

Well I'm not sure that I have a miracle solution to make sure that you're delivered dose is exactly like your planned dose, but hopefully I can give some insight into what's been going on in the field and incorporating what the previous two speakers have talked about into our dose calculations. So we have this great imaging method and we have this great registration method but how can we use this to the best advantage of the patient. I did, to acknowledge the people that I work with at Princess Margaret Hospital as well as the colleagues that have loaned me some slides to show you. So what's our motivation? In a very global sense, our motivation is to safely deliver higher doses to the tumor and reduce unnecessary dose to normal tissue and since this symposium's on 4-D, our method is to incorporate 4-D imaging, 3-D daily soft tissue imaging and deformable image

registration into the dose calculation with the hopeful result of having more accurate dose calculations which account for patient variations, both inter and intra-fraction motion at the time of and during the radiation treatment delivery. So what are the tools that we need in order to do this? The first is an excellent imaging method, both to characterize short term of inter-fraction motion and deformation such as 4-D CT, cone beam CT, cine MR, the second is to characterize long term such as deformation and changes of the patient, and capture the patient position at the time of treatment and both kV and MV cone beam imaging and CT on rails is a great way to do this. So once we have this imaging, we need to relate it back to our planning, our primary representation of the patient and so deformable registration can accomplish that, we need to have ability to

track the moving, deforming and changing regions of interest and then finally accumulate the dose that's delivered. So the outline of my talk is going to be to review the different methods of 4-D dose calculation to discuss the trade-offs between using predictive and direct dose accumulation methods, to review current research and integration of 4-D imaging and deformable registration into the radiation treatment planning and finally kind of some future directions in this area. So when including motion deformation and dose calculations, you can kind of divide this into two main models; predictive models which measure patient specific or determine population average motion and then apply this motion in the treatment planning process, calculate the delivered dose that you predict before the treatment begins and this is primarily used for respiration and intra-

fraction motion. Direct models would be to obtain patient position prior to each treatment fraction delivery and calculate the dose at that instance and map it back and this would be great for bladder, rectums, stomach filling and inter-fraction motion. So what data do we need for predictive models? Again, primarily for incorporating breathing motion so that's what I'll focus on. There's two main options, you can get two CT scans which is what was done before we had the great 4-D CT data at normal inhale and exhale and then interpolate in between these scans to simulate intermediate states that are necessary. Now that we have 4-D CT, we can get any where from two to ten or more intermediate states between inhale and exhale. So there's, I'm at the three primary methods of including or calculating the dose; the first is convolution and this is only

restricted to rigid body or 3-D transformations and these are some slides from Indrin Chetty at the University of Michigan that was, he published in Medical Physics that there's two methods that you can do, dose convolution and fluence convolution and I put this up to describe that when calculating dose, it's important to look at what dose calculation method that you're using because it can lead to different type results. The second is describing some data done by Paul Keall at VCU, where dose mapping was used. So he took a 4-D CT scan and divided it into eight respiration phases and then did deformable mapping of one to the other to create a four dimensional PTV that encompassed all of the motion. Calculated the dose on each of these 4-D CT

representations of the patient and then map them back to the primary data set that was used for the treatment planning to calculate the dose. So this assumes that the patient is breathing the same way all the way through treatment. The next one is dose interpolation, which is some work that I did at University of Michigan based on mutual information alignment between only an inhale and an exhale CT scan. We then interpolate, we knew the dose calculated on the exhale and the inhale dose grid and we interpolated for immediate positions based on a breathing phase so we took the breathing parameterization from Anthony Lujan and created this total dose at each X, Y and Z point so we did it on a voxel by voxel basis and incorporated the transformation, the time weighting and the dose on the inhale and the exhale data set. So once we have these 4-D

dose calculations, how can we evaluate whether it's influencing our plan, what we need to do to change the plan, how to make it better or what they, the error is if we use only a static plan. We can look at a change in plan descriptors such as dose volume histograms, isodose lines, dose difference plots or quantitative changes in prescribed dose if you use an NTCP dose calculation to prescribe your dose, you can look at quantitative changes. This is again a slide from Paul Keall using the dose that I showed in the previous slide, so this shows the dose volume histogram for the PTV where the colored lines are the single phase plan and the dash line in that combined with all of it. So you can see the PTV is pretty close together but that for the lung and especially the cord and heart, you're gonna have significant variations between what you would use if you only had a static plan

versus what you would get if you incorporate this breathing motion so this is quite interesting to look at. This shows the difference between using a actual motion tracking for a 3-D versus a 4-D and again you get great coverage for your PTV and sparing for your cord, heart and lungs. And this shows the difference in isodose contours between the 3-D and the 4-D plan so you can see the dose reduction when you incorporate this motion. This shows some results, again, from Indrin Chetty and Mihaela Rosu on the difference between using dose convolution and fluence convolution so again, indicating the importance of knowing what the limitations are of you dose calculation method and this shows the results, again, this is for a 3-D transformation but you can see between the static and the convolved dose that you can have a prescribed dose difference of up to

seven gray. So the normal tissue toxicity is underestimated when you only use a static calculation. This side indicates that at higher doses, there's a higher difference so as we continue to dose escalate for treatment plans, it becomes even more important to really

know how we're delivering the dose. This is the results of the liver deformation that I did at University of Michigan, so this is a difference between including deformation and a static between rigid body 1-D motion and the static plan and then the difference between deformation and rigid body so you can see that we really need to look at deformation and that rigid body alone is not necessarily enough and that for this case, you can see that the rigid body overcompensated for the motion compared to including the deformation and we had dose differences of up to 20 gray, or 20 percent. We also looked for the liver

cases at the changes in prescription dose, we had a clinical protocol that prescribed dose at a fixed NTCP and we considered a significant, a clinically significant change of something that changed the dose by more than one point gray because that was the fraction size. We looked at simulated tumors and this superior intermediate regions of the liver and then also the actual patient so this is data from nine patients and you can see that 3-D of the nine patients would have a significant change in the prescribed dose compared to the static calculation and if you only included 1-D rigid body motion compared to the deformation, you would still have that same three patients. So this is 33 percent of the cases would benefit from including deformation in the dose calculations. We also looked at, since we had 33 percent of the patients, is there some way we can pick

out ahead of time what patients would benefit from including deformation in their dose calculation and of course since we're the NTCP calculation as effective volume decreases, the importance of including deformation increases. The percent of the PTV volume outside the liver also somewhat correlated with the importance including the deformation, this is the absolute dose difference in gray here versus the percent volume of PTV outside the liver for the static and the difference between rigid body and static and deformation static. We also looked at bending energy which Sarang described a little about that's computed when you use mutual information, thin plate splines, and found that you can correlate this deformation and the dependence that that has on the significance of including deformation in the dose calculations as you would expect.

There's also, as I described, the direct methods of calculating and this would be if you could calculate the dose that a patient on the fly so every time the patient laid down, you would get a 3-D volume set for that patient and then replan and calculate what the dose was so we need daily 3-D soft-tissue imaging at the time of treatment. There's some work doing pseudo-direct methods which uses adaptive offline or some online and daily imaging and physiological motion that's not periodic, that can't be predicted, necessarily, ahead of time. You can get some general ideas of the range of the standard deviation but not the exact at the time of treatment, so this is good for bladder, rectal and stomach filling and prostate and cervical motion that's associated with it. So this is a organ dose reconstruction system that was developed by Di Yan and colleagues at William

Beaumont Hospital where they use a finite element registration process and set up the daily position of the patient and they do five imaging times and then do adaptive treatment planning on the patient so these, again, they used deformable image registration which is based on organ volume and surface delineation representation and true biomechanical material properties to describe it and then they have a point surface

displacement to set their boundary conditions for the finite elements analysis and they reduce the uncertainty in this point to point displacement by a minimum consuming energy principle and then run the finite element analysis calculation. This shows some of their representations of the bladder, prostate, seminal vesicles, and rectum, and the motion that they get from these results so you can see the bladder motion and the A/P

superior and inferior and right/left direction as well as the rectum, you can see that it's more biased than the anterior part. Prostate motion and deformation and the A/P, superior and inferior and right/left as well as the seminal vesicles. So they included that and looked at the difference in their isodose lines for conventional IMRT and these gray lines indicate the position of the bladder and rectum and prostate regions over these five CT imaging days so the darker indicates more frequent position and then you can see that adaptive IMRT feedback loop, they were able to minimize the dose to the rectum and the bladder. And again looking at a dose occupancy frequency chart, you can see that you're able to spare dose to the rectal region. So where can we go from here, how can we take this and do even more novel and exciting things, how can we incorporate deformation

into the dose delivery, possibly combine both predictive and direct methods to make the most conformal plan possible, how can we all get multi-organ deformation in dose calculation, so not just calculate the dose to the lung when it's deforming or the liver when it's deforming but if you have a tumor that's close to normal tissue and that's your limiting structure, how can we make sure that we're accounting for that correctly? How can we involve deformation in the desired dose placement and include deformation in dose response follow-ups and when we get an image three months or six months out that's changed, how can we map that back and see if we have a recurrence, where and what dose that actually got? So deformation and dose delivery we've heard a few talks that were very exciting at APM this year on tracking the tumor and deforming the beam's

eye view accordingly. There's the iris system at Massachusetts General Hospital, the system by Paul Keall at Virginia Commonwealth and the 4-D tomotherapy with the real time tracking that was described just to name a few. This is a picture of the iris system, from Ross Berbeco at Mass General and then this is a slide from Paul Keall showing the (inaudible) showing the tracking of the tumor as it deforms real time while you're delivering the dose. So can we combine a predictive and a direct method? We saw with the 4-D imaging, that the patients don't breathe the same and we've learned from active breathing control setups that your exhale position may vary with respect to your bones so how can we kind of combine in what we know about the patient and their breathing motion with what they're doing on that day and especially for lung tumor patients as they

get treated and as their treatment progresses, their tumor tends to respond during treatment and then their breathing may differ so how can we take that into account too? So by combining them we can allow optimum treatment plan development with the possibly of refinement during the radiation treatment course. So we can do daily soft tissue imaging combined with deformable patient models to allow predictive models to be refined by image guidance for both optimum dose delivery and accurate dose calculation. So some work that we're doing at Princess Margaret Hospital involves

multi-organ, finite element model based deformable image registration so we directly deform the liver in this case and then the kidneys and the stomach follow accordingly and we're developing this process to incorporate both multi-imaging modalities and some

cine MR and our cone beam CT to provide both the predictive and the direct optimization for the patient. So for example, we have a patient that we've CT scanned, for this case, it's just two phases at inhale and exhale and we deform these two based only on a surface projection method which I'll describe on Thursday in more detail, but the, we deform one liver surface into the other by assigning correct material properties at interfaces between the tumor and the liver we're able to get the tumor registration without applying specific boundary conditions or using any image intensity information from that so we can get an optimized PTV margin or way to calculate this into our treatment planning. So then how can we relate that to the way the patient is set up and the way the patient's breathing on that day? So this is a cone beam scan of a liver patient and you can see the liver in

contour with that but at this time, we're not able to actually see the tumor so using this method we're able to map on the tumor into that so then we would be able directly deliver the dose to where we wanted to so combining both the predictive and the direct method and you can imagine if this tumor was in the inferior region of the liver and we cared about the kidney dose then, that we would also be able to map on the kidneys even if we couldn't see it on the image or even if it was below the imaging, what we had imaged so we would know that as well and be able to calculate the dose to it on that time. Deformation dose placement, registration of MR PET, all these functional imaging modalities onto our next representation is another exciting thing to include and to make sure that we're delivering it exactly where we want to deliver it. Tracking deformation

and dose response, our interest in the patient doesn't end when they get done treating, we want to be able to look at where they respond, where they fail and what can we take home from that to refine our process and make it better so deformable image registration allows us to take our image down the road and map it back and find out, okay, this is where we're having a recurrence or something and find out what the dose was or this is where we're getting normal tissue toxicity that we weren't expecting, what was the dose there and how can we calculate it better. Just a few notes of caution on doing this, deformation and IMRT, Thomas Bortfeld has reported that when you have many fractions, that this tends to blur out and you don't have to worry about it but as hypofractionation becomes more and more common in our field, we really have to start

looking at whether this is gonna play a significant effect and what the relationship between this will be. Motion and deformation and patient breathing, this is some data by **Indrin** Chetty and Mihaela Rosu that shows the difference between and N equals three in the breathing parameterization and an N equals one, so not all patients breathe the same and not all of their dose should be weighted equally when mapped back and you can see that if the patient spends more or less time at exhale, this is gonna change and this example it shows that we have minus 15 and plus 20 into plus and minus 35 percent so we can have a significant change as well and we need to take that into account. So in

conclusion, the inclusion of deformation and dose calculation can significantly change the prescribed dose that we deliver to the patient and the change in normal tissue

complication probability. With the proper tools, including deformation and dose calculations, may not increase the treatment planning time, many of these are automated and can be done without having someone sit right there, so it can be done really quick. Hopefully with more and more work, we make it so that we can calculate it on the fly in a very short time so we can do it at the time of treatment. Including deformation can more, can more accurately deliver the dose placement and the response correlation and accuracy of 4-D dose accumulation is dependent on accurate deformable registration to relate multiple instances of the patient from one common representation for dose summation. So I can't stress this enough that this is, we can't include the deformation unless we have

an accurate dose or registration method and the inclusion of organ motion and deformation in 4-D dose calculations has the potential to reduce normal tissue toxicity and improve tumor control through safe dose escalation and margin reduction. Thank you.