Biochemical Engineering
Prof. Dr. Rintu Banerjee
Department of Agricultural and Food Engineering
Prof. Dr. Saikat Chakraborty
Department of Chemical Engineering
Indian Institute of Technology, Kharagpur

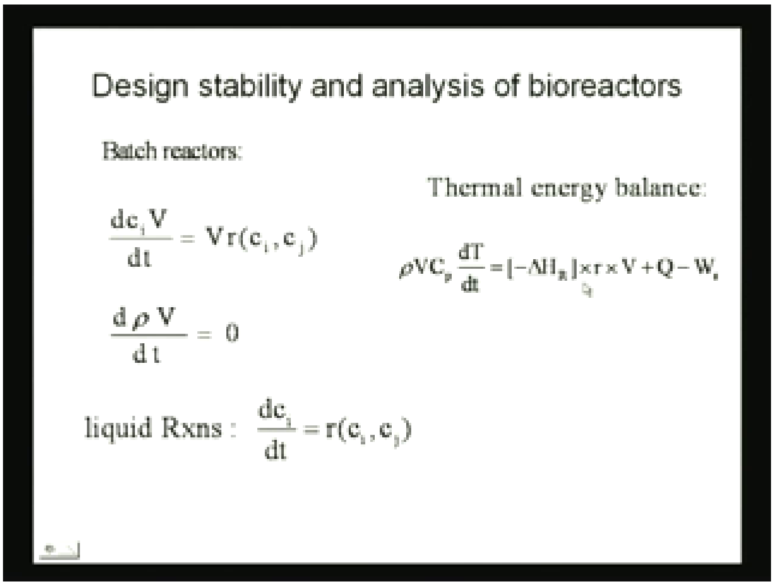
Module No. # 01
Lecture No. # 26
Design of Bioreactors

Today, we start a new chapter on design and analysis of bioreactors, and this chapter, in a way brings together, you know, much of what we had done in the last part of the course. And, the reason I am saying that, it brings together much of what we have done in the last part of the course because, we had looked at fundamental processes. So, we looked at the kinetics of enzyme; we had looked at the effect of mass transfer and that kinetics; we had looked at growth, cell culture and cell growth; we had looked at the effect of mass transfer and cell growth; we had looked at the effect of inhibition and so on, you know, on, on cell growth inhibition and a multiple substrates and so on and so. But, these are all fundamental processes, we look, we looked at. But, what happens to these fundamental processes when we bring them together into a real system, and that is a thing that we are going to study.

So, what is the real system? Because you are, if you are trying to culture a cell, you would need, on a, on a large scale, you would need a bioreactor. Now, the bioreactor could be, either a batch type of reactor, where you put in the stuffs and let it be there for a day. So, put in the stuff, we put it, put in the cell that you, excuse me, cells that you need to, that you are trying to incubate, put in the nutrients, allow it to stay there for a day or so, and then, you generate the products; so that, it could be a batch system; or, it could be a continuous system, that is, the feed, that is a nutrients and the cell is coming in, and it is going out at a continuous rate. Now, that continuous rate could be a very slow rate, you know. So, the resting time in the system of the reactor could be of hours and could be of, of the order of a day even; it could be a very slow rate; but still, you can have a continuous system. So, these are the two different kinds of bioreactors that we are going to talk about. But, what I am trying to say is that, these bioreactors bring in all the fundamentals, bring in the kinetics, the cell growth kinetics, the effect of inhibition, effect of substrates and so on. So, excuse me. So, as a result, what happens is that, any real system, when it brings in all the complicated kinetics and everything, turns out to be a little more complicated than the fundamental systems that we had studied. So, as a result, this is slightly more complicated, than what we had done before. Today’s lecture is going to be straightforward and simple. It is on just the design of bioreactors, but, when we go into the analysis of bioreactors, you will see, because of this different factors coming in, for example, the substrate and the, and the cell concentration, and that we, we have not, we may or may not even look at the effect of inhibition; but, when we do it, it is a lot more complicated; the effect of inhibition, the multiple substrates, because of all of these, coming in at the same time, in a real process.

Till now, we are looking, as I said, we are looking at only kinetics, or mass transfer, as the, as, as a theme, or a subject, to study; just as something of theoretical interest; but now, we are, we are trying to understand something, which is of engineering interest and this is a very engineering aspect of the course, where we are trying to understand and quantify, how much cells are going to be produced and what is the amount of substrates; very basic things; what is the amount of substrates that we, I need to put? What is the, how much cells are going to be produced? What it should be the size of the reactor? You know, what should be the resistance time in the reactor? In other words, what should be the size of the reactor? If it is a batch reactor, what should be the time we should give? These are questions that we will try to address and those will be coming in the analysis part, starting from the following lecture.

(Refer Slide Time 03:53)



Design stability and analysis of bioreactors

Batch reactors:

$$\frac{dc_i V}{dt} = V r(c_i, c_j)$$

$$\frac{d\rho V}{dt} = 0$$

liquid Rxns : $\frac{dc_i}{dt} = r(c_i, c_j)$

Thermal energy balance:

$$\rho V C_p \frac{dT}{dt} = [-\Delta H_R] \times r \times V + Q - W_s$$

Today's lecture, as I said is straightforward, and let us start it. It is called design and analysis of bioreactors. As I said that, the two kinds of reactors we are going to look at; our batch reactor and C S T R, Continuous Stirred Tank Reactors. And, the stirring, you know, has to be slow, because, you do not want very high stirring rate in these reactors with cells. So, if you write a batch reactor, you have studied batch reactors before. So, if you write a batch reactor, what would be the balance of batch reactor? What kind of balances you, you need to write? You just…

(( )).

What is that?

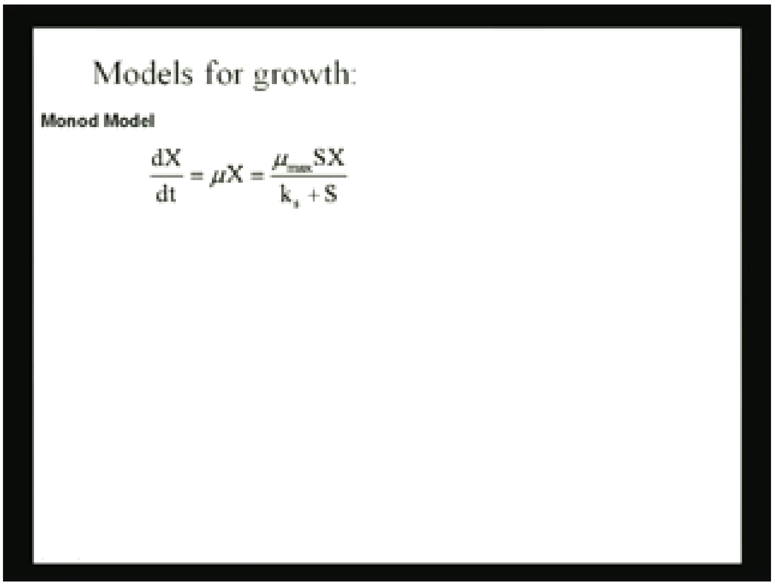
(( )).

It is just a volume balance and the product, one for the concentration of the products. So, this is, this is the balance for the concentration of the product, as you can see over here. So, d d t of c i times V. is V times r, r being the reaction rate, and r is the function of c i and c j, that is all components, fine. Now, my V is the constant out of that. So, if they, when it is going, it is going to be a constant? It is going to be a constant, if it is a liquid phase reaction, because, liquid phase reactions, typically do not change volume much; even if they change because of molar increase, it is not appreciable. So, if V, volume is a constant, then, you can take it out of the differential and cancel it, and you will get, d c d t equals r of c. So, this is the total volume balance. So, this is the balance for the particular components c i, and this is the total volume balance, rho being the density. For a constant volume-constant density system, this, you know, whole term would be 0 and you will, can take V out of the system.

So, this is for liquid reactions, or constant volume-constant density systems. Typically, more or less constant volume and actually, constant density systems. So, you can take it out of the differential, and you can write, d c d t equals r of c, right. And then, you can add in a thermal energy balance if you want, which is, if the temperature of the system is changing appreciably. Typically, it does not change appreciably, the reason being, you know, there is a, there is a range of temperature within which the system has to be maintained, and you try to maintain it typically within a small range. Within that small range, the changes are not large, and another, the, the reason the changes are not large because, these growth reactions that take place, do not have a very high activation energy. And, they do not really have, the heat of energy is not really very high.

So, typically, we neglect the thermal balance, but, if, to be on the safe side, and to be, you know, theoretically very correct, if you want to write a thermal balance, then, this is how it looks like; rho times v times C p and d T d t; so, rho being the density over here; V being the volume of the reactor; C p being its specific heat of the mass of, you know, whatever is there in the reactor, the liquid, average specific heat, T being the temperature and little t being time; minus delta H r is the heat of reaction of the growth reaction that is occurring. So, these are essentially, you know, any kinds of reactions, r could be any kind of reaction, but, what we are looking at essentially is, are, growth reaction. So, we are trying to culture cells over here, r being the reaction rate for the, for the rate of culture; V is again the volume; Q is, is any kind of heat source, or sink, that could be there in the reactor, apart from, apart from what is, you know, happening in the reactions. So, apart from the heat of reaction, if there is the, any other kind of heat source or sink inside the reactor, Q is that, and W is the work done by the reactor. This basic thermodynamics model, I am sure, all of you are aware of.

(Refer Slide Time 08:10)



Models for growth:

Monod Model

$$\frac{dX}{dt} = \mu X = \frac{\mu_{max} S X}{k_s + S}$$

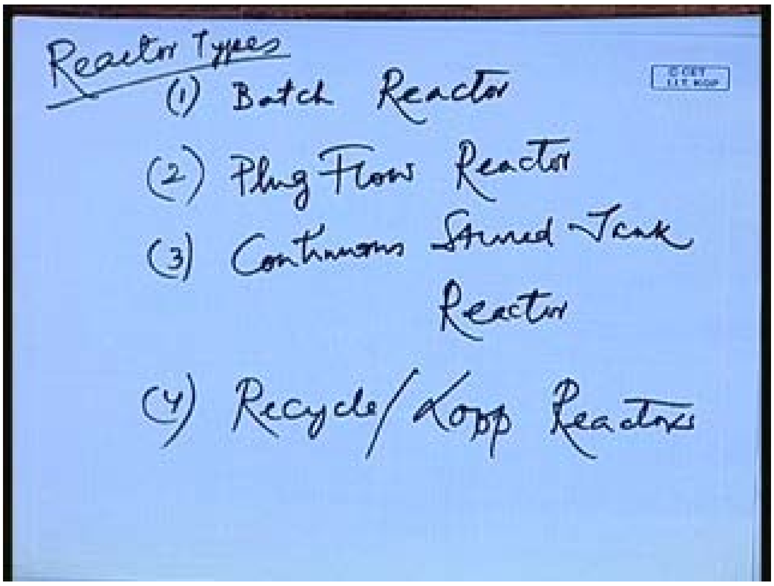
Now, the reaction rate. So, we had the reaction rate over here, r, and what should be the reaction rate? Now, as I said that, these equations are very basic equations and you can use them for all kinds of reactions that happen in bioreactors, but, we want to specifically look at, we have to specifically interested in growth reactions and we will use today, the very simplest kinetics of growth, Monod kinetics; and through much of this chapter, we are going to use Monod kinetics. But, you should be, you know, ready to deal with other kinds of kinetics, because, in the test, that is what I might give you; you know, with inhibition, like we did, with inhibition, with multiple substrates. So, what happens when you put these kind of kinetics? It is gets lot more complicated, the whole analysis, and you should be ready to do, do those kind of things; I, I tell you in advance. So, the Monod growth models. So, you know, you are aware of the Monod growth models. So, d x d t is mu X times mu, mu, mu x, where mu X is, mu is given as mu max time S over k S plus S.

Now, let me ask you this, is this, is this equation that I wrote for the Monod growth model, is this valid for all kinds of reactors? del x del t, whatever is on the screen, del x del t equals mu X, is that valid for all kinds of reactors, or is it valid for a specific kind of reactor?

(( ))

Resistance time is very large, no. In the limit of resistance time going to infinity, this is valid; not very large, but, that is a too theoretical answer. Why you do not give a more practical answer? That is correct, but, that is a very theoretical answer. Why do not you give a very, more practical answer to that? When is that valid? When is…Is it valid for…

(Refer Slide Time 10:10)



Reactor Types

(1) Batch Reactor

(2) Plug Flow Reactor

(3) Continuous Stirred Tank Reactor

(4) Recycle/Loop Reactors

See, for the kind of reactors we are used to, are, let me, let me go through this a little bit, and I wish, you know, I had. So, batch reactors, I think, this is the interesting thing I would do; I did not bring all the details of the notes. So, reactor types, then is…Then… So, these are the four reactors types you are aware of. Now, what I want you to tell me is that, I am not sure if you know, but, you can make a try that, which, out of these four, which was the first reactor that was discovered?

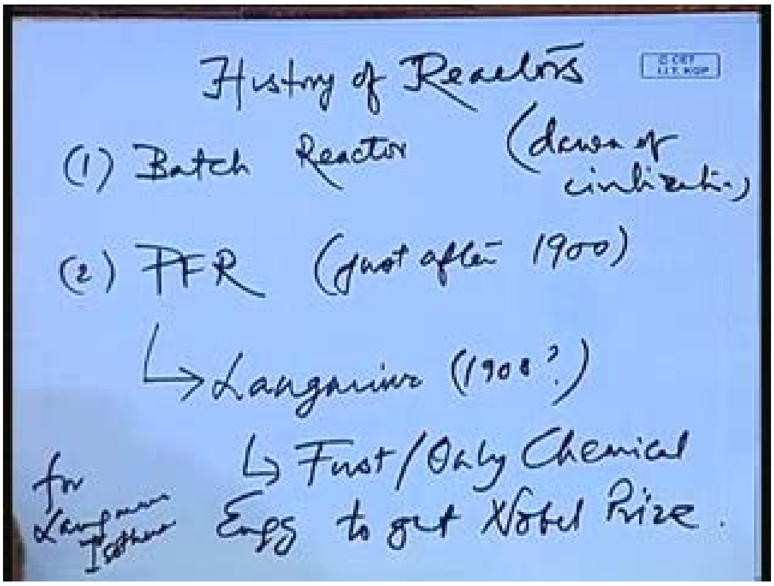
(( ))

Batch reactor; when was it discovered?

(( ))

Well, the batch reactor was the first reactor to be discovered, that is true; but, it was discovered at, not at 1800; it was discovered at the beginning of the human civilization; you know, cooking, for example, is a batch reaction. So, if you think that way, and, so, there is no account, exact account of when the batch reactor was discovered, because everything that had been there, had been a batch process, till now. So, the batch reactor is the most common, most natural of human reactors that had been used all through, through the whole of human civilization. As I said that, you know, fermentation came in much later; cooking is the, the very basic human activity, that started at the dawn of human civilization, is, is essentially, a batch reaction that occurs, right. So, that is true that, you know, batch reactor was in this around.

(Refer Slide Time 12:28)



History of Reactors

(1) Batch Reactor (dawn of civilization)

(2) PFR (just after 1900)

↳ Langmuir (1908?)

↳ First/Only Chemical Engg to get Nobel Prize.

for Langmuir Isotherm

So, let us say, history of reactors. Batch reactor was, you know, sort of dawn of civilization. The second one is a plug flow reactor, PFR; this is how we will refer to the plug flow reactor. This was developed in the early years of the twentieth century. So, 19 around 1900, just after 1900; just after 1900; I think, 1905 or something like that; do you have any clue, who could have discovered the plug flow reactor? It was discovered by, any guess?

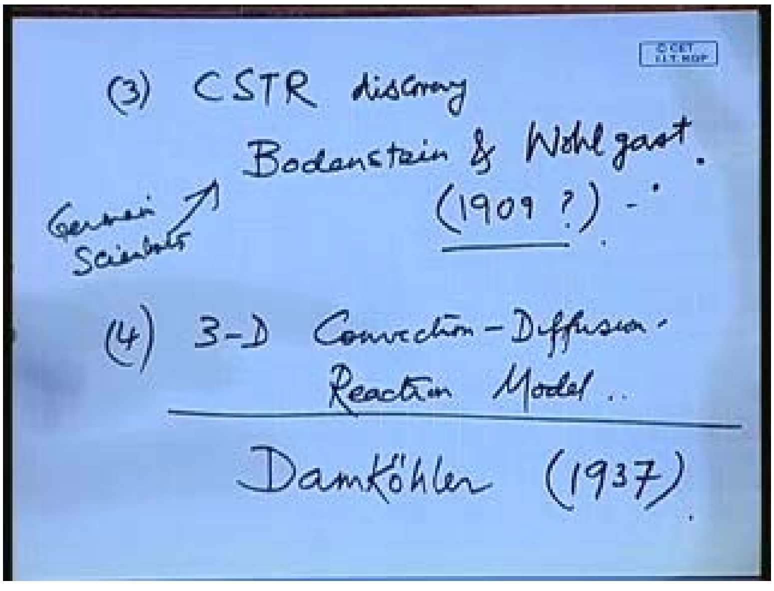
(( ))

Yes, discovered by Langmuir. Forget the year, around 1905 or something like that, 5 to 8, I think, around 1908 or something. Langmuir is the first and only chemical engineer to get Nobel; he is the first and only chemical engineer to get the Nobel prize. What did he get the Nobel prize for, do you know?

(( ))

Langmuir-Hinshelwood isotherm, yes, Langmuir isotherm. So, for, but, he was the one who, who discovered this. Now, the plug flow reactor was useful, you know, again, why was that useful, because, till then, processes are batch; which means that, you put the main and you know, wait for 4 hours, 6 hours and 12 hours, 24 hours to get the output. So, which mean, meant that, during the entire process, you got no output; but, the plug flow reactor was a first of continuous reactors, where you put things in at one end and you got things out at the other end; which means that, we had continuous supply of products, and that was necessary at the…And, this is, you know, even before the beginning of the industrial age. So, this was just, just before the beginning of the industrial age. And so, then, what happened was, the C S T R was discovered. C S T R was discovered little after that, and that became a big breakthrough in whole of chemical reaction engineering.

(Refer Slide Time 15:25)



© CET I.I.T. KGP

(3) CSTR discovery

Bodanstein & Wohlgast.

(1909 ?)

German Scientists

(4) 3-D Convection - Diffusion - Reaction Model

Damköhler (1937)

The discovery of C S T R. So, C S T R discovery was done by two German scientists Bodenstein and Wohlgast and I forget the year; I think it was around 19; again, I think 1908 or 1909, something like that; just, just around, I will, I will give you the years in the next class. I do not remember the, the year exactly. So, two German scientists, they were the one who discovered the C S T, the C S T R. Now, this was published, Langmuir's paper, I remember, was published in a Journal of American Chemical Society in 1908, I think, I remember the journal; I will give you the, all this references; I have these references with me, and I will give you those, those in next class and you can have a look at that. So, Bodenstein and Wohlgast discovered the C S T R model and that was quiet a breakthrough. The reason that was a breakthrough is that, you know, plug flow reactors are not always very useful, because, they are long and pipe kind of things. So, essentially, you know, a pipe kind of thing. And the problem with plug flow reactors is, you can, you do not have much control over the reactor; at least, not in those times. What it meant was, you only had control of what was going in and you did not really have control over what was happening inside; whereas, a C S T R is like a chamber, but, you just allow things to enter and take out. So, you have a continuous supply of products; you have continuous input of reactants and you have a lot of control on the system, because, you can stir it and you know, raise temperatures, decrease pH; do whatever you want to do to the system. So, C S T R model was a huge breakthrough and I am not sure, if this is 1909, but, around that time, Bodenstein and Wohlgast model. So, that, that was a huge breakthrough.

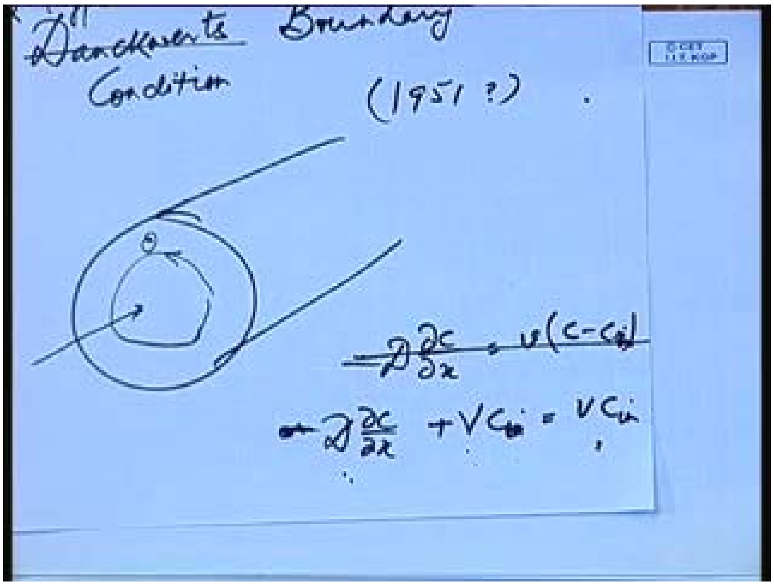
Now, what happened was that, this and this discovery of Bodenstein and Wohlgast was kind of, you know, did not come out to the Western world, alright. It, it did not come out to the English speaking world, alright; the reason being, this paper was published in German and it was not translated at that point of time and people did not get to know about this. So, this, there was a lot of obscurity that, this really happened and lot of other people tried to take credit for this; but, that the, that was, that was not correct and then, DamKohler also, you know, a kind of took, he is not directly, but, he was sort of, sort of trying to take credit for the C S T R model. But, the model was first discovered by Bodenstein and Wohlgast and that is kind of well known.

Now, the fourth thing, the important thing is not the loop and the recycle reactor models, but, something related to it. It is the three dimensional Convection Diffusion Reaction model. So, this is very important, also. The reason this is important is, this, the, the, this, you know, the way we write the convection diffusion reaction model now, including the diffusion terms, the reaction terms and the convection of the velocity terms out there, it was a matter of discovery. If you come to think of it, it did not drop from heaven. Somebody had to discover it, and that was the path breaking discovery in chemical engineering as well; in, in the whole of science as well, because, that was the first time, somebody showed that, it is not enough do some, you know, these, these are good practical models, the C S T R model and the P F R model; but, that was not enough. It was important to figure out, what are the basics of, of the model; what really goes into it and where the, how does the convection term combined with the diffusion term and the reaction term and so on. And, the person who did it is very famous scientist. He is a German again, and can you, can you, do you have any idea? Let us, let we try, what you think.

(( ))

Yes. So, I think, this was in, I have forgotten the year, but, with, this was in 1937 and this was a breakthrough paper, paper, you know, this DamKohler’s paper. And, this was again written in German and I am, I had a copy of this; I had a paper copy of this translated into English by one of my friends; he is a German scientist. And, so, this is the breakthrough paper, one of the greatest papers ever written in chemical engineering. The reason is that, what he does, he reviews the whole history of Chemical Engineering, DamKohler in 1937. And, he was the one, you know, who gave credit to Bodenstein and Wohlgast. He brought the, brought C S T R model into light. So, that… So, the C S T R model actually was discovered much before that, but, it was DamKohler who brought this into light, one more time, and, it was kind of lost. And then, he talked about the 3 D convection diffusion reaction model. He talks about simplifications of it. He showed, how the P F R model actually comes out of the 3 D convection diffusion reaction model under certain circumstances; a certain assumptions of axial diffusion, you know, negligible and so on. So, this was a breakthrough paper. The DamKohler's paper in 1937 was one of the greatest papers ever written in chemical reaction engineering and is a great review of everything that was going on. And, you know, so, he talked about the axial dispersion model; not just C S T R model, the axial dispersion model also.

(Refer Slide Time 21:31)



Danckwerts Boundary Condition

(1951 ?)

$$\cancel{-D\frac{\partial c}{\partial x} = v(c-c_0)}$$

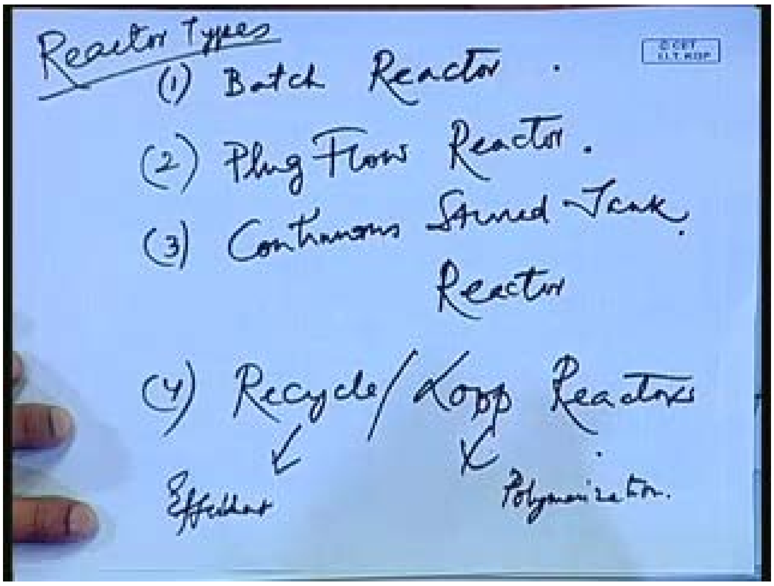
$$-D\frac{\partial c}{\partial x} + V c_0 = V c_{in}$$

And then, I think, Danckwerts. Then, Danckwerts, you know, he is one of the greatest known chemical engineering scientist. So, Danckwerts, we probably use Danckwerts boundary conditions a lot. So, Danckwerts boundary conditions is cited to 1951 or 52, something like that; 1951 say, to Danckwerts, but, it is essentially, was not developed by Danckwerts. It is now, now, it is clear, because of the, we have reviewed the history of it. And, it was first developed by Langmuir in 1908, in the A C S paper and then, by German, some German scientists like Bodenstein and Wohlgast, and then, again by DamKohler. So, this was shown again and again. So, Danckwerts boundary condition is, Danckwerts used to take lot of credit for this, Danckwerts boundary condition, but, it has now been shown that, the Danckwerts boundary condition was not found by Danckwerts and I can give you the exact years. I will bring the data in the next class. So, we would no longer call it the Danckwerts boundary condition; we just call it the flux type boundary condition.

So, it was, there is a lot of credit given to Danckwerts, because that, again, boundary condition was a path breaking thing; though we do not have, one thing you must know that, we do not have Danckwerts boundary condition or 2 D, two dimensional or three dimensional problems in the 3 D convection diffusion reaction model here. So, we have the 3 D convection diffusion reaction model and we are not aware of what the entrance boundary condition, flux type entrance boundary condition for the three dimensional system is. Till now, we are not aware of; but, what we are aware of is, if you write a 1 Ds model of this or a 2 D model of this, how to write the in boundary conditions. Because, what happens in a 3 D is, because, as soon as you take the reactor like this type, this is the reactor cross section and it goes like this. So, as soon as this 1 D or 2 D, it is all fine; but, as soon as this theta dimension comes in like this, this whole boundary condition can change; because, there could be a lot of effects of the theta direction. So, we are still not aware; but still, this, this was a breakthrough condition, the flux type boundary condition.

The reason that it was the breakthrough condition was, minus minus d del c, this is boundary condition, right, equals, v times c minus c naught, like this, or, c minus c. That what, what this said was that, whatever is coming in at the entrance, whatever is coming in, because of…What is the, what is the flux type boundary condition mean? It says that, whatever is coming in at the entrance, because of convection, equals what goes in, because of diffusion plus convection, right. So, that is the boundary condition. See, if I, if you look over here, then, you get minus c del c del x plus… So, if you put a plus over here, then, plus V times C in equals V times C in; yes, this is, yes, just take this form. So, this is what, this is what is coming in, V times C in, the velocity times concentration; I am going to pull this a little to the middle, yes; this is what is coming in to the system and what is going out is, diffusion plus convection, fine. So, this is the…So, there should not be any confusion about this, because, this is the very straightforward system. So, this is the, this is the boundary condition we have, the Danckwerts boundary condition. So, essentially… So, I will do a review, a little bit of more review of what is going on in the, in the, in this system, for the reactors; but, but, what I wanted to tell you is that, you know, there are these four different kinds of reactors.

(Refer Slide Time 25:49)



Reactor Types

(1) Batch Reactor.

(2) Plug Flow Reactor.

(3) Continuous Stirred Tank Reactor

(4) Recycle/Loop Reactors

Effluent

Polymerization.

Let me bring that page one more time, yes. So, there is a four different kind of reactors, the batch reactor, the plug flow reactor, the continuous stirred tank reactor, and the loop reactor. And, there is a certain history to it and as I said, this is the earliest reactor, the, at the dawn of human civilization. The plug flow reactor was around 1900; little before that also, may be 1800 and so on, before the start of the industrial age. The Continuous Stirred Tank Reactor was a huge breakthrough because, most of the industries shifted to the Continuous Stirred Tank Reactor, because of what, of, of the advantages of it. It was smaller; it was easy to handle; it was easy to control, easy to manipulate, and still you have a continuous product and a supply of products. And then came the recycle or the loop reactors. Can you tell me that, where are these recycle or loop reactors most used? Which kind of industry?

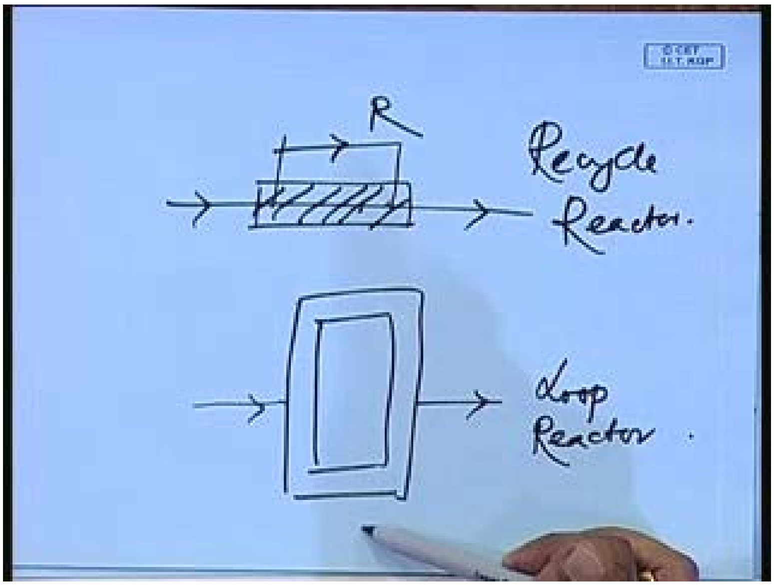
(( ))

Yes, that is one and what else?

(( ))

Yes. So, this is actually, recycle, loop is not used so much in a effluent treatment, and the recycle is used in effluent treatment, and loop is used in polymerization.

(Refer Slide Time 27:04)



So, do you know the difference between the loop reactor and a recycle reactor? So, the recycle reactor is something like this. So, you have the, this is the reactor, say, your main reactor; this is going out and this is the recycle; recycle ratio is r, say; this is the recycle reactor, clear. Something going out, things, things coming in, things going out, and there is a, the, there is, there is a recycle out here. And, loop reactor is little different. This is how it is. So, this is my reactor and this is the entrance, this is the exit. Do you see the difference? You see the difference between the loop reactor and the recycle reactor, the difference and the similarity. Similarity is that, things are being recycled in both cases, but, in a recycle reactor, the reactor is not, reactor is one straight thing and there is a little recycle going out; in the loop reactor, the reactor itself is a recycle. So, the major part of it, what is the major difference? In the recycle reactor, only a small fraction is being recycled; here, in the loop reactor, a large fraction is being recycled. Now, that would not work with this kind of setup. If you want to recycle a large fraction of it, that would not work with this kind of setup. So, you want to recycle a large fraction of it, you, you, you put this kind of setup, where the, everything goes around in loops and loops. You put in a, put in a little bit in, take a little bit out, but, rest of the things goes in again and again. Why are these recycle and loop reactors used especially for reactions which are very…

(( ))

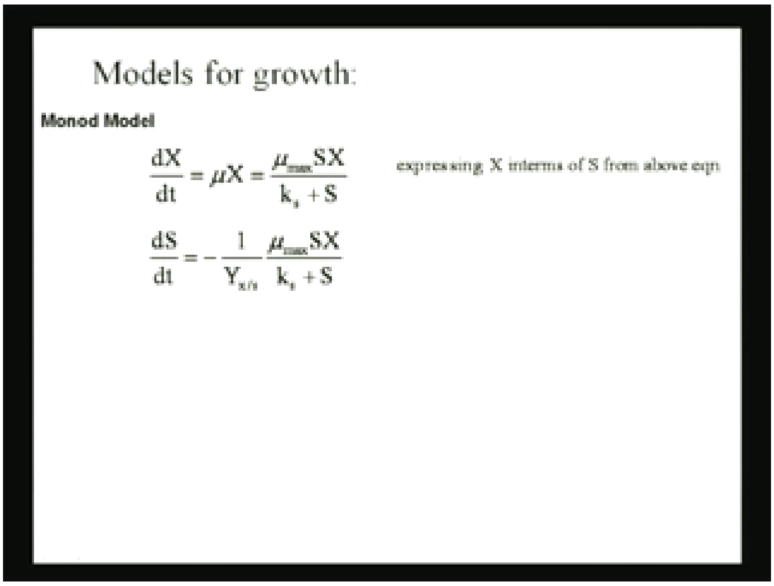
No, that is, that is not the point.

(( ))

Yes, reactions which are very slow, or low conversion reactions, so that, you tend to send them again and again and again to make, make it work.

So, these are the different kinds of reactor that we use. And again, you know, for biological systems, we can use all of these reactors, batch and plug flow and continuous and even recycle reactors; there is no, nothing stopping us from doing the same thing; but, when you use something like a recycle reactor, it is little hard, because, you have the cells within it and you, it is hard to recycle with the cells, without killing the cells; you know, slightly hard, but, you can. So, these are, in biological system, these continuous C S T Rs are called chemostats, and batch reactor is called the batch reactor and the plug flow is, is my…So, what I will do is, with this, history is interesting, but, I, I do not have, I did not remember that, I should give the history to depth. So, I do not have all the years. So, I will do quick review of the history in the next class and give you all the exact dates and the papers; you know, I, I have the citations to all the papers that were being written, and, and it is very interesting to be aware of the history of a process that we are, you know, part of. Because, unless, I think, this is something you probably, you are not aware of, what the history of these reactors are. So, there is a Danckwerts boundary condition; then, there is the axial dispersion model and you, you know, and you are also aware of the, of the surface renewal theory, right. So, surface renewal theory. So, that, there is a history to that also. Anyway, so, these are some of the things, I will quickly discuss in the next class.

(Refer Slide Time 30:28)



Models for growth:

Monod Model

$$\frac{dX}{dt} = \mu X = \frac{\mu_{max} SX}{k_s + S}$$

expressing X interms of S from above eqn

$$\frac{dS}{dt} = -\frac{1}{Y_{x/s}} \frac{\mu_{max} SX}{k_s + S}$$

So, let us go back to what we were doing, without the, you know, that was the creation, I think. So, what we are doing is the Monod model and what I asked you is that, that, this is where it started, is, are these, these are Monod growth model. Let us forget this; just look at this. So, d x d t equals mu X, that is my Monod growth models for X. What I asked you is, is this equation valid for all kinds of reactors and that is why, I digressed and started talking about different kinds of reactors. What, which kind of reactor is this model valid for? The way I have written it here, you should be able to tell this now.

(( ))

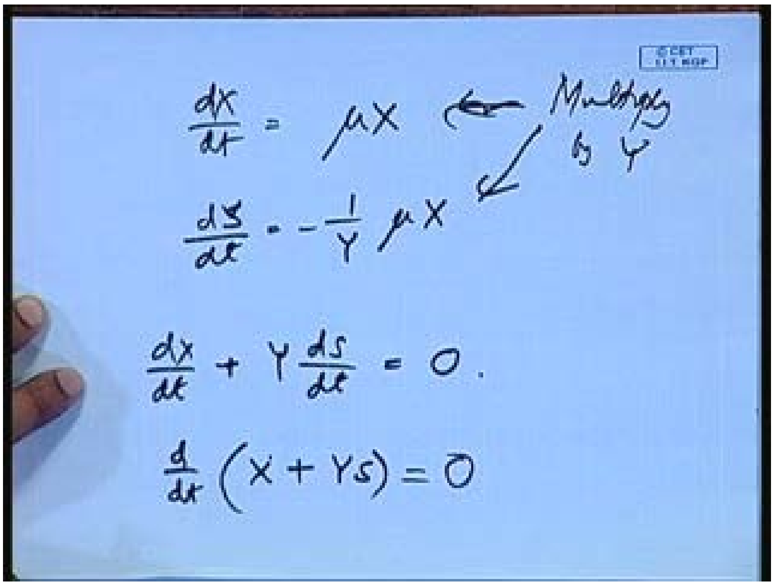
What about other reactors?

(( ))

Yes, because the batch reactor is the only kind of reactor which does not have a, which is not a continuous reactor. So, if you, if you have a continuous reactor, and obviously, they are going to be, there have to be input and output terms; so, the, it cannot, d x d t cannot be written in just a reaction rate. So, this is something I want you to be very clear, that… So, when it is a batch reactor, because, I see, see students keep doing it, despite telling them again and again. So, d x d t equals to reaction rate, only and only for a batch reactor; for all other kinds of reactors, d x d t is not just reaction rate, but, there are inputs and output terms that has to be added in. So, do not ever write d x d t equals reaction rate, unless it is a batch reactor, fine. So, this, this is, I mean, I tell students, but, I still keep seeing these mistakes on the answer sheets; so, very straightforward thing, but, you still need to remember it. So, in similar way, we can write the growth model, the d x d t; this is again for batch reactor, for the substrates. So, X is my cell and S is my substrate and the reaction rate is the same over here, except, there is a negative term outside, because substrate is being consumed in the reaction; whereas, cells are being generated and why is this Y x s, because, we discussed this in the last class, Y is the, Y is the yield of X per unit mole of S. So, here, we have used this as the, this is my yield, you know, reaction rate for X. So, you have to covert that into S; if you are doing molar balance for S, then, the yield of X per unit volume of S, if that is Y, then, 1 over Y is the yield of S per unit X, right. So, you just multiply it, that by that number, fine.

So, the, this is my basic equation for a batch reactor, and what we are, what we are doing now is that, we try to express X in terms of S. So, when we, when we try to do that…So, what do you see over here? You know, how do I, if I ask you to manipulate this system, how would you do that? Tell me quickly. If this two equations are there, forget it, you know, forget this; if I ask you to manipulate, so that, you get X in terms of S, how, how, what would be the first step? I, I discussed this in this earlier, in earlier, in this lecture, I think, when we were doing enzymes; there is something called method of invariants; what is that? (( )).

(Refer Slide Time 34:07)



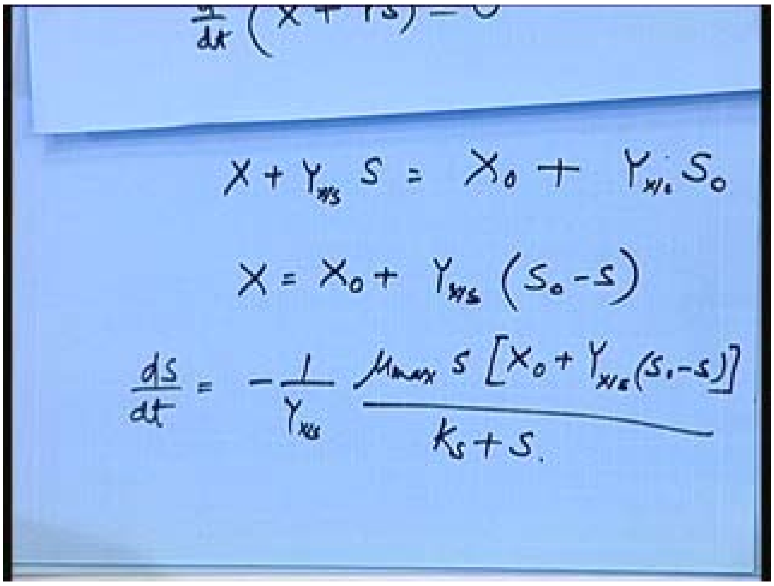
$$\frac{dX}{dt} = \mu X \leftarrow \text{Multiply by } Y$$

$$\frac{dS}{dt} = -\frac{1}{Y}\mu X$$

$$\frac{dX}{dt} + Y\frac{dS}{dt} = 0.$$

$$\frac{d}{dt}\left(X + YS\right) = 0$$

(Refer Slide Time 35:05)



$$\frac{d}{dt}\left(X + YS\right) = 0$$

$$X + Y_{x/s} S = X_0 + Y_{x/s} S_0$$

$$X = X_0 + Y_{x/s}\left(S_0 - S\right)$$

$$\frac{dS}{dt} = -\frac{1}{Y_{x/s}} \frac{\mu_{max} S\left[X_0 + Y_{x/s}(S_0 - S)\right]}{K_s + S}.$$

So, my d x d t…

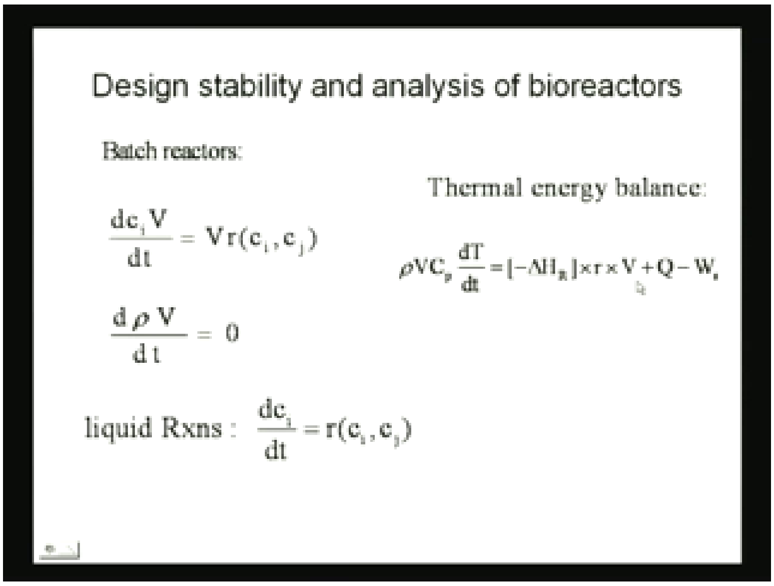
(( ))

Yes, no; do not divide it; you just use, what is known as method of invariants. So, d x d t equals mu X; d s d t equals minus 1 over Y times mu X. So, what you do is, multiply that first equation by Y, multiply by Y and then, add, fine. So, multiply, now, sorry, multiply this equation by Y and then, add. So, then you get, d x d t plus Y times d s d t equals 0, Y being a constant, fine. So, d d t of X plus Y S equals 0, fine. Then what? So, X plus Y x over s times S equals X 0 plus Y x over S 0. Now, if there is no, I think, what we are using here, yes, we still have X 0 here; so, then, X could be expressed as X 0 plus Y x over s S 0 S, fine. So, my d s d t can be now written as minus 1 over Y x over s mu max X 0 Y x over s S 0 minus S. So, that is fine and though this is non-linear, we can still integrate it, because, it looks like, we can use partial fractions to integrate this, right; appears to me, because, and just quadratic on the numerator and linear on the denominator. So, I think, you can use partial fractions (( )) fine. So, this is called the, what is this called? This is called the method of invariants, and you should not forget this, because, you know, this is the common trick.

So, whenever you see a nonlinearity out there, and here, for example, you know, let us see. So, here, for, yes, here, for example, whenever you see a nonlinearity out there, this is the nonlinearity and you see the same nonlinearity in both the equations; just constant, difference in constants; just manipulate the constant, add them up and get off, get rid of all nonlinearities, and then, you will get d d t of two, of a certain combination of two of the variables, any combination, but, certain combinations of two of the variables to be a 0. And, where have I taught this? Where you have, or where else can we talk about this? It is very straightforward; where else can we talk about something like this?

(( ))

(Refer Slide Time 37:30)



Design stability and analysis of bioreactors

Batch reactors:

$$\frac{dc_i V}{dt} = V r(c_i, c_j)$$

$$\frac{d\rho V}{dt} = 0$$

liquid Rxns : $\frac{dc_i}{dt} = r(c_i, c_j)$

Thermal energy balance:

$$\rho V C_p \frac{dT}{dt} = [-\Delta H_R] \times r \times V + Q - W_s$$

Which equation? It is on the screen. Which equation?

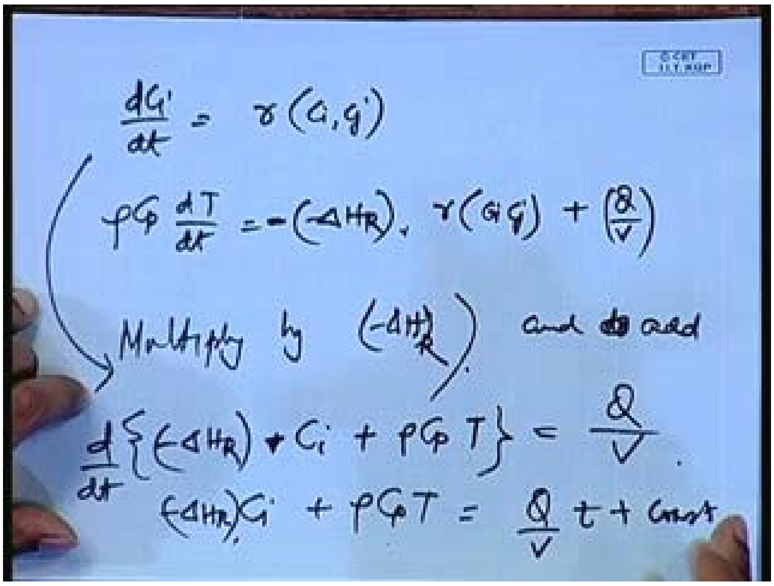
(( )).

First one, no. First one means, which one?

(( )).

(( )).

(Refer Slide Time 38:20)



$$\frac{dc_i}{dt} = r(c_i, c_j)$$

$$\rho C_p \frac{dT}{dt} = -(-\Delta H_R).\ r(c_i c_j) + \left(\frac{Q}{V}\right)$$

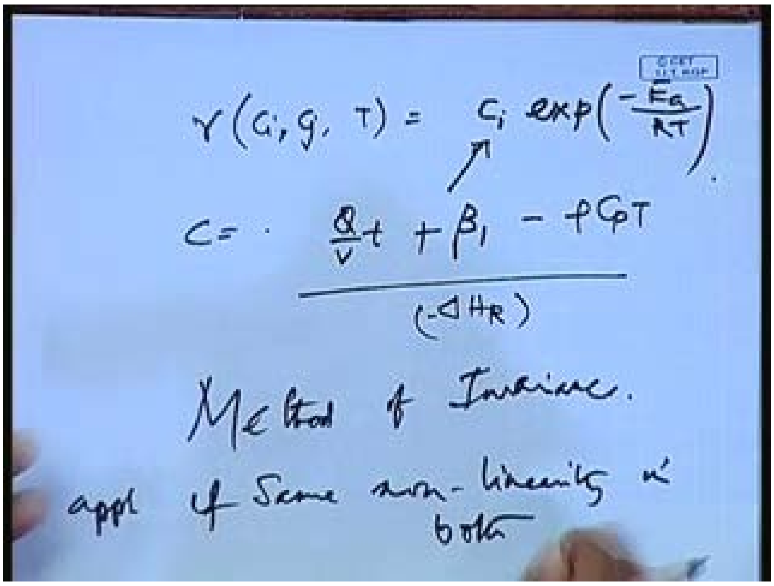
Multiply by $(-\Delta H_R)$ and ~~do~~ add

$$\frac{d}{dt}\left\{(-\Delta H_R) + c_i + \rho C_p T\right\} = \frac{Q}{V}.$$

$$(-\Delta H_R) c_i + \rho C_p T = \frac{Q}{V} t + \text{Const}$$

r is non-linear, yes. See, this equation, the temperature equation out here, and this equation, that is the last equation here and the temperature equation. So, let, let me show you, Q, typically Q and W are 0. Let us assume Q and W. So, W is the work done; Q is the amount of heat generated, apart from reaction in the system. So, these are typically 0; even if they are not zero, we can still take care of them; I mean, this is not a problem like, we, if you want, I can still assume it to be not zero, and still yes, we can do it, because it is a constant. So, let me show you. So, d c i d t equals r c i c j and rho C P d T d t equals minus delta H R times r c i c j plus, let us say, Q over V; Q over V is a constant. So, what do you do now? You multiply the first equation by…I think, there is a, yes, there is a sign mistake; I think, it should be minus of, minus delta H R; if that is positive here, then, that is fine. Yes, think, yes, it should be minus of minus delta H R; I think minus of minus delta H R out here; yes, this yes. So, what do you do? You multiply the first equation by minus delta H R. So, multiply by minus delta H R and add, and what you get is minus delta H R plus times c i plus rho C P T, the whole thing, d d t of that, equals Q over V, right; right, Q over V. So, this is the constant, Q over V; even if it is there, it is a constant. So, you can integrate this straight away and what you will get is, you will get a relationship between…So, c i minus delta H R, c i plus rho C P T equals Q over V, Q over V times t plus constant, constant. You know what your concentration was, at c equal t, time equals 0; you know what your temperature. So, you can evaluate the constant, but, you know, how does it help? The way it helps is, because, see, r, how is r, r typically?

(Refer Slide Time 40:36)



$$r(c_i, c_j, T) = c_i \exp\left(-\frac{E_a}{RT}\right).$$

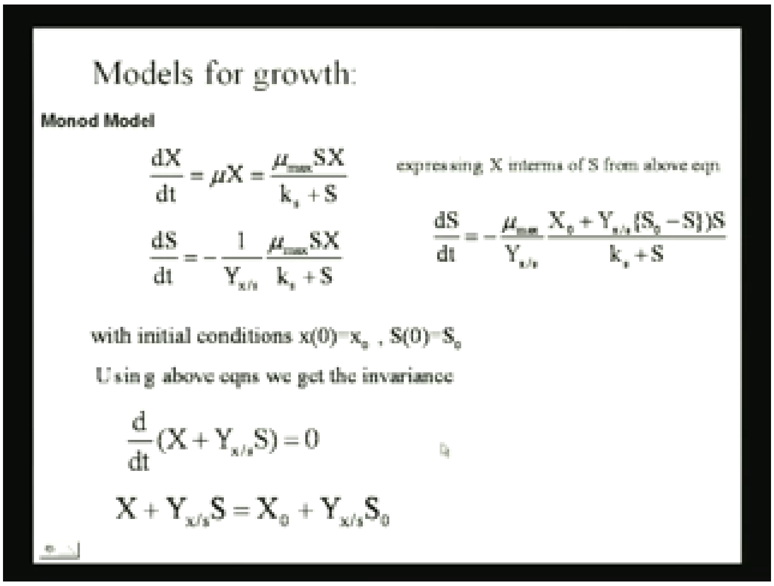
$$c = \frac{\frac{Q}{V}t + \beta_1 - \rho C_p T}{(-\Delta H_R)}$$

Method of Invariance.

appl if same non-linearity in both

r c i, c j, T, say for a first order reaction, it is typically c i times exponential minus E over R T, right. So, what you can do is, you can replace the c, because c is linear out here; you can replace this c, by what you got over here. So, c, you can write as Q over V times t plus, let us say, beta 1 is the constant, minus rho C P T divided by minus delta H R. So, you can replace that out here. How does it help? Here, when it is replaced, now, it becomes a equation in t alone, and you can go and straight ahead solve it, though it is still a non-linear equations. See, there is no escape from the nonlinearity; if it is a non-linear equation, however, you solve it, it is non-linear equation; but, the advantage is that, you have converted the nonlinearity of two equations to nonlinearity of single equation, with just one variable. And, that is much easier to solve any day, than two non-linear, I mean one non-linear equation is, obviously, half as easy to solve than two non-linear equations. So, that, and this is the method that you should always keep in mind. This is the method of invariants; because, always, when you get a system of equations which are non-linear, and you cannot solve them individually, or together also, just see, how you can manipulate these two equations; if, if…When can you manipulate these two equations? If the same nonlinearity occurs in both the equations. It is applicable, if same nonlinearity in both, fine. So, why I am saying all this is because, we are going to do, use some of these in the latter part of the course.

(Refer Slide Time 42:34)



Models for growth:

Monod Model

$$\frac{dX}{dt} = \mu X = \frac{\mu_{max} S X}{k_s + S}$$

$$\frac{dS}{dt} = -\frac{1}{Y_{x/s}} \frac{\mu_{max} S X}{k_s + S}$$

expressing X interms of S from above eqn

$$\frac{dS}{dt} = -\frac{\mu_{max}}{Y_{x/s}} \frac{X_0 + Y_{x/s}\{S_0 - S\})S}{k_s + S}$$

with initial conditions $x(0)=x_0$, $S(0)=S_0$

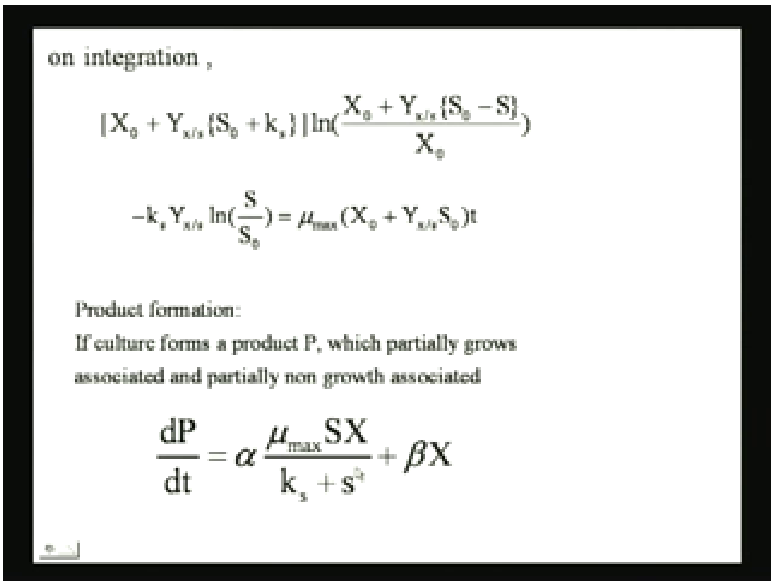
Using above eqns we get the invariance

$$\frac{d}{dt}(X + Y_{x/s} S) = 0$$

$$X + Y_{x/s} S = X_0 + Y_{x/s} S_0$$

So, so, anyhow. So, using the method of invariants, this is what we got. We just did the, did the calculation, I think, we have it out here; let us see here. So, here, on the page, if you see. So, we, we did this and the initial conditions are, X equals X 0 at t equal 0, S equals S 0. Now, this we have converted into a equation in S alone and we can integrate this, as we, as we said. So, this is the invariants and we walked through all of this.

(Refer Slide Time 42:23)



on integration ,

$$[X_0 + Y_{x/s}\{S_0 + k_s\}]\ln(\frac{X_0 + Y_{x/s}\{S_0 - S\}}{X_0})$$

$$-k_s Y_{x/s}\ln(\frac{S}{S_0}) = \mu_{max}(X_0 + Y_{x/s}S_0)t$$

Product formation:

If culture forms a product P, which partially grows associated and partially non growth associated

$$\frac{dP}{dt} = \alpha\frac{\mu_{max}SX}{k_s + s} + \beta X$$

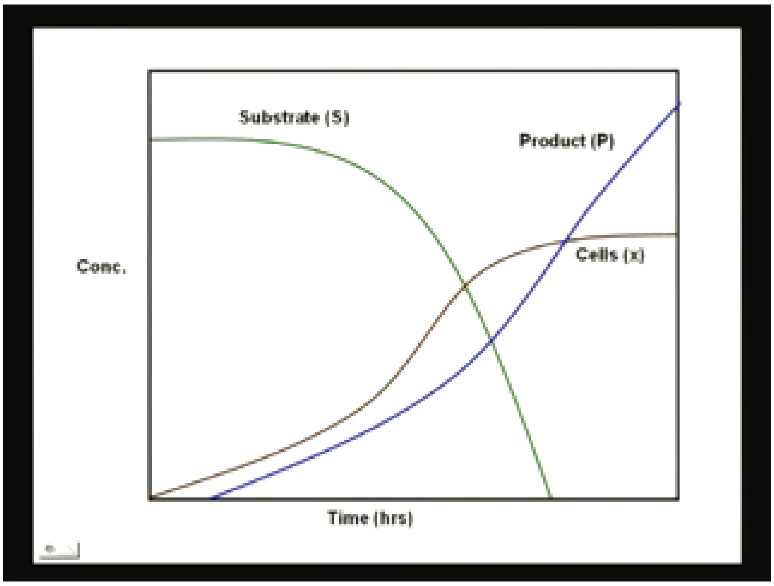
So, I think, I can just skip that, right. So, on integration, this is what you get. This is, this is the whole thing that you got, and how do you get this? Using, as I said, just using partial fractions, from this side, you know, just take it to the denominator, use the partial fractions; then, you will get exponential for both cases, and this is the solution you got. So, here X 0 is the cell concentration at time t equals 0 and S 0 is the substrate concentration at time t equals 0. There is a (( )) here, you know, and what is that? The (( )) is that, look at the, look at the equation; if X 0 is 0, then, this solution does not hold. So, you have to go back and resolve it, because X 0 is most typically, might be 0; you know, not, not most typically, but, might be 0; there might be cases, when you take a feed, which has no cell, I mean, not all times; but, there could be times, when you take a feed which has no cells at all, or very negligible concentration of cell, then, this will blow up. So, you just need to go back and put that, so, into the equation, and then solve it, rather than solve it and put it into the solutions.

So, if the product that is formed, is formed from a culture, that is, from the, you know, growth model that we gave, and there are some other sources of cell formation apart from the culture, then, what will you do? It is straightforward, you know. What is the growth model? The growth model is d x d t equals mu X. So, what you will do in that case is, just use that d x d t equals mu X plus beta X, where beta is from non-cultured sources. So, unlike mu, which is the function of S, substrate, beta is not going to be a function of S. It is simply going to be a constant, but, you will have a non-cultured sources, then you could use something like this. So, del P del t, the product formation would be, some alpha times mu times S X over X plus K plus S, that is the Monod plus model, plus beta X, and beta being a constant. And, how do you think, this will affect the product formation? It will, obviously, increase, but, in which way? In, in qualitatively which way it will increase? Obviously, it will increase, not to say that.

(( ))

Yes, slope will definitely change, but, what would, more than that change, is the saturation. Because, see, this, it reaches a level of saturation. Because, in the Monod growth model, there is a level of saturation; but, in this, the level of saturation would change. So, this is how it looks like, see. So, the product that you get…So, this is the product by the way, you know. So, slightly different from the cell; so, the cells are, you know, cell culture you are doing, and because of the cells, a product is being formed; I mean, I probably did not explain it, probably. So, this is the, we, this is different from what we did before. So, the cell, cell is being produced X, but, because of the cell, a product is being formed, which is, which is slope beta.

(Refer Slide Time 46:46)

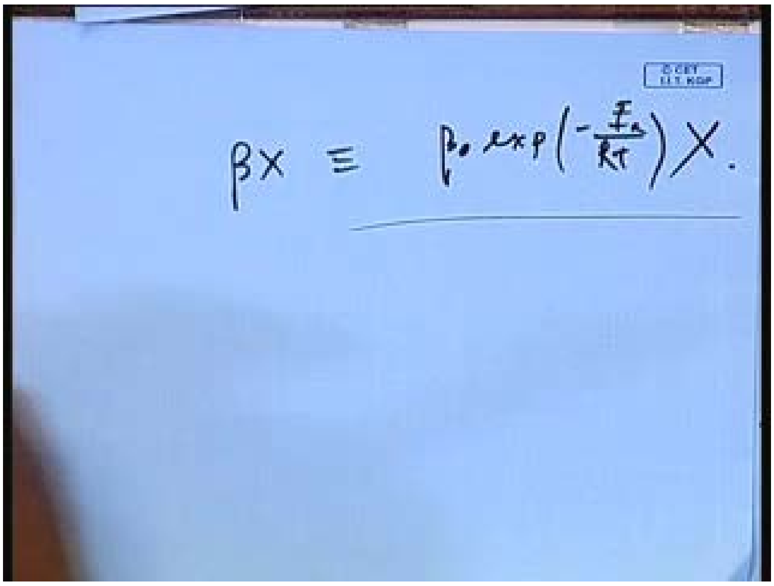


So, and the substrate is here, just like before, because the substrate is being consumed only in the cell formation. So, exactly the same, same way as before; the negative of Monod growth kinetics, as you can see, you know, just, just the thing flipped around, because, whatever is taken, the substrate is being taken up, consumed and not formed. So, it is exactly the Monod growth kinetics flipped around. The cells, again, you see, there is a Monod growth kinetics, the formation of the cell; but, the product formation is not going to saturate out as I said, because, there is a term, which is the, which is the constant and it goes, linearly increases, fine.

(( ))

It does not have to be linear, because, it depends on the product formation; but, it could be, it could even be beta x square, you know atmost; but, I, it is not going to be exponential of something. It does not have to be linear. See, big what is essentially happening, what we are trying to say over here, the cells are formed and the cells leads to some other products. Now, what that, could that reaction be? That could be a first order reaction; that could be a second order reaction; it can be third order reaction, or any higher order. It cannot be an exponential dependent. What, one possibility is that, the exponential depence on temperature; that, that is the possibility.

(Refer Slide Time 48:06)



$$\beta X \equiv \beta_0 \exp\left(-\frac{E_a}{RT}\right) X.$$

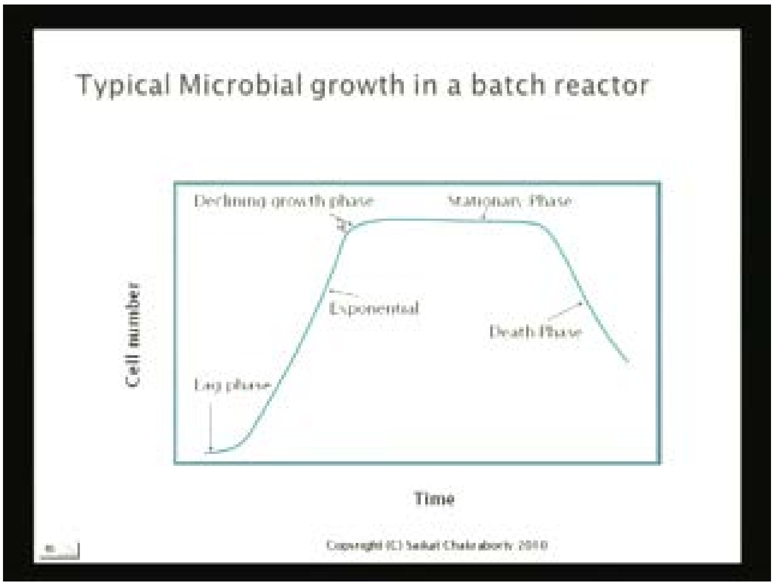
So, beta, for example, beta X could be such that, some beta 0 exponential minus E a over R T times X. So, that is the possibility. So, that is one possibility, or you can have, you know; or, beta itself could be, it could go as beta 1 or beta 0 times X, so, which, in which case, it could be a second order. So, anyhow. So, all we are trying to say is that, the products that are formed, you know, it, it is not going to saturate out; whereas the cell formation could saturate out and the substrate formation, substrate consumption could go on, and it can go reach 0, the substrate concentration; but the product formation will go, ok.

So, I think, the next thing that we will start is with, we do not have a lot of time today, but, just to give you a brief overview, is a concept of death of cells. We have been looking at the growth of cells, but, what happens when there is a death of cells, and the answer is…Would any of you want to tell me? It is very similar to what we did just now.

(( ))

Yes. So, this just could be minus beta kind of thing. So, if you remember, do you remember that, we did the microbial growth models and we talked about, I think, I have the slide with me, and I can even go in there; let us see; yes, here. So, here, you know we talked about the, yes, you remember this, right.

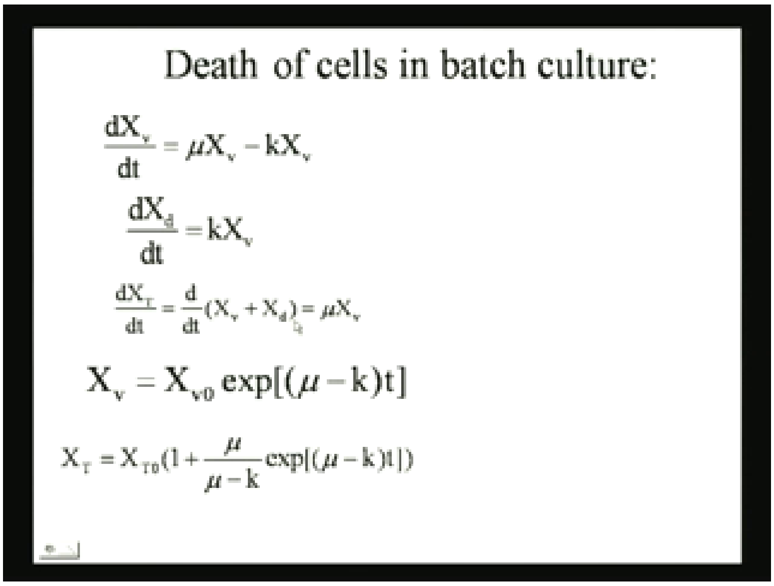
(Refer Slide Time 49:31)



Typical Microbial growth in a batch reactor

So, this is, this is, this is a phase; this is the exponential growth phase, right, and we model the exponential growth phase using this, and then, some saturation over that, and then, the stationary phase; the stationary phase was, when the growth of cells equal to the death of cells and the death cells is 1, when there is, growth completely stops and it is only death of cells, fine. So, this is exactly what we are trying to model over here.

(Refer Slide Time 49:55)



Death of cells in batch culture:

$$\frac{dX_v}{dt} = \mu X_v - kX_v$$

$$\frac{dX_d}{dt} = kX_v$$

$$\frac{dX_T}{dt} = \frac{d}{dt}(X_v + X_d) = \mu X_v$$

$$X_v = X_{v0} \exp[(\mu - k)t]$$

$$X_T = X_{T0}(1 + \frac{\mu}{\mu - k} \exp[(\mu - k)t])$$

So, this is the growth. So, the stationary phase and the death phase. So, that is what we are trying to model over here now. So, d x d t equals mu X minus k X. Why do I put the v? v is for some live cells, just for live cells. So, k is going to be, remember, k is going to be a constant; k is not dependent on the substrate, whereas mu is dependent on the substrates. d x d x d t d t equals k v, d d v, dead cells, right. And, I went on and talked about the whole experiment, if you remember, of doing another microscope and checking, how to check the number of dead cells, do you remember all that? So, this is, this is the very natural corollary of the entire incubation process and there is no running away from the fact that, there are always going to be a lot of dead cells, when you deal with them. So, again, you see that, we, we do some kind of invariants out here. We say the total number of cells that you have in the system, like we did in the last class, is not a constant, but, it is increasing with time, or decreasing with time, whatever is this, is that, and that is mu times X v, fine

So, X v is X v 0 times exponential mu minus k times t, right, from the first equation; very straightforward; and, X T is this. How do you get this? So, you just solve for X v, put it up into this equation, and then, you can directly solve for X T. So, this is what we get here. So, this, this number, you know, it depends, now. Now, what does it depend on? Like, you see, whether this is going to be a stationary phase, or whether it is going to be a decay, so, how, how do you define that? When mu is very close to k, for example, it is more or less in the stationary phase; because, this term is kind of 0, and you know, this, this term is close to 1, so, it will be a constant. When mu is less than k, then, it starts to decay in the death phase. So, typically, in the first part of it, the mu is much larger than k. So, it keeps increasing, and then, mu is, when it is close to k, then, it is in the stationary phase; and then, when it goes to decay...So, here is plot for that, yes. So, here, here is, here is the plot. So, in this, this, in this phase, mu is greater than k, much, much greater than k; in this phase, mu is more or less close to k. So, as a result, there is more or less constant and this phase, mu is much less than k.

So, I think, we will stop. There is some something else in the next slide is yes, next slide we go into the ideal C S T R models. I think, we will stop here with the death of cells and that concludes everything to do with the batch reactor model. And next class, we will start the chemostat, but, I will try to, I will remember to bring the years, and the references for the history, because, that is a pretty interesting thing, I think. So, is there any questions before we conclude, in today's lecture? Then, we will stop here today and we will continue with the C S T R in the next lecture.