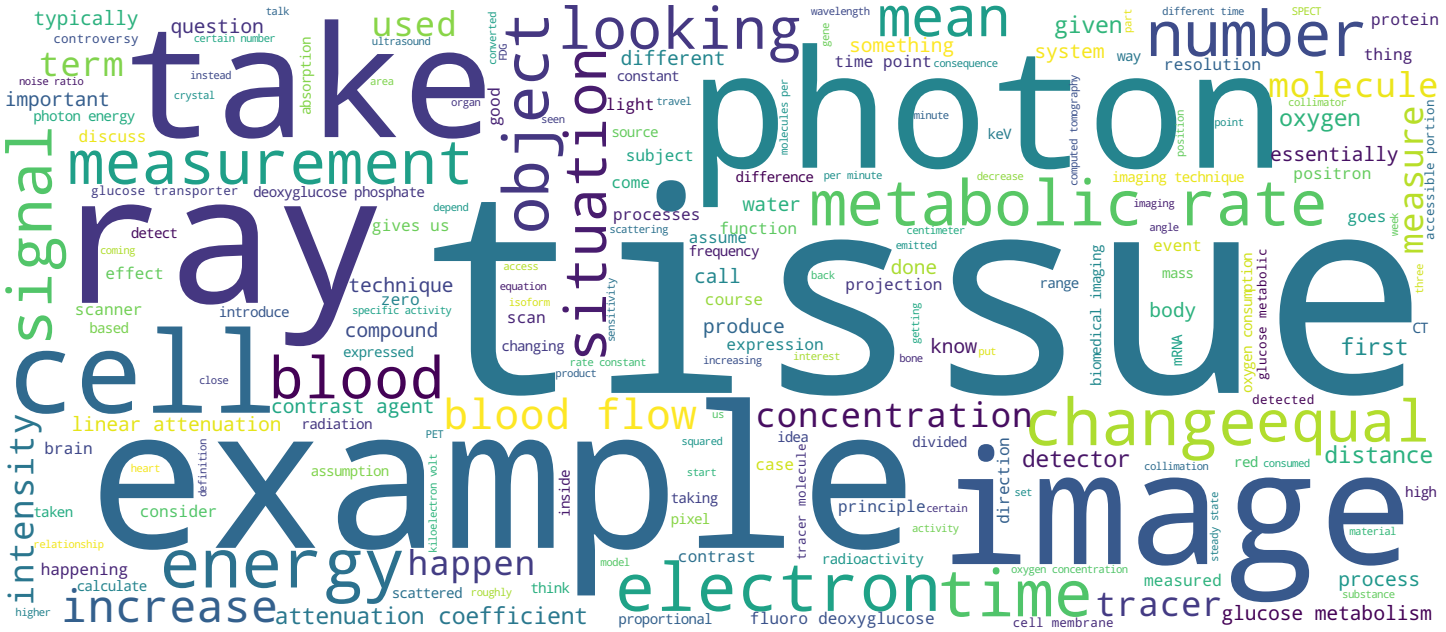
ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

7.1 Compartmental modeling

Fundamentals of Biomedical Imaging

Prof. Rolf Gruetter



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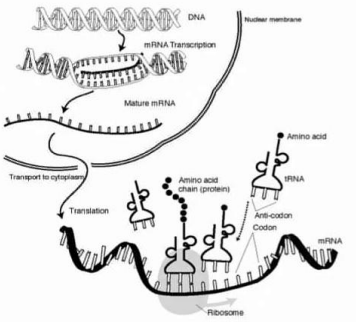
Video

EPFL

Why is it important to understand basic modeling of linear systems ?

Situation I: Team A measures a high expression (mRNA) of a gene. Team B finds a low protein level at the same time point

Situation II: A year later, Team C reports low mRNA of the same system. Team D finds a high protein level



Today's lecture is going to be a bit different than the previous lectures as we are not going to discuss an imaging modality per se. However, I feel that the topic of understanding how traces of contrast agents, how they enter the tissue and how we can understand their appearance in tissue is of wide-ranging importance. It's also important for processes well beyond biomedical imaging such as pharmacokinetics, etc. And therefore, I wanted to spend this small segment this week on understanding the kinetic models and how we obtain metabolic information or information on the processes. And so, here the first question is: why is it important to understand basic modeling of linear systems? So let's take a situation. It's here presented as a hypothetical situation but it actually does have some relevance to what I've experienced in my career and what is not infrequent to happen. So we'll take a situation here where we have a team A, research team A, that measures a high expression of the message of a gene, the mRNA. Team B measures at the same time point a low protein level. A year later, team C reports a low mRNA of the same system whereas team D finds a high protein level.

Notes

Summary

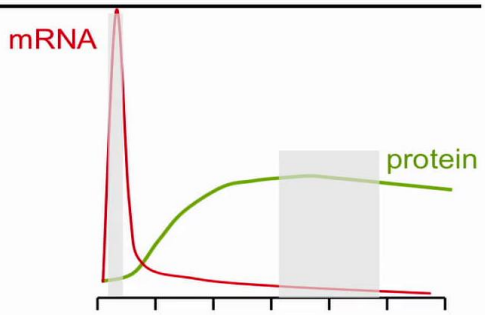
0m 03s

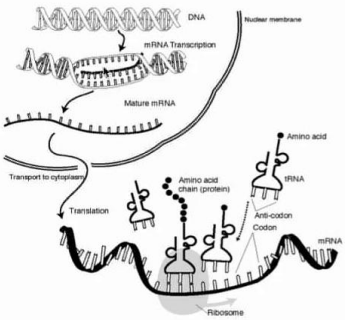
Why is it important to understand basic modeling of linear systems ?

Situation I: Team A measures a high expression (mRNA) of a gene. Team B finds a low protein level at the same time point

Situation II: A year later, Team C reports low mRNA of the same system. Team D finds a high protein level

Controversy or is there a common underlying explanation?





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So the question is: Is this a controversy, or is there a common underlying explanation? Trust me, looking at these things as they are reported for research teams, conflicting findings this does give rise to quite some controversy at scientific meetings. So, let's try to understand the situation. I'll plot here on the x-axis, we'll have the time here and now, what we are plotting here in red, is the expression of the gene that's the mRNA as it has been measured or as it... let's say this is what's happening in the system. And then let's look at the protein level of that particular gene, so the protein that's being expressed. Those two time courses are not the same. So we have here now situation 1 when the measurement was done, at this time point. Situation 2 corresponds to a measurement at a later time point. So, if in the discussion of these seemingly controversial results we omit the factor time here on the horizontal axis we can very well enter into considerable controversies that are actually, if you look at now this graph we're not looking at a controversy-- we're just looking at different time points. The system we're discussing here is TNA2. Expression, the mRNA, and finally the translation to the protein.

Notes

Summary

1m 35s

Why is it important to understand basic modeling of linear systems ?

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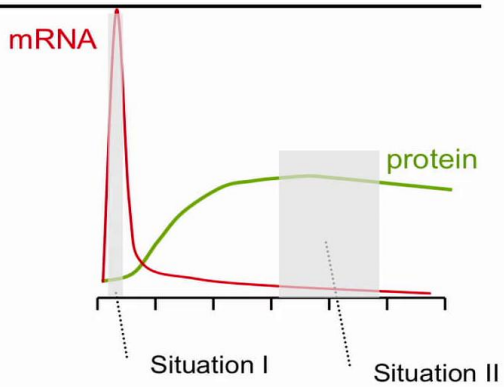
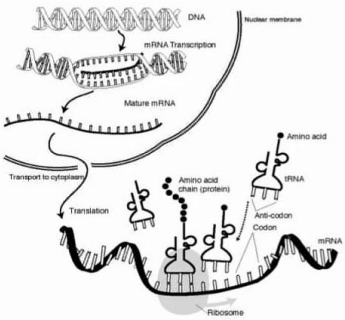
Controversy or is there a common underlying explanation?





NB. Underlying mathematical principles also applicable to

- Contrast agent dynamics

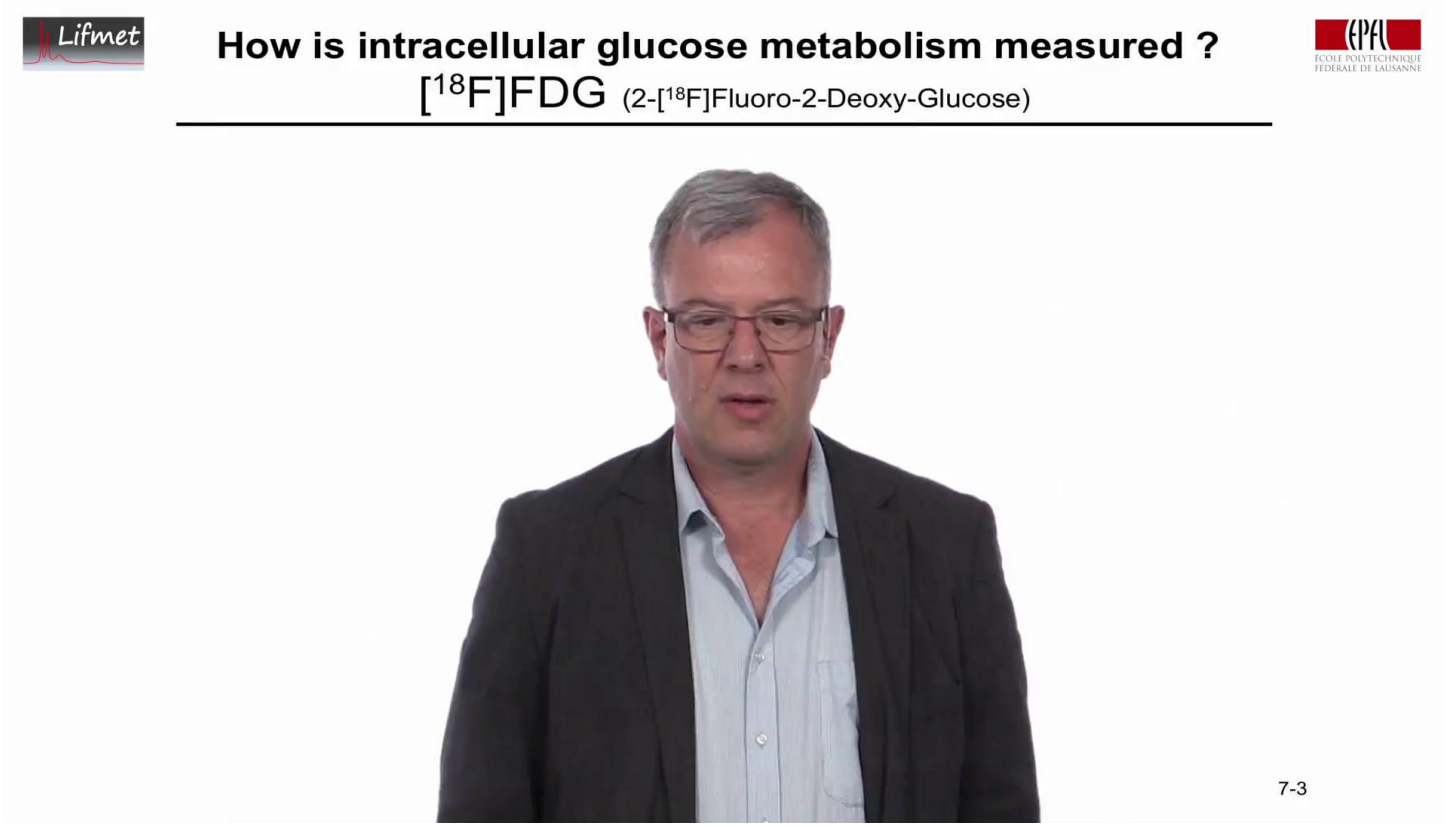
7-2

And what we're looking at here is essentially a biochemical reaction. We have the precursor, that's the mRNA and we have the product, which is the protein. Clearly, we cannot have protein being expressed before we have the gene being expressed or the protein's not synthesized before we have the signal in the cell that this protein should be expressed. So there's a causality issue here, and the mRNA has to precede the expression of the protein. So this is situation 1, and this is situation 2. Two different time points, if you look at it from this standpoint then actually our conclusion must be there is no controversy we've just been looking at different time points. Now the system of product-precursor relationship can be ascribed mathematically, we can set up a model and the underlying mathematical principles as we'll see in this lecture they're actually fairly generally applicable. We can apply them to contrast agent dynamics, uptake of contrast agent, so instead of mRNA we have contrast agent in the blood and instead of protein we have contrast agent in the tissue. Enzyme kinetics, we have the reaction velocity that goes up first, for example, and the product buildup will come later.

Notes

Summary

3m 20s

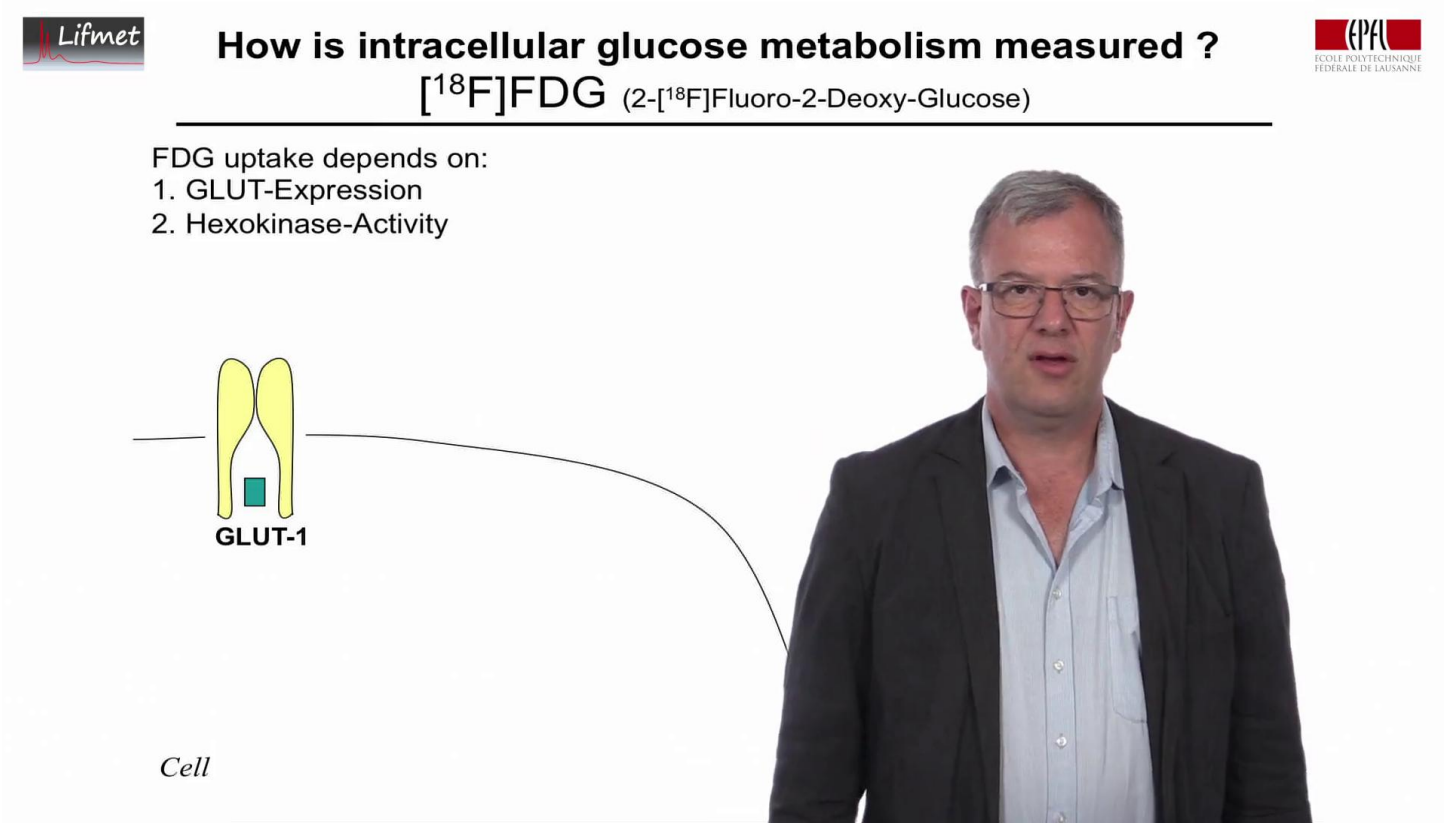


This cannot happen any other way around. Take diabetes as an example. We have insulin, patients with diabetes very often have to inject insulin, and the effect on glucose uptake is delayed, so insulin first, then change in glucose uptake predominantly in the muscles, comes later. Sailing, for those of you who have experience with sailing you know very well that if you change the rudder or the sail position, the change in direction or the velocity of the boat that this takes some time. Economics is also an example. If we change the financial incentives in the system, until that changes the production and the availability of the product in the market that is also a relationship, a causal relationship where we have a delayed response to the input that's changing. So the underlying principle here in all cases, it is about inertia. Its resistance to change. Things don't happen instantaneously and this is the concept of inertia. We've had, for those of you who remember your freshman physics course we have talked about inertial mass in those courses. Mass is the resistance to change to velocity, Newton's second law also there, the concept exists in there, and this is taken here in the example of sailing.

Notes

Summary

4m 41s

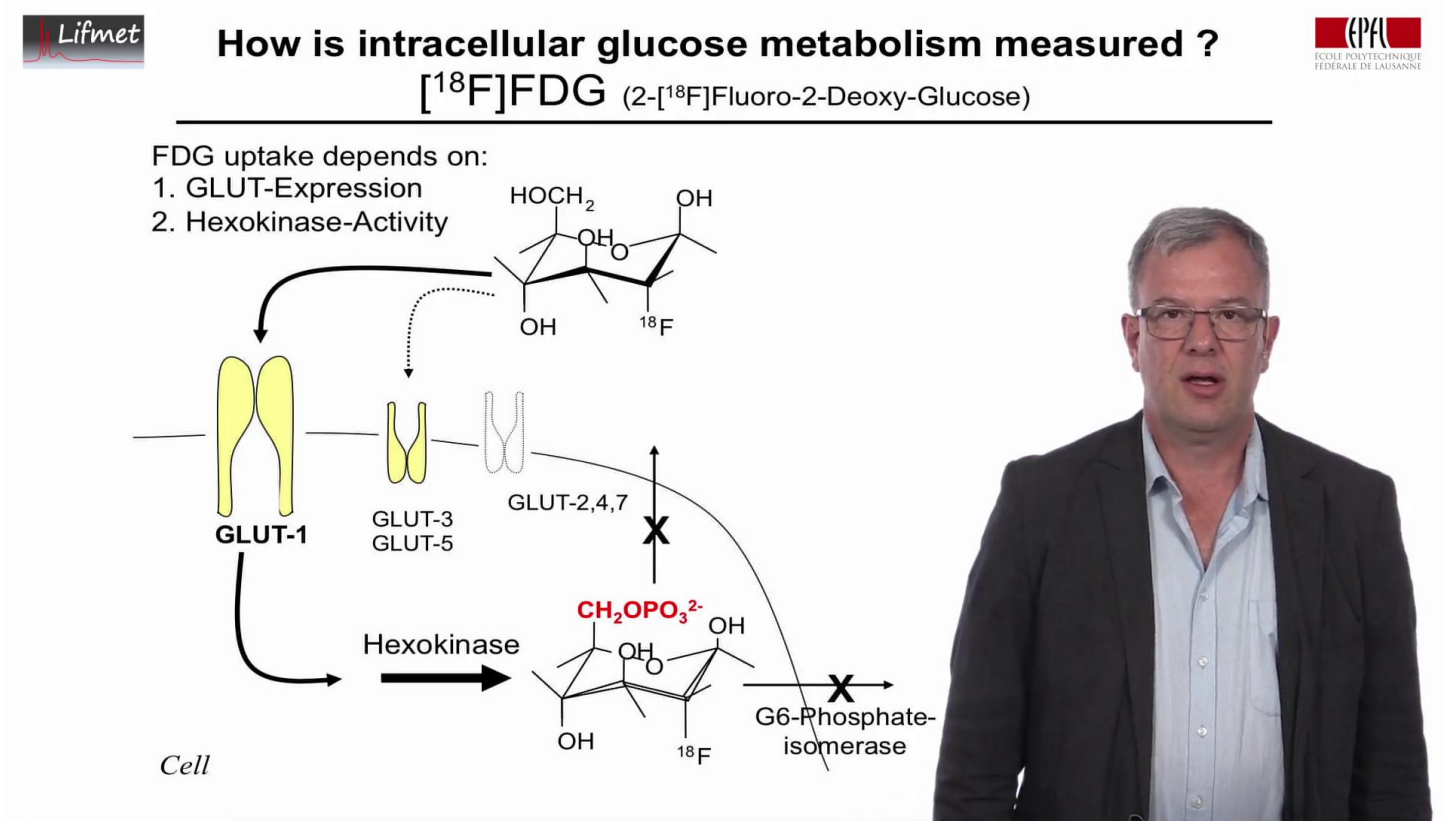


Of the techniques that are highly dependent on this description and on a good understanding of the kinetics that are happening is the FDG PET technique. And this is a technique to measure intracellular glucose metabolism. So before I go into the specifics of kinetic modeling I want to just give you an overview of the processes involved in measuring intracellular glucose metabolism using fluoro-deoxyglucose, or deoxyglucose. Now, the tracer molecule here, FDG, is taken up into the cells and this uptake depends on the expression of a protein called GLUT. GLUT here stands for glucose transporter. So, glucose cannot go across the cell membranes. It needs a protein, sort of like a channel that allows it to cross the cell membrane and these are the glucose transporter proteins. It also depends, obviously, on the glucose metabolism the uptake depends also on the activity of the first metabolic step of glucose metabolism, that's glucose phosphorylation mediated by the enzyme hexokinase. So, we'll look here at a cell. This is the cell membrane. We have here our glucose transporter molecule, GLUT-1. This is one isoform of many isoforms, There's roughly nine glucose transporter isoforms they've been described in the literature.

Notes

Summary

6m 14s



GLUT-1 is the one that's present in the membranes of red blood cells and in most cells in our body. Here's the molecule, that's the fluoro-deoxyglucose. We administer it, it comes to the cell membrane and then traverses the transporter, and thus the FDG molecule ends up inside the cell. This transport into the cell can happen by GLUT-1. It can also happen by other isoforms such as GLUT-3, GLUT-5, GLUT-3 being the isoform at the neurons and GLUT-2, for example, being the predominant transporter in the pancreas, important for diabetes. So now we are in the situation that we have fluoro-deoxuglucose inside the cell, and now comes the first metabolic reaction mediated by hexokinase, and this process happens here in attaching a phosphate at the sixth position, thereby producing fluoro-deoxyglucose-6-phosphate. This molecule now has interesting properties. Number one, it cannot be further metabolized by the next enzymatic step in glycolysis so glucose-6-phosphate isomerase does not metabolize glucose deoxyglucose-6-phosphate, so this, it does not go on. And glucose-6-phosphate, or deoxyglucose-6-phosphate is not transported out of the cell.

Notes

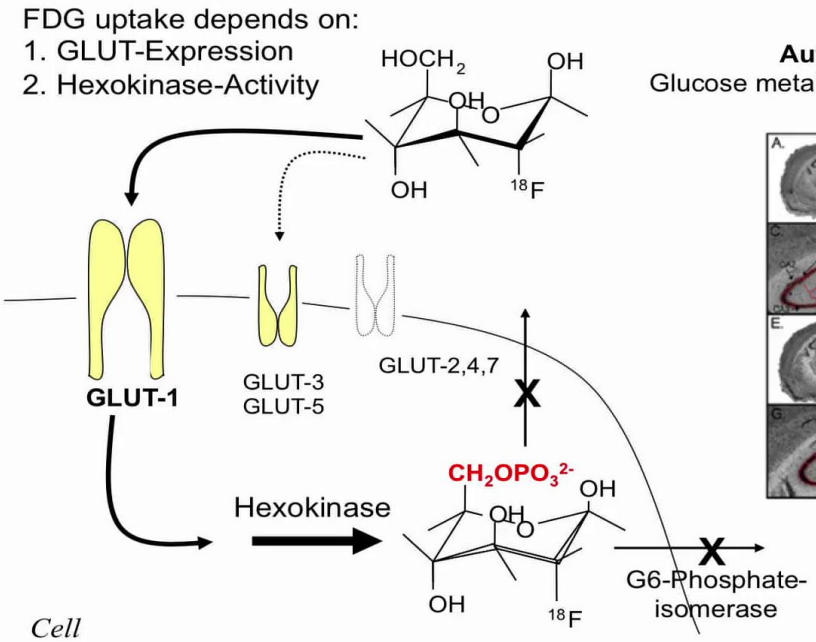
Summary

7m 49s

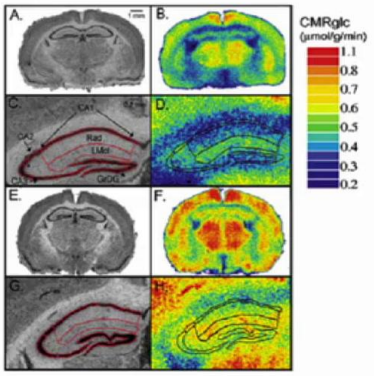
How is intracellular glucose metabolism measured ?

[^{18}F]FDG (2-[^{18}F]Fluoro-2-Deoxy-Glucose)

FDG uptake depends on:
1. GLUT-Expression
2. Hexokinase-Activity



Autoradiography:
Glucose metabolism using deoxyglucose



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So, in a first approximation and in simplification of the reality, we have fluoro-deoxyglucose-6-phosphate, or deoxyglucose-6-phosphate, is now metabolically trapped inside the cell, and this is how FDG PET, or deoxyglucose methods, measure glucose metabolism. Now, to give you an example here, we'll take, actually not FDG but we'll take another deoxygluose, it's the C14 or tritiated deoxyglucose and the technique used here, the example I'm giving is autoradiography. So what we're looking at here are images of the brain in greyscale. These are brain slices, so the brain has been harvested cut into thin slices, on the left you see the images, and on the right in the color code we see the glucose metabolic rate with warms colors being the higher metabolic rate and cool colors being the lower glucose metabolic rate. So these brain slices are placed on a radiographic film and then the emission of the radioactivity from C14 and/or tritium, those are beta particles, is being recorded on the film, and this gives us the color coded images. This is an autoradiography of a rodent brain, and here is an example, a close-up, this is showing the columnar organization of the whisker barrel cortex, where each of those columns corresponds to a specific whisker with a higher uptake.

Notes

Summary

9m 29s

How is intracellular glucose metabolism measured ?

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FDG uptake depends on:
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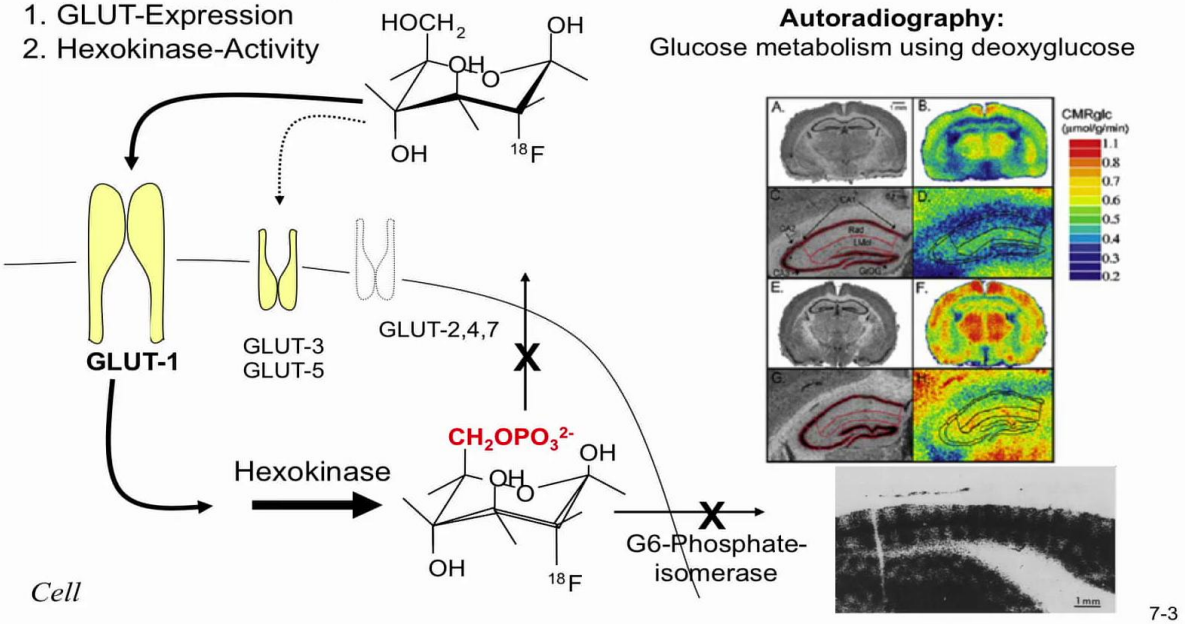


Autoradiography:
Glucose metabolism using deoxyglucose

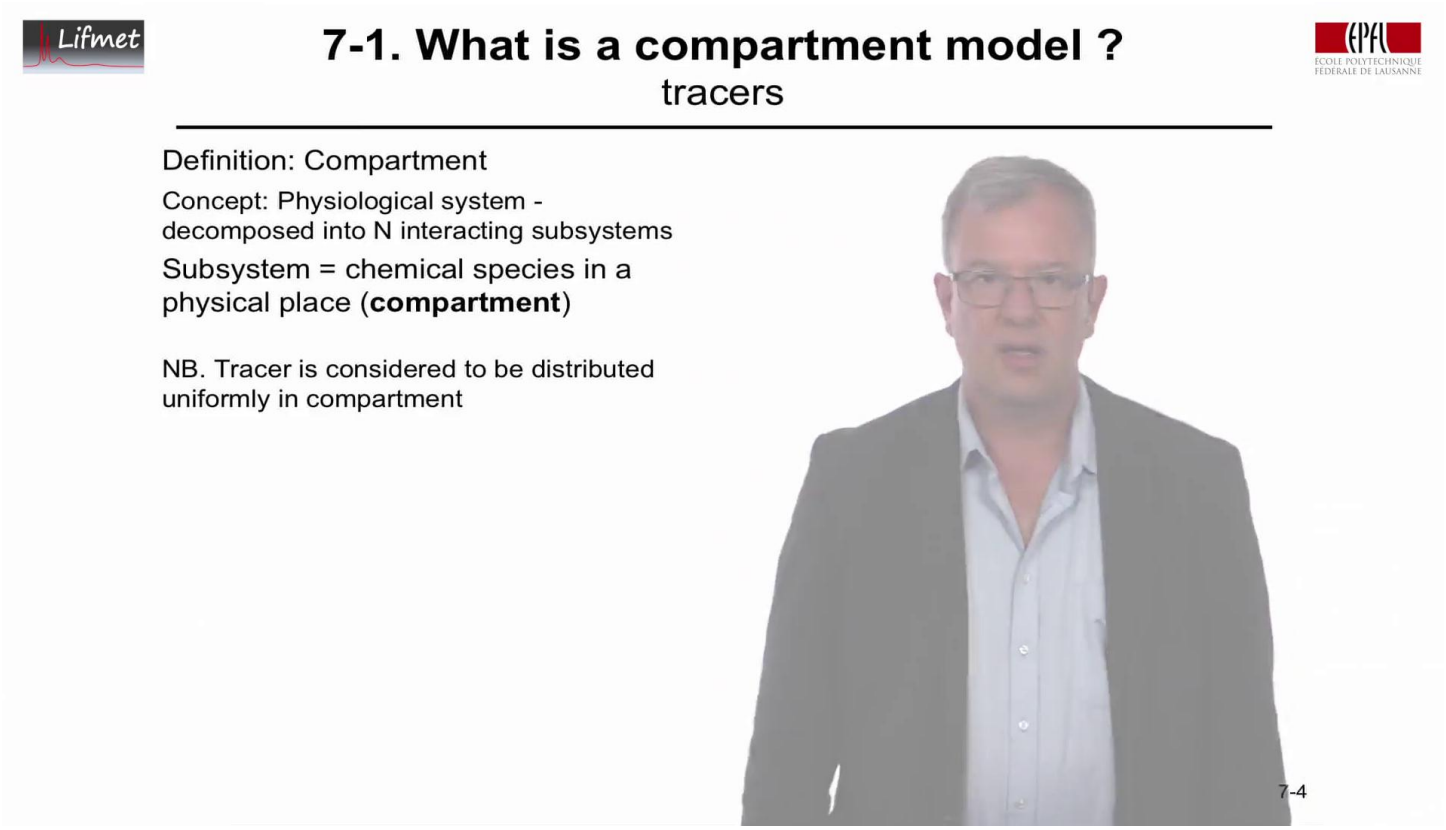
7-3

So this is a very powerful technique to measure glucose metabolism, and we will use it as an example throughout this lecture, Lecture 7, and in the end explain how the FDG technique functions.

Notes

Summary

11m 08s



So first, however, I want to introduce some basic principles. First of all, the question: what is a compartmental model, or compartment model, and this asks the question of what is a compartment? So we'll take the definition of a compartment here that... we'll take the concept that we have a physiological system and we'll decompose it, model it into certain number N here, given interacting subsystems. Those subsystems are typically a given chemical species in a physical space. That physical space is typically called a compartment. So we have, when we give dexocyglucose we have glucose in the blood, that's one compartment, glucose in the cell, that's another compartment, and then we have phosphorolytic glucose that's the third compartment. We'll make the assumption here that the tracer is considered to be uniformly distributed in a given compartment. There are very elaborate experiments that would allow us to say something about where in the cell this particular compound is located, but they are very complicated experiments, and for practical purposes, in the context of biomedical imaging this is an assumption that one makes. So what are the key elements of compartmental modeling?

Notes

Summary

11m 27s

7-1. What is a compartment model ?

tracers

Definition: Compartment

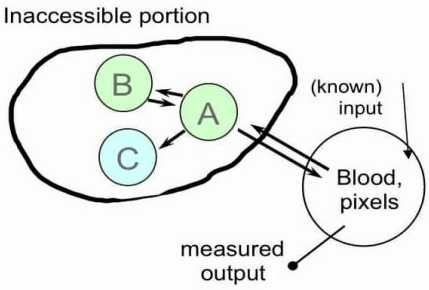
Concept: Physiological system - decomposed into N interacting subsystems

Subsystem = chemical species in a physical place (**compartment**)

NB. Tracer is considered to be distributed uniformly in compartment

Key elements of compartmental modeling

1. Predict inaccessible features of system
2. Measurement in the accessible portion



7-4

Let's look at some major elements. First, the first one is, the key element is we're going to try to make a prediction of what's happening in a part of the body that we have no direct access to. So, these are inaccessible features of the system. With deoxyglucose this would be intracellular glucose metabolism. So the inaccessible portion is something inside the body, inside the cells, and we want get some ideas of what's going on here. So for example we could say we have a model taken from the chemistry of metabolism. We have a chemical species A that interconverts into species B and is also being converted to species C. That would be an example here. The second element of a compartmental model is that we do the measurement in an accessible portion. So what is the accessible portion? That is essentially the measured output, and what do we have access to? Well, we typically have access to the blood vessels, so we can take blood samples. And we, typically in imaging, we have access to the measurements that are being done with the imaging technique that is, to the value of the pixels. So those are our accessible features of the system.

Notes

Summary

12m 50s

7-1. What is a compartment model ?

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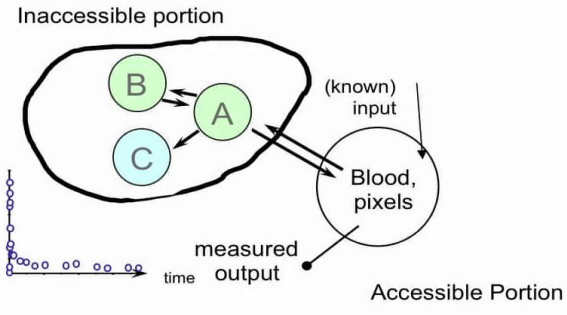
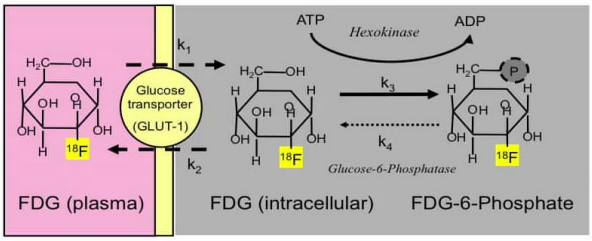
Key elements of compartmental modeling

1. Predict inaccessible features of system
2. Measurement in the accessible portion
3. Estimation of specific *parameters of interest*.





So we'd like to have, from the measurement in the blood from the pixels, this is our output, we'd like to say something about what's going on here inside our cells. We have also, of course, a known input into the system. So this is a given example here of what's happening in the blood. We inject here something very rapidly, and this compound is decreased, this can be a tracer, this can be a contrast agent. So this part here, that's our accessible portion the blood measurement is here. And then, based on the measurements in the accessible portion we're going to try to estimate specific parameters of interest. One example already mentioned is the metabolic rate of glucose. So here is an example. We have fluoro-deoxyglucose in the blood in the plasma, we have the transport into the cell. Then we have the free deoxygluose, or free fluoro-deoxygluose, inside the cell. And we have, then, through the glucose metabolic rates we have the fluoro-deoxygluose-6-phosphate, or deoxygluose-6-phosphate. So these are the three compartments: blood, brain, the species; metabolic-- we have three compartments, free glucose in the blood free glucose in the tissue, and phosphorolytic glucose in the tissue.

Notes

Summary

14m 12s

7-1. What is a compartment model ?

tracers

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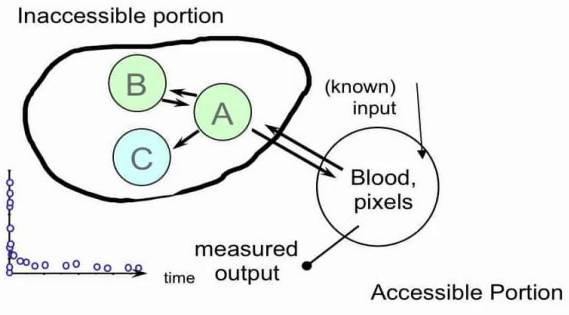
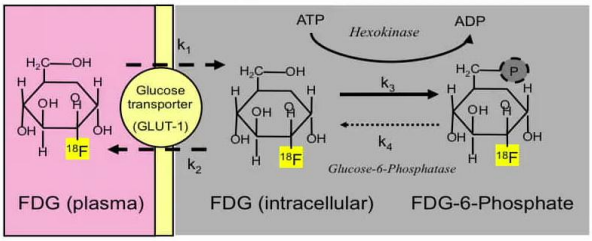
3. Estimation of specific *parameters of interest*.

Steady-state assumption:

1. metabolic rate of process is not changing with time
2. concentrations are constant during the evaluation period.



processes can be described with pseudo-first-order rate constants.

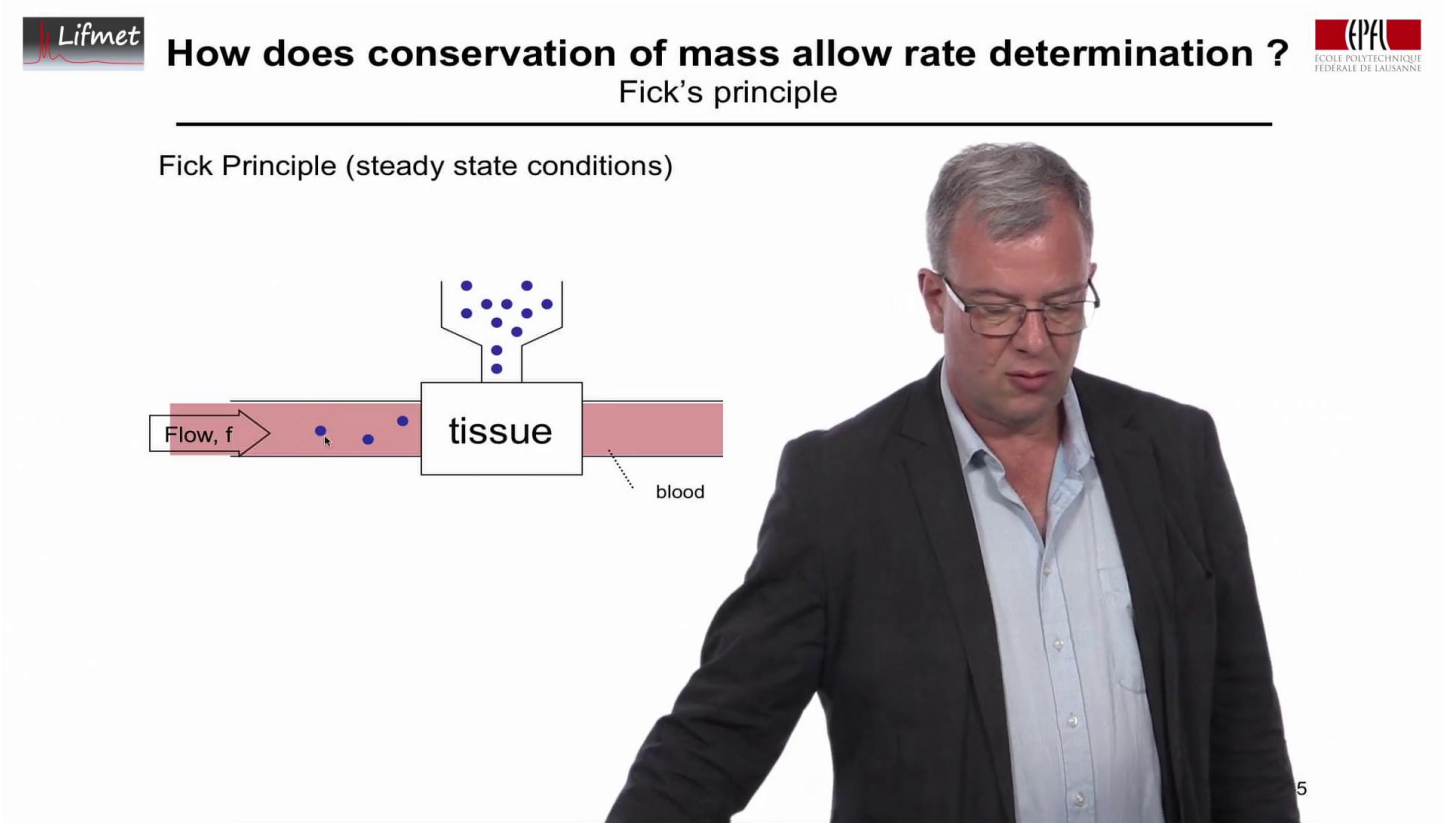


Now, modeling... assessing the kinetics, we're making steady-state assumptions. And there are two assumptions here that are important to mention. One is that the metabolic rate of the processes is not changing with time. So, we are assuming that, for example, the rate of glucose metabolism inside our cells as we do the measurement is not changing. It may change, but what does it mean if we make this assumption? It means we're calculating an average value of glucose metabolic rate. We're also assuming, as a steady-state assumption that the concentrations of all the compounds involved and the enzymes, etc., are constant during the evaluation period. With these two steady-state assumptions, we can actually have a relatively straightforward mathematical description of what is going on, and that is, as we shall see, that we can describe the processes, the metabolic processes with first-order rate constants. They are not true rate constants, so we'll call them pseudo-rate constants.

Notes

Summary

15m 44s



Before we go into the specifics of the mathematical description of predicting what's going on inside the cell based on what we measured in our pixels, and based on what we measured in the blood I want to introduce, however, a technique that was used more than a half-century ago that also allows a rate detemination. And here, the principle that is being used is conservation of mass. That already allows us to make some statements regarding what's going on in the organ of interest. And this is based on the Fick Principle. So, let's consider here the situation. We'll draw here the tissue, that's our organ of interest or the tissue. We have, of course, blood vessels that supply the tissue with nutrients and oxygen and that remove the metabolic end products. So, this a perfused organ. This is the blood, and here we have the blood that flows and the flow is indicated by the parameter *f*. So as the blood flows, it flows through the tissue, the number of molecules that goes in is equal to the number of molecules that goes out, if this molecule is not being used by the tissue. So now, let's assume that we are looking at a particular molecule here. We'll just stay abstract for the moment.

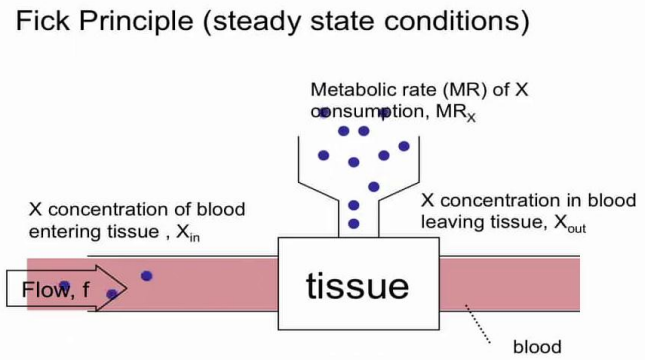
Notes

Summary

16m 59s

How does conservation of mass allow rate determination ?

Fick's principle

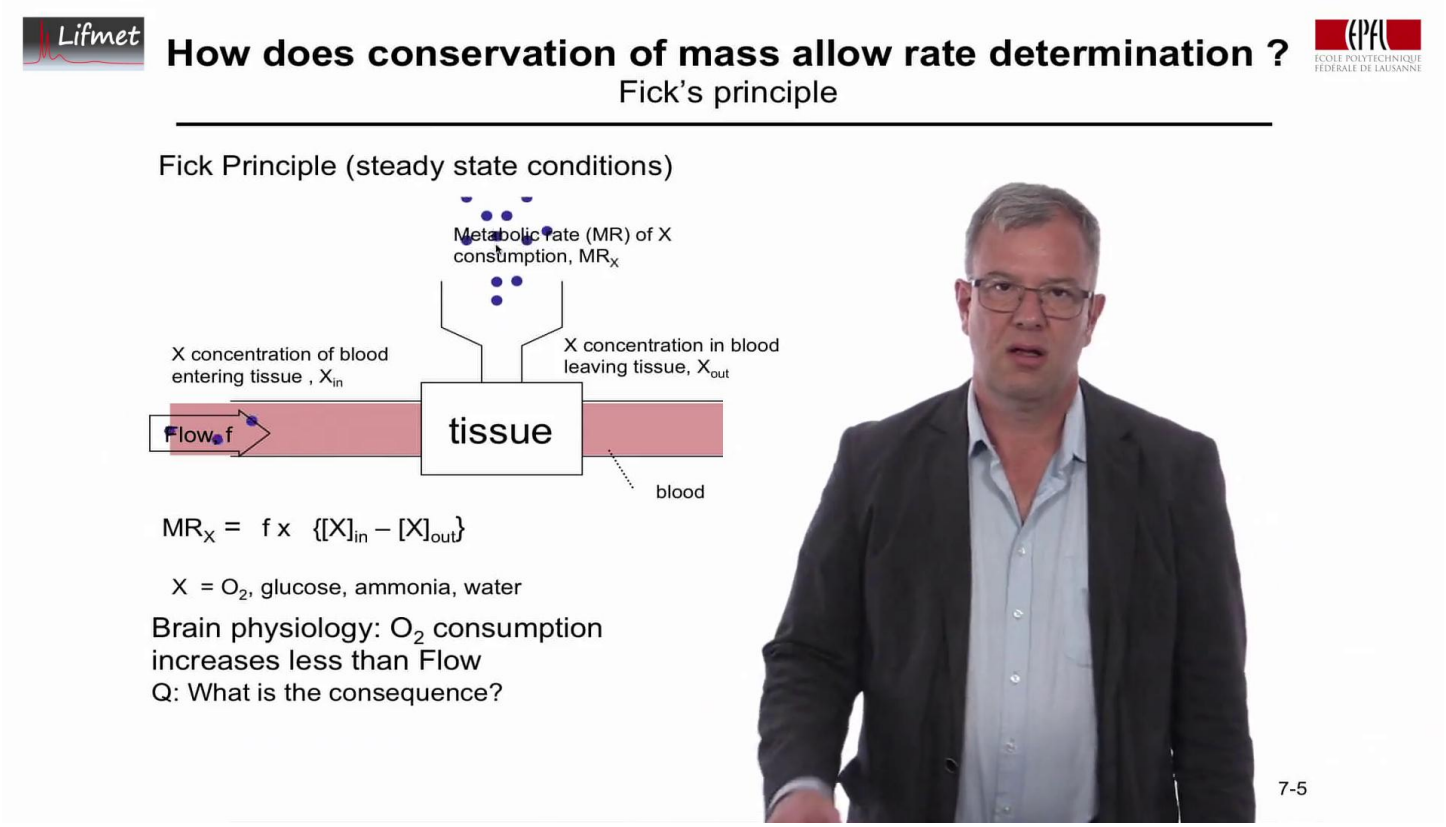


Here, these are the molecules that are coming in. And now the tissue is taking up these molecules. Taking it up, storing it, or taking it up and converting it to something else that we don't measure. So an example is, if we take oxygen oxygen 15, we've seen last week, it is a PET tracer, so if we take oxygen 15, molecular oxygen 15, we breathe it, then we get the oxygen here coming in and what goes out is H2O 15. We can say the same thing with other compounds. So, now we'll define this consumption of this particular compound x here I'll call it x. We'll call that the metabolic rate of x, or MRx. That's the metabolic rate in the tissue at the rate at which this compound is being consumed. Now, we'll have a certain concentration of this compound on the supply side, so, on the arterial side, that is, on the blood entering the tissue. I'll call this concentration "x in". And we'll have a concentration of this compound in the blood that leaves the tissue, and we'll call that "x out". And so now what we have is the blood supply is a certain number of molecules per second, a certain number of molecules per second or per minute is being removed and so, fewer molecules per minute are leaving the tissue, are leaving by the bloodstream.

Notes

Summary

18m 27s

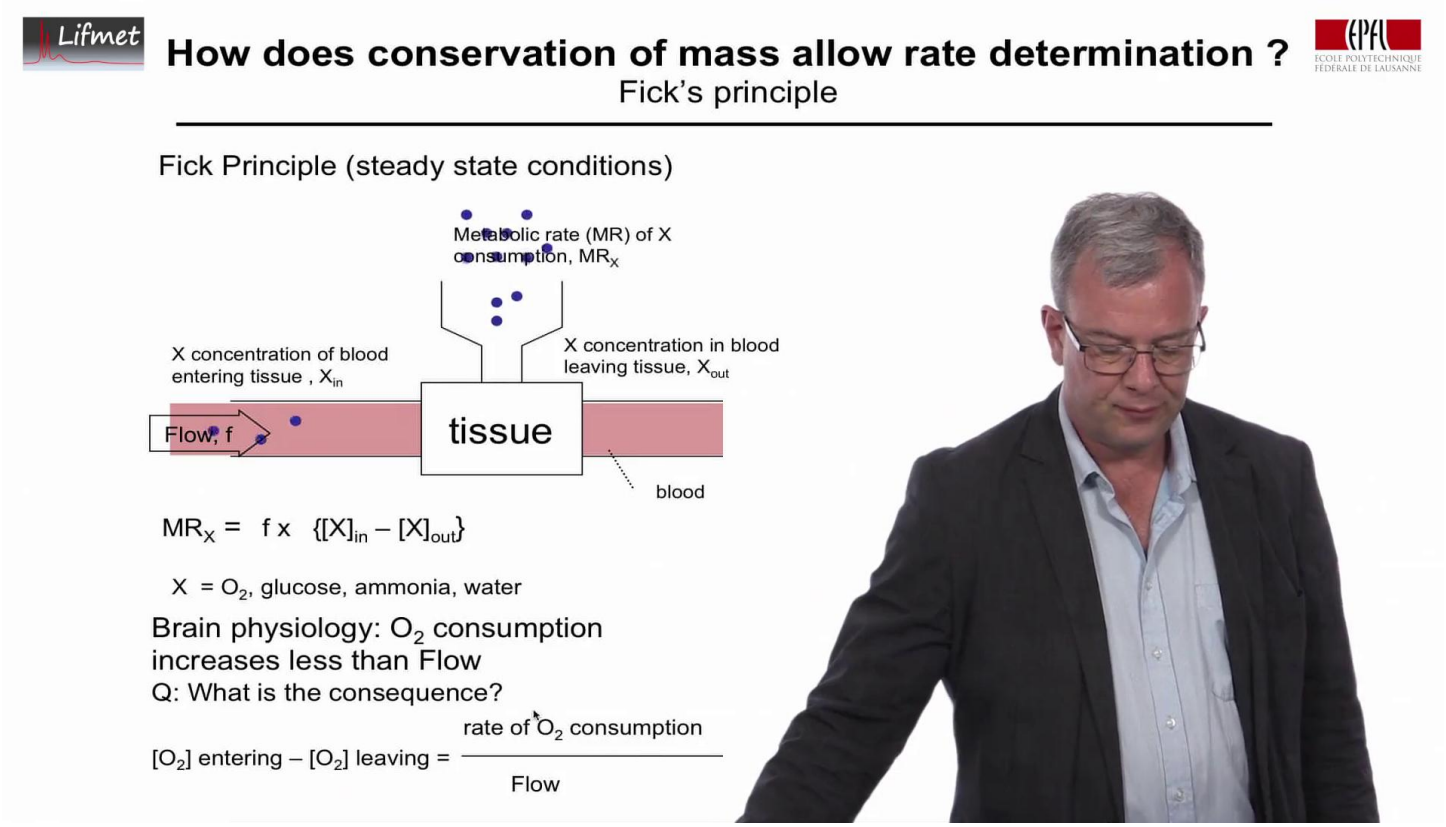


And if we now look at mass conservation this simply dictates that the number of molecules that is, the metabolic rate, that are being consumed is equal to the number of molecules coming in that's blood flow times the concentration of blood entering the tissue, minus the number of molecules leaving the tissue; that's blood flow times the concentration of blood leaving the tissue. So this gives us the metabolic rate of this compound. Now, *x* here could give you something specific. *x* here can be oxygen, so we have oxygen coming in, oxygen leaving, and oxygen being consumed. It can be glucose, can be ammonia, or it can also be water for this principle. Now let's look at brain physiology as an example. We know from physiological experiments and by experience that if we are in a dark room and we suddenly look, for example, at an image, we have in certain regions of the brain a quite strong increase in blood flow but hardly a change in oxygen consumption. So, oxygen consumption does not increase in parallel with the blood flow. So what is the consequence? Think about it. So we're increasing the blood flow much more than the consumption here, the metabolic rate. You can think of it...

Notes

Summary

20m 00s

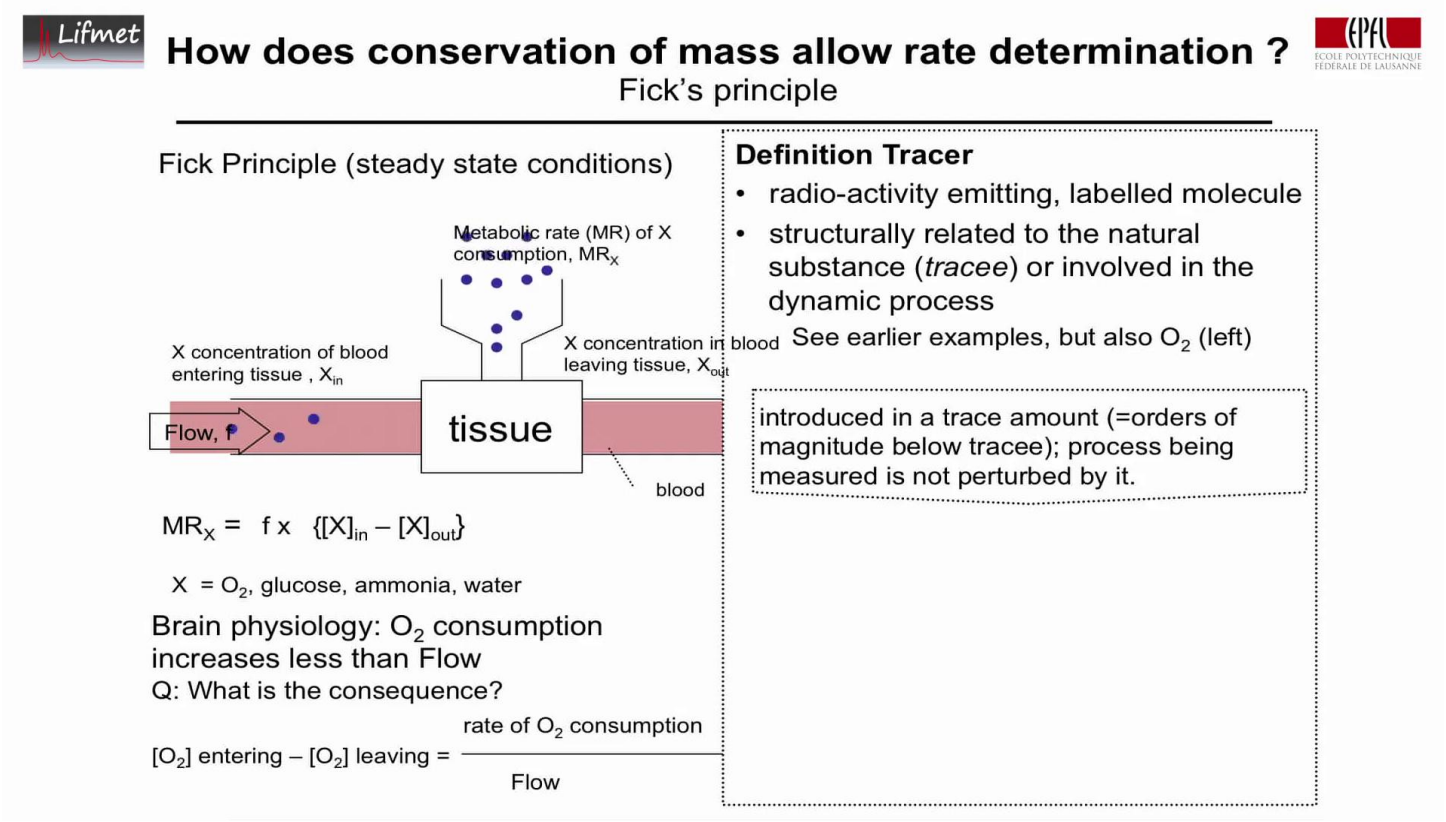


take an extreme case. Let's assume that the blood flow is increasing but the metabolic rate is not changing. So we have no change in oxygen consumption but we have an increase in blood flow. If we have no change in metabolic rate but this increases, the blood flow increases then the difference in concentration between what's happening in the supply side and the output side in the blood flow this difference has to reduce. So, now, the arterial concentration of oxygen is not going to change. There's no mechanism by which an increased supply will change the concentration of oxygen of the blood entering the tissue. So by consequence, the only thing that can happen here is that the oxygen concentration in the venous effluent from the tissue is increasing, and so, therefore, the concentration difference between in and out decreases. So, we'll take this particular equation here. We'll rewrite it in terms of oxygen, so oxygen concentration entering minus oxygen concentration leaving is equal to the rate of oxygen consumption divided by the flow. This hardly changes, this increases, this must be reduced this doesn't change, so the oxygen concentration in the veins has to increase.

Notes

Summary

21m 31s



And this, as we will see in a few weeks, is a major biophysical basis of a major imaging technique to study brain function, namely functional MRI. So, here I want to bring in some definitions. We'll talk about the tracer. Classically a tracer is a radioactive molecule. So it is emitting radioactivity, it is labeled with the isotope. It is typically linked to the molecule that we wish to characterize or sometimes even identical. So the natural substance is called tracee here. And that would be... one example we've already seen-- that's glucose, that's the tracee, and the tracer would be fluoro-deoxyglucose. But we can also have the native molecule so that the tracer is equal to the tracee and that would be oxygen, the example of oxygen 15 PET. Now, the term tracer also implies that the substance is administered in trace amounts. So that is very small compared to the concentration of the tracee. So in the case of deoxyglucose with PET, we can introduce very small amounts of fluoro-deoxyglucose on the order of nanomols, or micromols, micromolar, whereas the glucose concentration is in the range of millimolar. And this has the advantage that the introduction of the image contrast generating molecule does not perturb the process that we wish to measure.

Notes

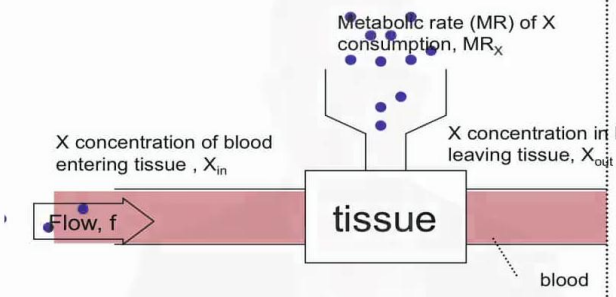
Summary

22m 54s

How does conservation of mass allow rate determination ?

Fick's principle

Fick Principle (steady state conditions)



$MR_X = f \times \{[X]_{in} - [X]_{out}\}$

X = O_2, glucose, ammonia, water

Brain physiology: O_2 consumption increases less than Flow

Q: What is the consequence?

$[O_2]$ entering – $[O_2]$ leaving = $\frac{\text{rate of } O_2 \text{ consumption}}{\text{Flow}}$

Definition Tracer

- radio-activity emitting, labelled molecule
- structurally related to the natural substance (*tracee*) or involved in the dynamic process

See earlier examples, but also O_2 (left)

introduced in a trace amount (=orders of magnitude below tracee); process being measured is not perturbed by it.

few tracer molecules contain radioactive isotope; others contain "cold" isotope

Specific activity (SA) = "hot" / "cold" tracer molecules

SA is always measured; [MBq/µmol or mCi/µmol]

→ convert measured radioactivity concentrations in tissue and blood to mass (correct for physical decay)

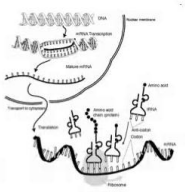
Now, we have the situation that the tracer molecules, they're not all going to contain the isotope. Some contain also the cold isotope, so they're not radioactive. And so what is important here is to look at the specific activity, and that is simply the ratio of hot to cold tracer molecules. Since the cold tracer molecules are predominantly dominating the molecules, this gives us a percentage of the molecules that are emitting radioactivity. This specific activity is always measured. It's typically measured in megaBecquerel per micromol or milliCuire per micromol. So it's given in a per-concentration unit, and we have to know it. So, the measured radioactivity is converted. The concentrations in the tissue and in the blood are converted to mass units, so that we have the correct physical units.

Notes

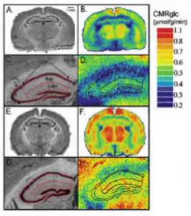
Summary

24m 34s

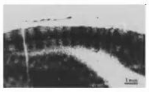
Credits



National Human Genome Research Institute
http://www.daviddarling.info/encyclopedia/G/gene_expression.html



Increased rates of cerebral glucose metabolism in a mouse model of fragile X mental retardation.
Proc Natl Acad Sci USA 2002, 99:15758-15763. Qin M, Kang J, Smith CB.



Unidentifiable source *(from the Internet)*

In all the discussions that we have today we are going to neglect physical decay, that is, we're going to assume the natural half-life of f18 which is 110 minutes, that we've taken this into account, we've corrected for the fact that without anything happening the signal intensity, the specific activity will decrease with a half-life of 110 minutes.

Notes

Summary

25m 43s