

Well, they tell if my talk is really a risky talk...a computational anatomy in radiation therapy and I think most of you probably are not aware of computational anatomy so I will..first of all, let me do a formal disclosure statement. I have no formal training in radiation therapy or physics and I'm at a AAPM meeting. I've gotten all my training in this from lucky from excellent mentors particularly Ed Cheney, Dr. Rosenman, \_\_\_\_\_ Chang, and also I've had fantastic luck in collaborating with wonderful people like Paul Keel, Keith Majors and George Jenkins, \_\_\_\_\_ and I'll be showing results in collaboration with them. One of the things most..first, here's an outline of my talk. I'll be going with motivation, then introduction to computational anatomy, why is it important and go through some mathematical foundations of computational anatomy since when looking at constructing these transformations for registration that's becoming

popular. And then finally go through some of the radiotherapy applications that we're working on. The motivation's pretty obvious. The previous speaker gave us a wonderful intro..talk on really what's coming down the line. We have beautiful data that's being collected by RCCT and now cone beam RCCT, and in the treatment room 3D imaging provides us with data showing interfraction treatment, and now 5D signal data system I'm sure are going to come within a year or two and which would collect multiple photo datasets to \_\_\_\_\_ the treatment. But the big problem is how do we really effectively use all this data to improve radiation treatment planning and delivery. I mean, that's the real goal and that is really an important goal to keep in mind. Bottom line is the data as you can see just visually can really provide us with an explicit model of tissue deformation and algorithm motion. I'll..for the first time everyone knew this but you

have to stop..fundamentally stop treating a patient as a static model. It was great to go from 2D to 3D with the CT, but now we have to stop treating the patient as a static single object, collective planning CT and really take into account the full 4D nature. And this I believe personally requires integration of what I'm calling image understanding algorithms in relation to treatment planning and delivery. In my opinion or in my mind image processing is the actual processing of images to collect and make beautiful images that humans can understand and interpret, but finally we need to get this into your dosimetry optimization, planning and \_\_\_\_\_ology, and for that you need to understand a deep structure in images and that's what I'll be talking about. And towards this end there's an emerging field of computational anatomy that I believe radiation therapy is ideally suited for. So what is computational anatomy? Well, the

study of an anatomical variability really traces back to the origins of modern science. And today what I'm going to talk about is really more than computational anatomy, it's really based on the mathematical theory of metric pattern, a pattern theory of Grenander from the Department of Applied Mathematics at Brown University. And this is has been extensively applied and most prolifically in brain mapping where people have been doing this for now a number of years successfully in trying to understand function of the brain and looking at the structure of the brain. Now, interestingly I've looked and find a study so what is computational anatomy? It's a precise computational and mathematical study of anatomical variability. And the first attempts to bring the mathematics into study of anatomy were really pioneered by Dion Thompson and I'd like to quote from him and which will be the kind of followed throughout my talk is that in a very large

part of the essential task is really not as much a precise definition of forms but rather the

formation of complicated figure. So it might be that the underlying figure remains undefined but the changes of these complex patterns can be understood. And that's really what a lot of this deformable image registration computational anatomy is about. And to give you a precise idea, I hoping most of you people in the audience are physicists and not neuro-anatomists. This will predate back to 1993 and I would like to really acknowledge Gary Christensen who was my co-office mate during my PhD years and Rick Gravit who is a mechanical engineer, and Mike Miller, my mentor, and these are two images of a macaque monkey occipital lobe. And if you have never seen a brain anatomy it's really hard to understand that this is actually an area of the visual cortex or the particular sulcus in it's name but it's very easy to understand that these two images, this structure is the same as this structure but a rather different shape. This structure is the same as this structure but the different shape. So what is possible is that we believe is that to

get a computer to understand these several differences and to quantify them precisely, and one way we have been doing that is imagine we painted this image on kind of a pseudo viscoelastic fluid and had one image deformed, left image, into the right image. And here you see on the right the algorithm deforming the left image into the right image. Now on here what you see on your right is what has to happen to the underlying coordinate system to make the images look similar, to make them match. Now note that there's no change being done to the actual image intensities. The only transformation is being applied to the underlying coordinate system. This completely now captures the shape variation in a detailed anatomical variation between the images. Now what are some of the mathematical foundations now, this is a mathematical theory of pattern and things..I would like to make some things precise. Basically homogenous anatomy

is characterized by a four \_\_\_\_\_.  $\Omega$ , the underling coordinate system.  $X$ , a space of transformation that you're going to allow on it.  $I$ , which is really the imaging modality. To set up your imaging modalities you're going to collect on..from that coordinate system of the anatomy. And  $P$ , a property measure on the set of transformations is going to characterize your actual deformations that are going to..happening. So the whole thing is a base of a bayesian framework in which we think of understanding anatomical variability as being able to build probabilistic models. There is no deterministic motion here. I mean as you saw from the previous speaker, it's not true that the person breathes exactly the same way day in and day out. So you task have been incorporated in a fundamentally and a probabilistic nature. So the set of transformations is going to accommodate, so what is  $\Omega$ ? If I take  $\Omega$  to be a collection

of 0, 1, 2 and 3 dimensional compact manifolds. Zero dimensionals are landmark points of fiducials used in radiation therapy. One dimensionals are lines. Two dimensionals are surfaces. Three dimensionals are full sub volumes. So you should think about anatomy mathematically abstract as the his..the visualization of a model of anatomy that's constructed of these manifolds.  $X$  is a set of transmissions on the underlying coordinate system that are computed biological variable data I have mentioned. And a set of anatomical imagery is..can be as varied as CT, MR, PET, ultrasound, whatever and the new emerging modalities that are coming that is inferring inclination about these con..objects in them. And  $P$  is qualitative property measure. So, actually let me talk a little bit more detail about these transformations. They're really constructed from a group of diffeomorphisms of the underlying coordinate system  $\Omega$ . Now what are

diffeomorphisms? It's very important to be a diffeomorphic transformer because we want to preserve the \_\_\_\_\_. We don't want to introduce tears or folding or any kind of ripping. You need one-to-one correspondence in variability. That's precisely what diffeomorphic transformation is. And finally, as I mentioned using a Bayesian framework, and anatomical variability is understood via an empirical construction of property measure on the set of transformations. As you know, if you can talk probabilistically how these transformations are viewed in your data set, you can imagine..you can then make a statement that you've understood to some extent your anatomical variability that's going on. So in general the problem is it's two steps. First is given a family of images. You are to construct transformations that map all the images to a single template. So given a set of 4D images that may be time indexed, or a set

of independent 3D images that are static, you want to map them all to a single template image. And then given a set of transformations estimate, a property model for the anatomical variability. Now, I'll be talking mainly about the first aspect in brain mapping we've done. We've had lot more progress in actually doing the second in which we're actually talking about statistical shape variations, statistical shape variations between populations. I'll be for today's talk I'll be focusing mainly on the first part. OK, so how are registration transformations constructed? They're constructed from a hierarchy of transformations including dimensionality. The first transformations are the simplest ones. These are the affine transformations. This is classic register registration either with scale or without scale and they're accommodated global scale, rotation and translations. Then you have medical landmark deformations. These are driven by

various landmarks information provided, the fiducials that you know of. If there..if you only have three fiducials you can basically \_\_\_\_\_ global rigid motion. If you have more fiducials then you get more interesting deformations that we'll be talking about. And then finally we have high dimensional \_\_\_\_\_ in fluid transmissions that have the dimensionality on the order of your imaging modalities. If you looking at..if you looking at a 256 cube volume or a 512 cube volume isotropic 1 millimeter, than that's the number of degrees of freedom you have and that's the amount of deformation that you want to allow your transmissions to have. So now how do you construct transmissions? So, first of all let me exemplify all this with the landmark base transformations because they use this to explain and then we'll go to the fluid. So..and this was really done..this was binary work in small deformation settings was done by template lines and I

believe a lot of people in the audience are probably familiar with this work now, it's rather classic in which you'll be given a set of landmarks, say intuitively  $x_i y_i$  that goes somewhere someplace else that you know you want to find the transformation that minimizes a bending energy. That estimates that so the basic mechanical problem becomes given  $x_i y_i$ , find a transformation  $xx$ , that minimizes certain second order differential norm on the transformation. This guarantees the transformations are smooth because they have to be twice differentiable. But they're not guaranteed to be diffeomorphisms. And you say what's wrong with that? Well, this is what's wrong with that. Simple deformation here we have two points, all four point corners are kept fixed. So the corners of the images are fixed. Point A maps to point B, point C maps to point D. Very, very obvious transformation that can happen in anatomy. The solution you get

from the template slice emission is in the middle. You see the grid lines crossing each other.

You have introduced force and non-\_\_\_\_\_ transformation, but you would ideally like to see the transformation but you see on the right a diffeomorphic transformation. So how do you do this? Well, it comes that 4D not only is inherent but it's also natural mathematically to work on and what you have to do is you have to introduce time into your transmission even if it's not present in the data. This is an interesting concept that you have to grapple with. And that is you have to define an indexed family of transformation indexed over time and space that are being box-traced by points as they move from one image to the other. Now this spot time that the..you're talking about can be simulation time just for this mathematical construct, or it can be real time if your data is real time indexed. And then we define transmission by a solution to an ODE, ordinary differential integral..equation. And the reason we do that is ordinary differential equations always generate diffeomorphisms. And it's easy to prove that, approval although

technical proof is rather involved, but one of the easy ways to see it is if you ever lost your field and you take two particles and let's assume you do a proof by contradiction, let's assume that you lose one to one that aren't two. That would mean that two particles actually flow through velocity field and come to a single point. But the invariability of time in ordinary differential equations says that if we were to run the system backward in time we should be able to recreate these spots. But the uniqueness and..of solution of 4D tells us that there can only be one solution. So we can never have two particles actually meet into a single point if your transmission is a solution of ordinary differential equation. And this time in a fundamental way diffeomorphic image registration problem is inherently 4D in nature. OK, so now the diffeomorphic landmark margin problem becomes is you induce an energy to make the velocity

fields differentiable in time..in space and minimize the energy and the velocity while getting the points to match up. This is a classic shooting the moon problem which is you want to shoot the points to where they want to where they want to end up while estimating the entire trajectory over space and time. And again, this is what you're seeing here the results of that. Now we get to image mapping. So that was the...So how now do we do for images when you're given two images? When you're given two images the same framework is..follows through which is you define the similarity metric between image data and a transformed image data after some time T, so you define that. And a small deformation model will tell you to just directly minimize the energy associated with the deformation by some differential known. You can use a bending energy or elastic energy and people have got, you know, it's an entire mill of differential \_\_\_\_\_

you can keep on using. And then the estimate of the transmission is simply you regularize the deformation while minimizing the similarity metric versus a regularization \_\_\_\_\_. Now the similarity metric you..again many choices will fit. If you've got calibrated CT data set that means could add a metric as the appropriate one to use. If on the other hand you have desperate modalities that you try to match and you want to go to a much more complex metric such as \_\_\_\_\_ information or other correlation metrics, but again with this small transformation you have a major problem that transmissions are not guaranteed to be smooth and differentiable. And if you look at the amount of variation the anatomy goes through then one has to reaffirm that you have to fundamentally take into consideration the large transformation model. You cannot get away with trying to do something cheap with just doing a small transformation model.

So the large information image mapping problem becomes the same thing. You induce energy in your velocity fields while you define your transmission by an ordinary differential equation and you estimate the velocity field while trying to minimize the disparity between the deformed images. That basically..and the velocity field you again use a differential energy on the velocity fields, light, bending energy of the velocity fields are the \_\_\_\_\_stokes operator or whatever your favorite operator is. OK. So now let me give you..bring this back home to radiotherapy and talk about some of the applications of using this \_\_\_\_\_ imaging as mapping and how we use this. An example of this is in the breathing example I was showing. This was data before the really full 4D CT data sets came on line and here we're looking at end expiration and inspiration studies. And we'd like to do is given these just these two 3D volumes estimate a full

diffeomorphic transformation through time that's going to allow us to map expiration to inspiration. So now this is where there's no data and there's no time in the data, they're just collected at two static points. We would like to estimate a deformation that through time is able to deform one image to the other. And what you see here is exactly precisely that. This is now the..what you see here is complete simulated breathing. This is not real breathing by the way. This was created from two static images by estimating the formation field, then integrating forward the velocity fields in time with speed controlled by a spirometer trace of that subject. And this data again I would like to thank Gig for providing this data from Memorial Sloan-Kettering. Here's a validation example and here's what you see once we start getting 4D simulator sets. It's like oh, we can now do validation. How close is this image registration with

your diffeomorphic mapping compared to real 4D dataset? On your left is real 4D dataset. On the right is the simulated 4D dataset generated by deforming an inspiration to an expiration phase, and you can see this tracks really well. Here's a quantitative validation study, again this is with Gig Majeson in which looking at multiple 4D datasets with..at multiple phases manually contouring them at different phases and then using the deformation algorithm to form and automatically transform the contours from one phase to the other and then comparing the validation. I'd like to say that Alex is going to give us a talk on this and present his results at 11 on Thursday so I'm not going to go into details of these results. I'd like you to go and see his talk. Basically it's a four observer, six patient study with repeated measures and what we've shown is that the accuracy by doing this deformable image registration is within..is very

comparable to the \_\_\_\_\_ of the segmentation variability. Here's an example of the kind of results you see when you do a \_\_\_plot image. We're able to get down the error to be under one voxel in the 4D dataset, there's about 3 millimeters and the error is in the direction..in the Z direction where you have 3 millimeter slice thickness. In the XY direction you're down to right in the middle here, you're down to 0 to 1 millimeter what's the resolution of the data. So we're able to basically match manual contouring to an order of the voxel by using these image registration algorithms. Here's other example of validation study in which what you see are two blending images and this is data \_\_\_\_\_ of those kinds \_\_\_\_\_ providing if you look at blending with an expiration in phase 4 off an image if you're not to do anything, and on the right is the blending of the estimated transformation that they \_\_\_ phase 4. Not only the full inhale

and expiration phase were inputted into the algorithm and you see, notice that you've got very

little motion, residue motion left here to do mismatch of the deformation algorithm. OK, next is application of these algorithm for intertreatment CT images where now the time even with the 4D problem but the time scale is slightly different. The time scale is not in a single breathing phase but it's daily fractions in radiotherapy. We're lucky enough to have CT and \_\_\_\_\_ data because you have segments in which scanning the subject every day and here's an example of what these images look like. So here are daily CT images collected on the scanner as the patient is positioned. And you notice tremendous motion. A, you notice a lot of rigid motion just out of due to setup errors, you notice interesting motion due to the change in the anatomy from day to day of the patient. You can see the bladder's having large changes in the deformations. You've got rectal filling and ball gas. So what do we do? We apply the same technology to deform your

planning CT onto your daily CT slices. Again there are diffeomorphic matters so that you are able to maintain the topology of the image data. And once you're able to do that you cannot only..the first thing we're going to do is automatically contour the daily images. Or vice versa if the daily images are contoured we can bring them all back onto the coordinate system or the planning image and here you notice now the..this is the top row is \_\_\_\_\_ rigid alignments so you do your algorithm registration based on \_\_\_\_\_ landmarks. And on the bottom is the result of the residue of the image deformation left after doing a fluid registration. The registration was only done in the region of interest in the blue box, so what you notice is the rest of the anatomy there's no deformation applied to it and you notice that changing. But notice that inside the anatomy compared to what you see up here you've very little \_\_\_\_\_ residue motion left. So

you're able to accommodate automatically. And this \_\_\_\_\_ this procedure's completely automatic after you've identified or gotten the coordinate system in. The reg..alignment is automatic. That's old news. And you have nowadays the deformation that's completely automatic and multi-stage fashion. And what do you do with this data? Oh, and here's the kind of the accuracy that you see with this. What we did was we had all the intra-subject patients carefully manually contoured in the..of the prostate and mapped back, all the contours were mapped back onto the planning CT. So here you see the residue defor..error changes in the prostate day to day if you were to do with raw images. This is what's left out of rigid alignment and then this is what's left after you do full deformable registration. OK. Now what do we do with this? And one of the things that we've been working on and I think that Christine is going

to talk in the next talk is actually using this for dose calculations. Once you collect daily images it's straightforward to calculate daily dose for histogram, and daily dose distributions on your collected CT images. And here's what you see, here's day one, here's day two, here's day three, day four, day five, day six, day seven, day eight. But now what you'd really like to know is not just daily dose for the histogram but what dose and what dose volume histogram have you really delivered to the patient. That's what Julian tells me you would like to know. And how do you do this? Well, we have to redefine dose volume histogram. When a static dose for the histogram is classically defined as the volume of a particular structure that gets a dose greater than a \_\_\_\_\_. A general 4D dynamic dose volume histogram can be..is defined as not just the dose..constant dose but a dose indexed and tracked while the deformation process. So we can map back the

doses, all the doses computed on the daily images back onto the base image and accumulative. And that's what we see here as the total delivered dose. On the left is the planned dose and on the right is the delivered dose. Now, of course, the main challenge now left is now that you've seen how poorly we've done is how do we get the delivered dose to look like the planned dose that everyone is happy with. Because when Julian says oh my God, if you're showing me this plan, I would have never signed off on it. And that remains to be an open challenge and I hope Christine will talk more about how to do that. And I think I'd like to thank here, thank you for your patience.