

MR Image Assisted Drug Delivery in Respiratory Tract and Trachea Tissues Based on an Enhanced Level Set Method

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Abstract— In medical diagnosis and therapy, finding an appropriate method to evaluate the effect of various drugs is crucial. There are several ways to qualify a drug for a specific disease and one way is through medical image analysis. This process varies with the tissues we want to analyze and the imaging technique that is employed. For hydrous tissues such as nasal and trachea, Magnetic Resonance Imaging can be helpful for further evaluations. Trachea can be challenged by an antigen which will increase both nasal vascular permeability and intranasal pressure. Another effect of antigen challenge into nasal cavity which may cause nasal blockage, is swelling of nasal mucosa and a decrease in nasopharyngeal airway. In this paper, we study the effect of an antihistamine drug on swelling of mucosa. This antihistamine is called Azelastine and is injected to guinea pig to evaluate the swelling changes of nasal and trachea mucosa. After 20 minutes of injection, a MR image of the motionless animal is taken and this imaging will continue for 30, 40, 50 and 60 minutes from injection. Due to the ambiguous nature of respiratory tract, finding a precise method for processing has useful results. Watershed algorithm has widespread function in medical images but its defects in segmentation can be modified by different methods. An enhanced level set method is used here; a nonparametric active contour for nasal and trachea detection. This automatic image segmentation and tissue detection can help physicians evaluate the effect of a specific drug from medical images.

Keywords— *Nasal and Trachea, Magnetic Resonance Imaging, Azelastine, Watershed Algorithm, Level Set Method.*

I. INTRODUCTION

One of the most important symptoms of allergic rhinitis is nasal blockage. Nasal blockage happens when the nasal mucosa starts to swell and this is a reaction to antigens. The antigen challenge will increase vascular permeability dilate the

capacitance vessels of nasal mucosa [1]. Antigen challenge can be moderated by some drugs such as histamines and arachidonic acid metabolites. Histamines and antigens effect on nasal mucosa has been evaluated by some previous methods [2]. A new method for drug evaluation on various tissues is through image analysis and numerous works have developed this method [3],[4],[5].

Image guided drug delivery is a concept in which the specific effect of a drug is evaluated through medical images. The imaging techniques are consisted of MRI, CT, PET and Ultrasound [6], [7]. Another issue in medical image analysis for drug evaluation is how to process the image in order to achieve the maximum similarity to manual segmentations of doctors. Hence, finding an optimum method for processing is a critical task. We suggest that our enhanced image processing technique should be applied for the tissue we want to analyze [8], [9], and [10]. In this article, we combine some segmentation algorithms, offering a new way to maximize the efficiency of drug evaluation which can also be compared to the physician's results of drug evaluation [11], [12], [13].

The paper is organized as follows. In section II, we discuss two image processing techniques. In section III, a fusion of these methods is presented for evaluation of MR images of nasopharyngeal. We also define a modified active contours algorithm to detect trachea. We implement our proposed method on MR images of guinea pig to evaluate the effect of the Azelastine drug in the same section. The results of this method is compared with manual processing and previous works. Section IV is devoted to defining a 3D model of trachea and trachea airways in order to have a better comprehension of the effect of our desired drug. Finally, in section V, we discuss the whole idea of our method on image guided drug delivery issues and some viewpoints for future works are presented.

II. RELATED WORK

A. Watershed Algorithm

The watershed idea has been introduced in 1979 by S. Beucher and C. Lantuéjoul and its concept in image processing deals with how a drop of water falls through topographic relief until it finally reaches to a minimum. When water fills local minimum, many regions will appear and by increasing water, these regions may merge which at this point, some dam can prevent this merging. These dams are

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watershed lines [14], [15]. The main procedure of watershed algorithm first happens with a selection of a point, then neighboring pixels of this point are inserted into a priority query with a priority level corresponding to the gray level of the pixel. The pixel which has the highest gray value will be selected and labeled with its neighbors that have the same label. This will continue until all pixels get into priority query [16], [17].

B. Level Set Method

The level set method which was presented by Osher and Sethian in 1987, is a simple method for computing and analyzing the motion of the interface in two or three dimensions. Level sets are used to implement force curves. These curves are represented as Equation 1. If a curve C moves in a normal direction with speed v , the level set function F will satisfy Equation 2 [18], [19].

$$C = \{(x, y) | f(x, y) = 0\} \quad (1)$$

$$\frac{\partial f}{\partial t} = \nabla |f| \quad (2)$$

One of the most important problems of level set is that it needs to be re-initialized which may cause the side effect of moving the zero level set away from its interface. In addition, the re-initialization step is a highly costly and very time consuming operation. A new way to solve this problem is presented in [20] that uses a Gaussian filter to make the level set function regular.

III. PROPOSED METHOD

Our method here uses a preprocessing step in order to signify the boundaries of the image. This step is consisted of a distance transform on the image for using watershed algorithm which will segment and highlight the boundaries of the processed image. After this step, a level set method can be implemented on the new image, however, we use a new level set which is devised by Kaihua Zhang in [20]. According to Zhang's work, two constraints c_1 and c_2 which are average intensities inside and outside of the contour, should be evaluated by minimizing the energy function such as below [21]:

$$E^{cv} = \lambda_1 \int_{inside} |I(x) - c_1|^2 dx + \lambda_2 \int_{outside} |I(x) - c_2|^2 dx \quad (3)$$

Therefore, we have:

$$c_1(f) = \frac{\int I(x) \cdot H(f) dx}{\int H(f) dx} \quad (4)$$

$$c_2(f) = \frac{\int I(x) \cdot (1 - H(f)) dx}{\int (1 - H(f)) dx} \quad (5)$$

Where $H(f)$ is a Heaviside function [20]. Consequently the variable level set function f should satisfy Equation 6.

$$\frac{\partial f}{\partial t} = \frac{I(x) - \frac{c_1 + c_2}{2}}{\max(|I(x) - \frac{c_1 + c_2}{2}|)} \times v |\nabla f| \quad (6)$$

In this equation, the first term is a Signed Pressure Force (SPF) and is constructed based on the above equations [20]. This term can control the direction of contours so they can shrink outside and expand inside of a desired object in image I . Also, v represents the speed of contours. The enhanced level set method is a combination of watershed algorithm as a preprocessing step and the new level set method which is summarized as follows:

- Implement a watershed transform on image
- Regionally segment image with Watershed algorithm and highlight the specific segmented parts
- Calculate $c_1(f)$ and $c_2(f)$ according to Equations 4 and 5
- Extract the level set function in 6
- If $f > 0$, then $f = 1$, else $f = -1$ and a local segmentation will occur

In our MR set of images, there are some slices containing nasal respiratory tract parts. Due to complexity of these parts, we applied an active contours method based on local energy fitting [23]. Therefore, we define an energy function as follows:

$$E^{LIF}(\phi) = \frac{1}{2} \int_{\Omega} |I(X) - I^{[F]}(X)|^2 dx \quad (7)$$

where $I(x)$ and $I^{[f]}(x)$ represent our image and our modified image with a Gaussian window, respectively. Then, we used a level set function ϕ with a modified Dirac function $\delta_\epsilon(\phi)$:

$$\frac{\partial \phi}{\partial t} = (I - I^{LIF})(M_1 - M_2) \delta_\epsilon(\phi) \quad (8)$$

At this point, we can use a same algorithm as the previous one with our new level set function:

- Define I and $I^{[f]}$
- Extract the level set function in Equation 8
- If $\phi > 0$, then $\phi = 1$, else $\phi = -1$ and a local segmentation will occur

A. Data

The main goal of this article is to find out how a drug can make changes in trachea and nasopharyngeal airways. Data are gathered by University of Osaka in Japan. The dataset consisted of 5 sets of Nasal and trachea MR images. Each set has 29 slices of images and represents a specific time after the drug was injected into the subject. Image matrix of each data set is $256 \times 256 \times 29$ with voxel size of $0.14 \times 0.14 \times 1 \text{ mm}^2$.

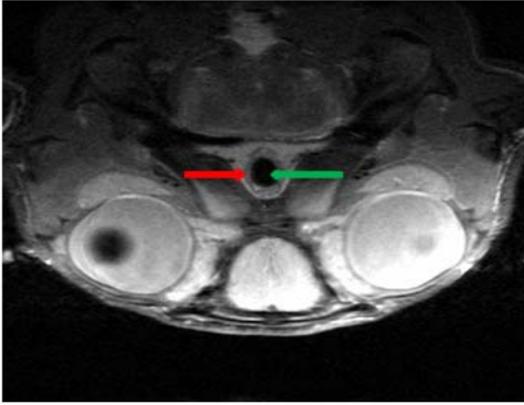


Fig. 1. Nasopharyngeal airway (green arrow) and trachea mucosa (red arrow) of guinea pig.

The subject in these data are guinea pigs which are sensitized by aerosol inhalation of antigen and this antigen challenge into the nasal cavity increased both nasal vascular permeability and intranasal pressure. Another effect of antigen challenge into nasal cavity which may cause nasal blockage is swelling of nasal mucosa and a decrease in nasopharyngeal airway [22]. Here, we study the effect of Azelastine drug, an antihistamine on swelling of mucosa. A slice of guinea pig's nasopharyngeal and its mucosa is shown in Figure 1. Antigen would swell the mucosa (red arrow) and antihistamine would inhibit that (green arrow).

B. Method Execution

In order to implement our method, we should follow the block diagram in Figure 2. In this block diagram, first we must insert our data for a preprocessing step which is a watershed method implementation. In the next step, level set algorithm is applied to these data and results of trachea area segmentation is extracted. With these results of segmentation, we can calculate the trachea area for 20, 30, 40, 50 and 60 minutes after Azelastine injection. This process will continue for every slice of a MR image. For example, if a data set has 6 sets of 10 slices of MR images, we should implement our method on every set (which is related to a specific time after injection of Azelastine) and also on every slices of the desired set. After using our method, and finding nasopharyngeal airway area of each slice of an image, we will build a 3D model of nasopharyngeal airway area and its total volume will be extracted.

After injection of Azelastine, 5 sets of images were taken. The first set had been taken after 20 minutes of injection, while the second set after 30 minutes, the third set after 40 minutes, the fourth set after 50 minutes, and the last set after an hour of injection were taken. Therefore, in order to evaluate the effect of Azelastine, we should consider two points. First, the trachea variations should be calculated through time

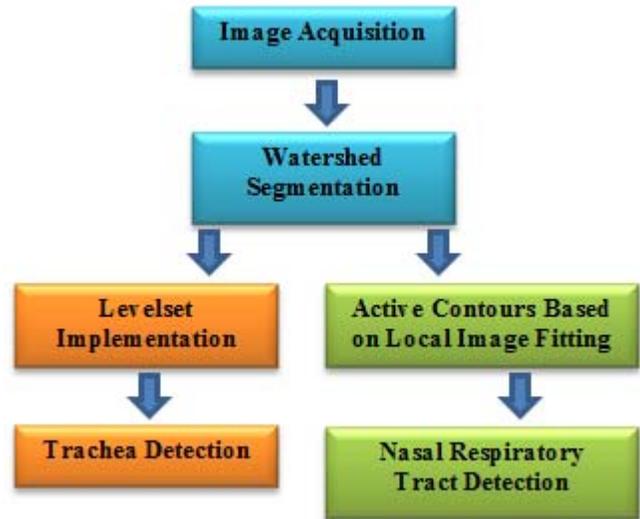


Fig. 2. Block diagram of our proposed method for drug evaluation in trachea and nasal respiratory tract.

sequences of the images. Second, the total effect of Azelastine should be evaluated and compared against previous works [22].

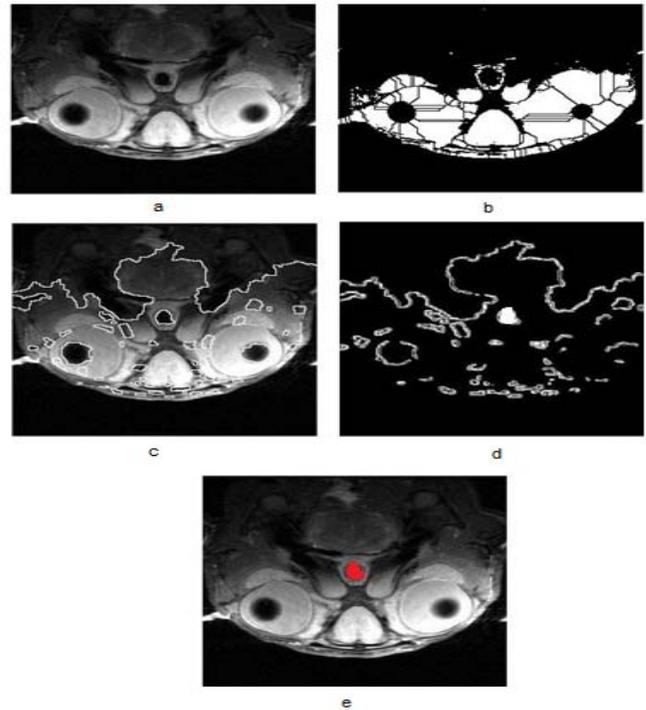


Fig. 3. The Enhanced Level set method for finding nasopharyngeal of guinea pig. (a) Original image. (b) Watershed regional segmentation. (c) Watershed region and boundary finding. (d) Level set after 70 iterations. (e) Final image with specified trachea area.

TABLE I AZELASTINE EFFECT IN NASOPHARYNGEAL AIRWAY AREA AND VOLUME: A COMPARISON OF OUR PROPOSED METHOD WITH PREVIOUS STUDIES.

Methods	Trachea after antigen inhalation		Azelastine effect in Trachea area (mm^2)					Decrease in area (%)	Total volume after 1 hour of Azelastine administration
	area of one slice(mm^2)	total volume(mm^3)	20 min	30 min	40 min	50 min	60 min		
Enhanced Level set	64	574.6	70.62	74.87	77.9	79.05	81.4	9.95	716.32
Region Growing	70.04	533.2	70.2	72.35	75.9	76.6	77.82	13.9	659.11
Manual Segmentation	63.2	549.64	67.43	70.4	75.09	79.74	82.69	8.5	738.82
M.Y.Yamasaki [22]	61.7		-	-	-	-	80.8	11	

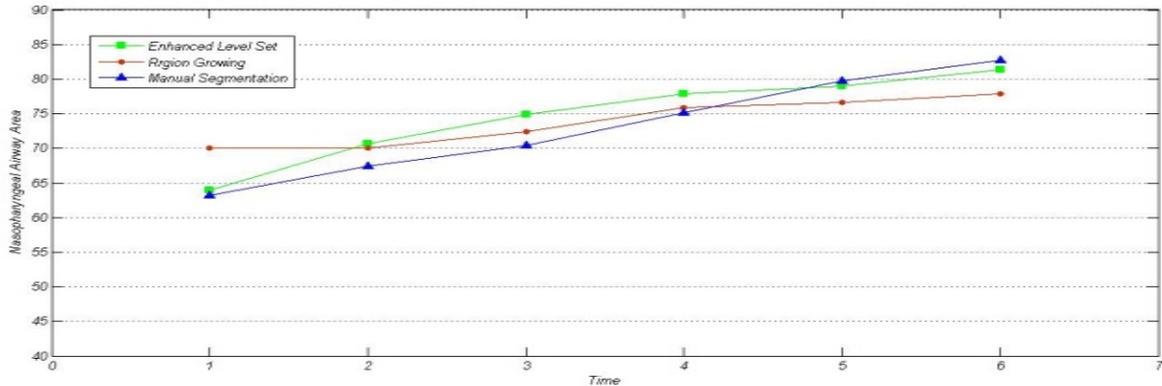


Fig. 4. Trachea area (mm^2) before and after 20, 30, 40, 50 and 60 minutes of injection of Azelastine.

As mentioned in the previous section, we would implement our Enhanced level Set method on our MRI data to segment and find out it's efficiency for finding nasopharyngeal airway of guinea pig. Figure 3 shows the steps of our method as discussed in the proposed method section. At first, the watershed algorithm is applied on our image shown and the result of local segmentation can be seen in Figure3.b. After this step, the boundaries are highlighted and the new image is ready for the level set method (Figure 3.c). At the beginning of evolving, the level set function, $c_1(f)$ and $c_2(f)$ are estimated according to Equations 4 and 5. Then, by using Equation 6, the level set function is calculated (Figure3.d), and finally by setting the positive level set to 1 and otherwise to -1, the local segmentation of nasopharyngeal will be achieved as can be seen in Figure 3.e. In this task, the contours are stopped after 70 iterations as can be observed in Figure 3.d. This is while more iterations would be time consuming, and less iterations would lead to global segmentation.

By finding the trachea area now, we can estimate the variation through time, total variation and total volume change which is discussed above.

First, we study the effect of Azelastine after injection as time goes on. The area of trachea after injecting antihistamine will vary and these changes can be seen in Figure 4. In this figure, the trachea area size after 20 minutes of Azelastine injection until 60 minutes after injection is depicted. As can be seen in Figure 4, three different methods are used to find

trachea area from a slice of a MR image. These methods are enhanced level set, region growing and manual segmentation.

The exact area of trachea is shown in Table I with comparison to manual detection of trachea area and the simple Region Growing method. Table I shows that our method produces similar results to manual detection of airway areas while Region Growing method has sporadic results for the last images. In addition, in this table, the total effect of Azelastine after 60 minutes is compared to previous works [22]. Note that the actual area of trachea before any inhalation is $90.4mm^2$ [22].

According to Table I and Figure 4, we can say that our method has results with most similarity to Yamasaki work [22]. It is also notable that the Enhanced Level Set method has faster results than manual segmentation results, especially when we face large amount of data for processing. An important point from these results is that various methods had proven that after some time has passed, the Azelastine will reduce and quell the swelling effect of antigen. In Table, I the trachea area is increasing for consecutive images through time and this increase is proven with different methods. Moreover, we can realize that this increase is a demonstration for decrease in swelling of nasal mucosa which is a result of antihistamine administration.

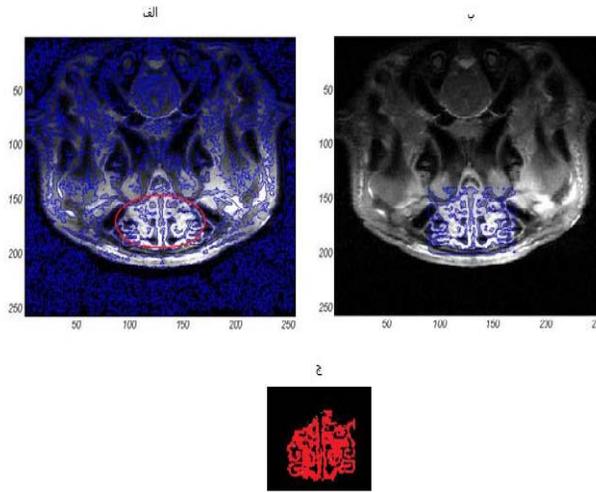


Fig. 5. Segmentation of nasal respiratory tract airways based on local image fitting [23].

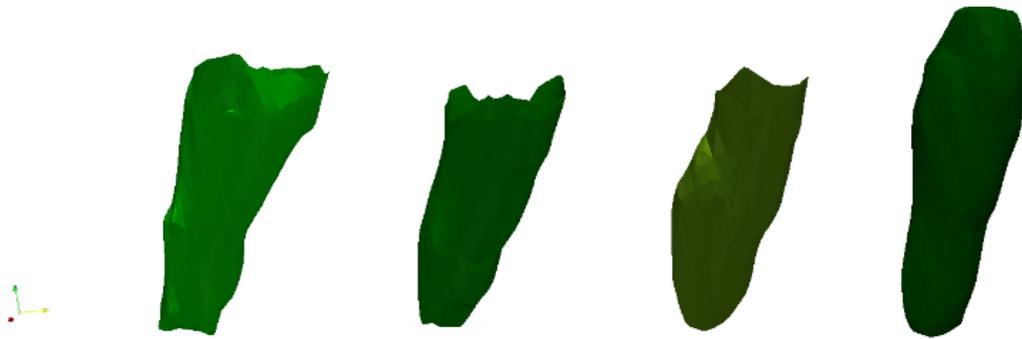


Fig. 6. 3D model of trachea volume of guinea pig before injection of Azelastine and after 20, 40 and 60 minutes of injection (from right to left).

Using active contours based on local image fitting allows us to segment nasal respiratory tract parts of our images which is shown in Figure 5. After detecting nasal respiratory tract through continuous slices of MR images, we can create a 3D model of the trachea.

IV. 3D VISUALIZATION

Another way to compare our results with previous works is to find a three dimensional model of trachea area. This way we can evaluate the total effect of Azelastine drug and figure out how the volume of trachea area will vary through time sequences. Figure 6 shows trachea volume in three different times. The first trachea volumetric model is before injection of Azelastine, and the two others are after 20, 40 and 60 minutes of drug injection. With this 3D model, we can estimate the volumetric changes of trachea in order to evaluate the effect of Azelastine.

Volumetric comparison of trachea area can be done by overlapping the results of our proposed method and manual volumetric model. For this aim, first a 3D model is constructed based on manual segmentation of trachea areas from slices of the MR image. After that, we use our enhanced

level set method to find trachea areas of the same image and again a 3D model is constructed based on these segmentation results. Finally, we overlap these two 3D models to find out an intuitive concept of nasopharyngeal volume and also to compare the model which is based on our enhanced level set method with the model rooted from manual segmentation. Figure 7 represents this concept, and as it can be seen, our method has meaningful overlaps with the manual segmented method.

The total volume of trachea area before and after injection of Azelastine is shown in Table I for different methods. This volume can help the physician to understand the effect of Azelastine in the trachea area. In this table, the total volume before Azelastine administration (antigen inhalation) and after 1 hour of Azelastine administration is calculated. Note that the total volume of trachea has an increase before and after Azelastine administration which shows that swelling of nasal mucosa has a decrease after the injection of Azelastine.

The same procedure can be used in order to create a 3D model of nasal respiratory tract airways based on our segmentation results for each slices. Therefore results of our detected nasal respiratory tract area from consecutive slices can be visualized into a 3 dimensional model as shown in Figure 8.

V. CONCLUSION

In this paper, we presented a new fusion of segmentation methods for evaluating the trachea area. Our method combines active contour algorithm with the watershed method. The aim of this work is to find out how an antihistamine drug can prevent nasal mucosa swelling. This work can help the physician to define and query the effect of a drug from medical images and thus they can anticipate the probability of allergic rhinitis. This diagnosis is extremely crucial, because the developed forms of allergic rhinitis could lead to asthma. The conclusion process in this work is based on the sequential variations in the trachea area and its total final area after histamine drug (Azelastine) injection. In addition, we extracted a 3 dimensional model of trachea area in order to observe the total volume changes due to Azelastine administration. The results of this work show that an antihistamine drug (Azelastine) has good effect on swelling of nasal mucosa and will reduce it. As a future direction of this work, we plan on estimating the total volume of trachea and see how its volume will change after histamine injection.

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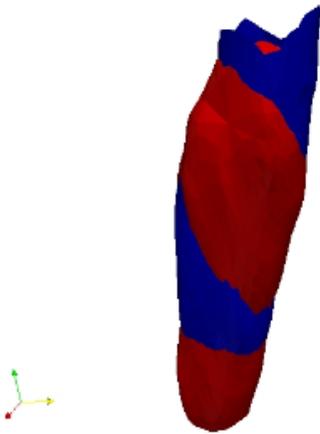


Fig. 7. 3D model of trachea volume based on manual (red) and enhanced level set method (blue) segmentation.



Fig. 8. 3D model of nasal respiratory tract airways based on local image fitting segmentation.

Finally, for a set of MR images which is consisted of 29 slices, we can create a 3D model in which some slices just show nasopharyngeal, while others include the nasal respiratory tract area which is shown in Figure 9.

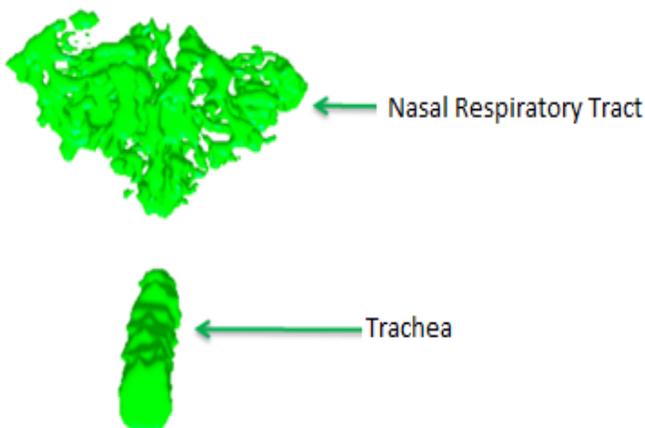


Fig. 9. Complete 3D model of nasopharyngeal and nasal respiratory tract airways for 1 set of 29 slices of MR images.

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