliliter or kilobecquerel per milliliter over time, so we have the rapid injection; we get the bolus, and then a relatively rapid reduction. What then happens, as a second step, is that the tracer's distributed to the capillary bed, and then undergoes exchange with the tissue. So, the uptake into the tissue in moles per fusion, moles' permeability of the endothelium, it involves the blood volume as a factor, it involves transport across cell membranes, possibly specific binding to receptors, or non-specific binding, or enzyme activity. So these are all factors that influence the ultimate uptake of the tracer in the tissue.

Notes

Summary

18m 55s

What is the input function ?



So, as we have given our bolus here, we're getting a sudden increase in tracer, we're also getting a concentration increase in tracer in the tissue, due to extraction from the blood. And if we now look at the output-- so this is the tissue radioactivity here, we have the concentration in the tissue on the y-axis, the time on the x-axis-- then this is what we are seeing, the concentration that we can measure with the imaging techniques, that's the black line here. This particular graph here is a simulation of a metabolic process, where multiple compounds are involved; the red and green are just some intermediate. Other compounds that contribute to the overall tissue-rate activity, since we cannot distinguish chemical species based on their x-ray activity alone. We have of course this tracer, it's not going to stay in the tissue. There is backward transfer-- We take, for example, oxygen. If you have oxygen, you breathe oxygen, it's converted to H_2O^{15}, and this H_2O obviously then at some point leaves the tissue again, and for glucose, if you take up glucose, you look at C11-glucose, for example. This will ultimately leave the tissue in the form of CO_2, C11 labeled CO_2, so the backward transfer can be in the same species, or can be a different chemical species, but this, ultimately, reduces the concentration of the tracer in the tissue.

Notes

Summary

20m 32s