3D Visualisation and Analysis of Skin Lymphatic Drainage Patterns in Melanoma

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Abstract

This thesis aimed to improve visualisation and analysis of potential patterns of melanoma spread from the skin to lymph nodes. For this purpose, anatomically based geometric models of the skin and lymph nodes have been created. A three-dimensional (3D) finite element (FE) skin model has been constructed using the Visible Human (VH) male dataset and a Sawbones head and neck model. A discrete lymph node model was also created using the VH dataset.

This study has been conducted in collaboration with the Sydney Melanoma Unit (SMU), in Sydney, Australia. Clinicians at the SMU have recorded an extensive lymphoscintigraphy (LS) database, accurately mapping skin lymphatic drainage from over 5000 patients with cutaneous melanoma. The SMU's entire LS database was mapped from two-dimensional LS images onto the 3D anatomical model. Melanoma sites were mapped onto the skin model using free-form deformation and projection techniques, while draining node fields were mapped onto a reduced lymph node model.

Spatial heat maps were created using field fitting to visualise the likelihood that any area of skin would drain to a particular node field, or a specified number of node fields. An interactive skin selection tool was also developed to provide dynamic predictions of the draining node fields from any region of skin. The heat maps and interactive skin selection tool quantified that lymphatic drainage of the torso was highly complex, where the most unpredictable regions were located near Sappey's lines. Drainage from skin on the upper and lower limbs was the most predictable, almost always draining to ipsilateral axillary and groin node fields respectively. Skin on the head and neck were shown to usually drain to two or more node fields, where the most common node fields were the cervical level II and preauricular node fields.

Detailed statistical analysis was then conducted to investigate widely accepted assumptions about lymphatic drainage. Sappey's lines were shown to be highly inaccurate at predicting lymphatic drainage from the skin of the torso. At least 12.5% of all melanoma sites located on the torso showed drainage across Sappey's lines, and nearly the entire torso demonstrated ambiguous lymphatic drainage. A multinomial statistical model was fitted to the LS data to investigate whether lymphatic drainage was symmetric about the body's vertical midline. Results showed that a signif-

icant proportion of the skin was likely to have symmetric lymphatic drainage patterns. Asymmetry that was shown within specific regions was likely due to an asymmetric distribution of melanoma sites within that region and/or a sparsity of data. Regions that indicated symmetry were reflected, providing a larger LS dataset to improve the statistical accuracy of drainage predictions.

A cluster analysis was conducted using this reflected LS dataset to group regions of skin that drained in a similar manner. Results indicated that the dominant axillary, groin, cervical level II and preauricular node fields drained significant areas of skin. Clustering resulted in division of the torso into regions similar to Sappey's lines, although an additional cluster formed in the middle of the anterior and posterior torso where predominantly ambiguous lymphatic drainage occurred. Confidence intervals were calculated using non-parametric bootstrapping to further determine the statistical accuracy of drainage predictions from each of these clusters.

This body of research has been presented as four papers, which have either been published or will be submitted to international peer-reviewed journals:

1. Reynolds, H. M., Dunbar, P. R., Uren, R. F., Thompson, J. F. & Smith, N. P. (2007), 'Mapping melanoma lymphoscintigraphy data onto a 3D anatomically based model', *Annals of Biomedical Engineering*, **35**:(8),1444-1457.

2. Reynolds, H. M., Dunbar, P. R., Uren, R. F., Blackett, S. A., Thompson, J. F. & Smith, N. P. (2007), 'Three-dimensional visualisation of lymphatic drainage patterns in patients with cutaneous melanoma', *The Lancet Oncology*, **8**:(9),806-12.

3. Reynolds, H. M., Smith, N. P., Uren, R. F., Thompson, J. F., & Dunbar, P. R. (2008), 'Three-dimensional visualization of skin lymphatic drainage patterns from the head and neck', *Head & Neck*, **accepted**.

4. Reynolds, H. M., Walker, C. G., Dunbar, P. R., O'Sullivan M. J., Uren, R. F., Thompson, J. F. & Smith, N. P. (2008), 'Redefining the understanding of skin lymphatic drainage through statistical analysis', *submitted*.

This work has also been presented at the following three international conferences:

1. 28th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, New York, USA. Aug 30-Sep 3, 2006.

2. Biomedical Engineering Society 2007 Annual Fall Meeting, Los Angeles, California. Sep 26-29, 2007.

3. 6th International Sentinel Node Society Meeting. Sydney, Australia. Feb 18-20, 2008.

Dedication

This thesis is dedicated to my brother:

Wayne Matthew Reynolds

15 Feb ‘88 - 18 Nov ‘05

who lost his fight with leukemia after a courageous 18 month battle. He was a large part of the motivation behind this work.

My hope is that this study will contribute towards the ongoing fight against cancer. Although, regardless of how much money we throw at the health system or into scientific research, all men are ultimately destined for the grave. There is still only one man who has conquered death:

John 16:33

Jesus said: ‘In this world you will have trouble.
But take heart! I have overcome the world.’

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Glossary of Symbols

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(X, Y)	Melanoma site coordinates
$(randX, randY)$	Random melanoma site coordinates
Chapter 2	
ξ	Local or material coordinate
ϕ_n	Lagrange basis function
ψ_n^m	Hermite basis function
$\mathbf{u}_n$	FE geometry (x,y,z) or field value at node n
$\mathbf{u}(\xi)$	FE continuum field evaluated at ξ
$\left.\frac{\partial \mathbf{u}}{\partial \xi}\right\|_n$	FE geometry (x,y,z) or field derivative at node n
s	Arc-length
L	Arc-length scale-factor
$\mathbf{z}_d$	Global coordinates of data point d
D	Least-squares distance function
F	Fitting objective function
w_d	Weight of data point d
F_s	Sobolev smoothing term
N	Total number of data points
α_i, $i = 1..5$	Sobolev weighting terms
η_i, $i = 1..3$	Slave mesh material coordinates
ξ_i, $i = 1..3$	Host mesh material coordinates
Chapter 4	
N_X	Approximate number of elements in the X-direction per grid unit
N_Y	Approximate number of elements in the Y-direction per grid unit
G	Side dimension of a body map grid unit
$(rand\xi_1, rand\xi_2)$	Local coordinates of a random melanoma site $(randX, randY)$

Chapter 6

θ	Angle of Sappey's midline plane
$\mathbf{u}, \mathbf{v}, \mathbf{w}$	Geometric coordinates (x,y,z) on Sappey's midline plane
$\mathbf{n}$	Normal vector to Sappey's midline plane
$\mathbf{u}_m$	Melanoma site coordinate
e	Equation of Sappey's midline plane
e_m	Equation of a plane passing through melanoma site $\mathbf{u}_m$
w_v	Vertical width of ambiguous drainage on the trunk
w_h	Horizontal width of ambiguous drainage on the trunk
n_t	Number of trials
p_i, $i = 1..k$	Probability trial classified in category i, out of k categories
Y_i, $i = 1..k$	Number of times outcome i observed out of k categories
f_i, $i = 1..q$	Likelihood of drainage to node field i
β_i, $i = 0..k$	Multinomial model parameters
γ_i, $i = 1..k$	Linear predictor
$\hat{\sigma}^2$	Estimate of the error variance
K	Number of multinomial model parameters
(ξ_{1r}, ξ_{2r})	Local coordinates of a reflected melanoma site
n_c	Number of samples for cluster classification
m	Number of characteristics to define samples
X_{ij}, $i = 1..n_c$, $j = 1..m$	Number of objects in sample i, classified by characteristic j
d_{ik}, $i = 1..n_c$, $k = 1..n_c$	Euclidean distance between samples i and k
d_{check}	Check distance
n	Number of observations
$\mathbf{x}$ or x_i, $i = 1..n$	Set of n observations
$s(\mathbf{x})$	Statistic of interest of observation $\mathbf{x}$
$\mathbf{x}^{*i}$, $i = 1..B$	Set of B bootstrap samples
$s(\mathbf{x}^*)$	Sample statistic

Glossary of Acronyms

1D	One-Dimensional
2D	Two-Dimensional
3D	Three-Dimensional
AAO-HNS	American Academy of Otolaryngology-Head and Neck Surgery
ABI	The University of Auckland’s Bioengineering Institute
AIC	Akaike Information Criterion
AJCC	American Joint Committee on Cancer
CLND	Complete Lymph Node Dissection
CMGUI	CMISS Graphical User Interface
CMISS	Continuum Mechanics, Image analysis, Signal processing and System Identification
CT	Computed Tomography
DOF	Degree of Freedom
FE	Finite Element
GEE	Generalised Estimator Equation
GLM	Generalised Linear Model
L2	Second Lumbar Vertebra
L3	Third Lumbar Vertebra
L4	Fourth Lumbar Vertebra
LL	Lower Left
LR	Lower Right
LS	Lymphoscintigraphy
MRI	Magnetic Resonance Imaging
RMS	Root Mean Square
SNB	Sentinel Node Biopsy
SMU	Sydney Melanoma Unit
SN	Sentinel Node
SPECT	Single Photon Emission Computed Tomography

TIS	Triangular Intermuscular Space
UL	Upper Left
UR	Upper Right
VH	Visible Human