Department of Electrical Engineering, Chiang Mai University
"Computer Applications in Automatic White Blood Cell Counting"
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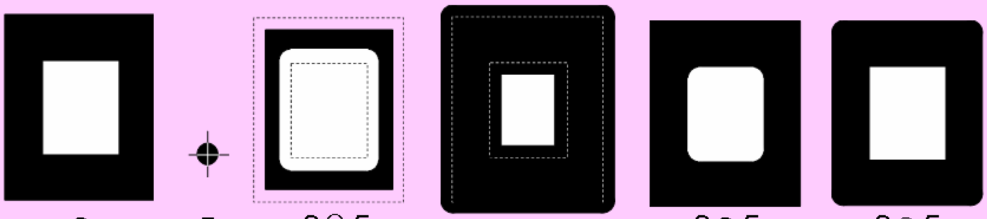
Methodology

- Morphological Granulometries
  - Morphological operations involving image *S* and structuring element *E*



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Methodology

- Morphological Granulometries
  - Let $\Omega(t)$ be area of $S \circ tE$ where t is a real number and $\Omega(0)$ is area of S
  - $\Omega(t)$ is called a *size distribution*
  - Normalized size distribution $\Phi(t) = \Omega(t) / \Omega(0)$, and $d\Phi(t)/dt$ are called *granulometric size distribution* or *pattern spectrum* of image S

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Methodology

- Morphological Granulometric Analysis of WBC

Structuring Element Used in the Experiments

0	1	1	0
1	1	1	1
1	1	1	1
0	1	1	0

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Methodology

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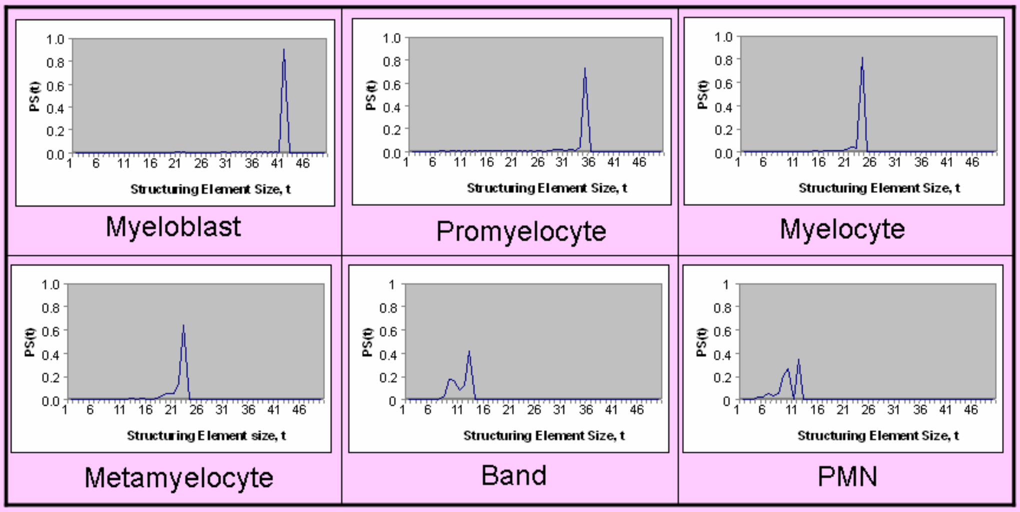

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Data Descriptions

- Data set : 20 Myeloblasts, 9 Promyelocytes, 139 Myelocytes, 33 Metamyelocytes, 45 Bands, and 185 PMNs
- Classified by Dr. C. William Caldwell, Professor of Pathology and Director of the Pathology Lab at the Ellis-Fischel Cancer Center, U. of Missouri, U.S.A.

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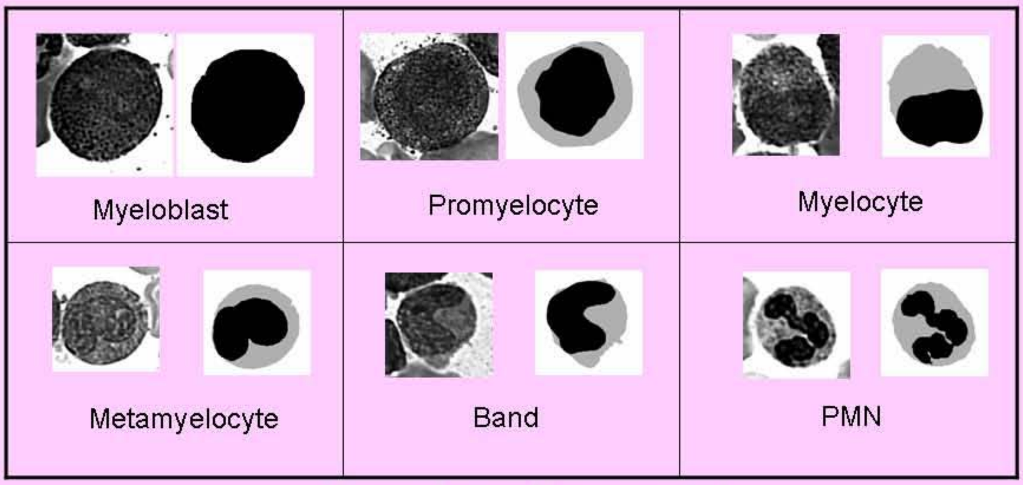
Data Descriptions

- Sample grayscale and corresponding hand-segmented images of white blood cells



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Data Descriptions

- 6 features are extracted from each single-cell image
  - area of cell,
  - nuclei-to-cytoplasm ratio,
  - maximum value of a pattern spectrum,
  - location where the maximum value of a pattern spectrum occurs,
  - first granulometric moments, and
  - second granulometric moments

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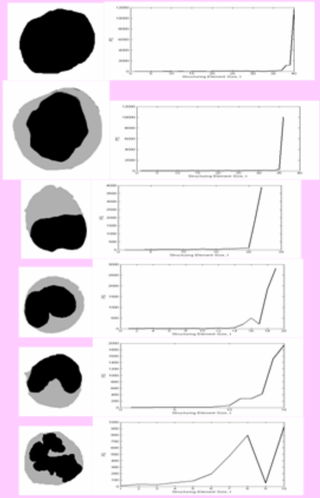
Feature Extraction

Cell Class	Input Images & Pattern Spectrum	Features
(a) Myeloblast		$\mathbf{x}$ = [4.1872 1.0414 1.1592x10^4 40 38.587 1.5074x10^3]
(b) Promyelocyte		$\mathbf{x}$ = [4.3570 0.3228 1.0002x10^4 36 34.439 1.2104x10^3]
(c) Myelocyte		$\mathbf{x}$ = [4.1004 0.3123 3.884x10^3 22 21.054 4.4863x10^2]
(d) Metamyelocyte		$\mathbf{x}$ = [4.0317 0.3361 2.8090x10^3 19 17.883 3.2364x10^2]
(e) Band		$\mathbf{x}$ = [3.8874 0.3950 1.9380x10^3 15 13.810 1.9348x10^2]
(f) PMN		$\mathbf{x}$ = [3.7077 0.3219 9.290x10^2 10 8.0521 6.8245x10^1]

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Experimental Results

- Classifier: Neural Network with 1 hidden layer consisting of 10 nodes
- Training Method: Levenberg-Marquardt (LM) algorithm
- Stopping Criteria: Max # epochs = 100, MSE = 10^{-6}
- Performance Evaluation: 5-fold cross validation

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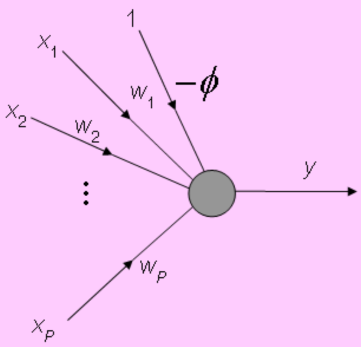
Classifier: Artificial Neural Networks

- Computational Node



$$y = f\left(\sum_{i=1}^{p} w_i x_i - \phi\right)$$

- ϕ is an offset
- f is a nonlinear function
- *E.g.* $f(x) = \tanh(\beta x)$, $\beta > 0$

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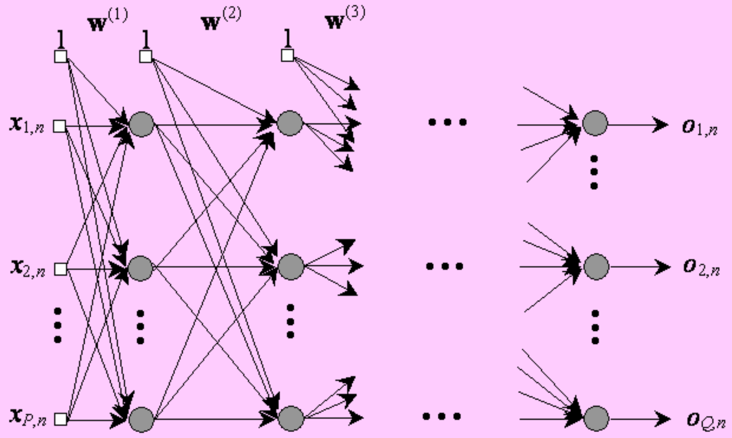
Artificial Neural Networks

- Artificial Neural Networks: Universal Approximator



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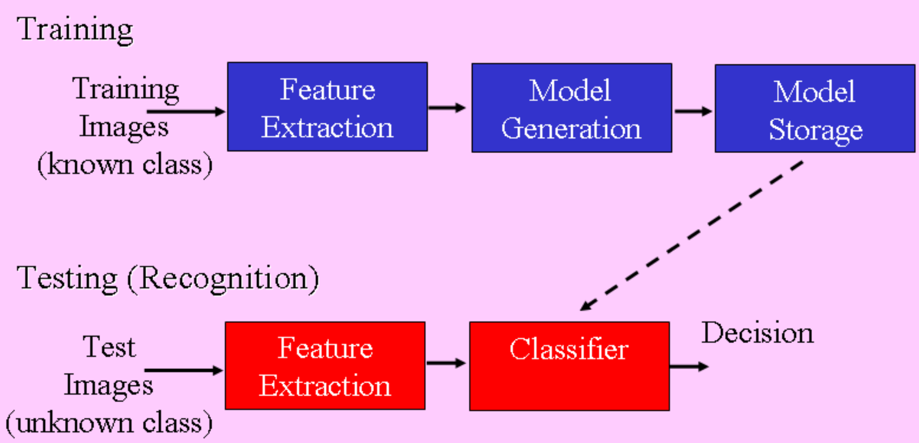
Training & Testing

- Neural Network (Model) Training and Testing



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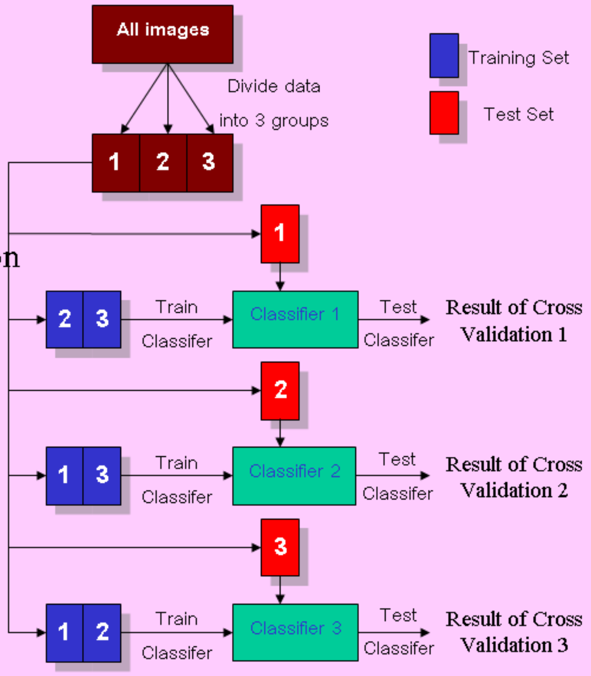
Cross Validation

N-Fold Cross Validation

E.g. 3-Fold Cross Validation



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Experimental Results

- Training by setting **Desired output 0.9 and 0.1**

Training

Alg → Actual ↓	Blast	Pro	Myelo	Meta	Band	PMN
Blast	80	0	0	0	0	0
Pro	2	26	7	1	0	0
Myelo	0	2	535	8	1	10
Meta	0	5	45	68	5	9
Band	0	0	1	0	140	39
PMN	0	0	12	6	8	714
Classification rate (Train) = 90.66 %						

Testing

Alg → Actual ↓	Blast	Pro	Myelo	Meta	Band	PMN
Blast	16	0	1	0	3	0
Pro	1	1	7	0	0	0
Myelo	0	6	116	8	0	9
Meta	0	0	17	9	3	4
Band	0	0	0	4	17	24
PMN	0	0	7	6	20	152
Classification rate (Test) = 72.16%						

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Experimental Results

- Trained by setting **Desired output** $d_j = 1 - \frac{n_j}{\sum_{j=1}^{6} n_j}$ **and 0.1**

Training

Alg → Actual ↓	Blast	Pro	Myelo	Meta	Band	PMN
Blast	80	0	0	0	0	0
Pro	0	27	9	0	0	0
Myelo	0	15	508	16	2	15
Meta	0	0	50	72	7	3
Band	0	0	0	4	139	37
PMN	0	0	22	19	63	636
Classification rate (Train) = 84.80 %						

Testing

Alg → Actual ↓	Blast	Pro	Myelo	Meta	Band	PMN
Blast	19	0	0	0	0	1
Pro	1	3	4	1	0	0
Myelo	2	4	114	14	1	4
Meta	0	0	17	10	4	2
Band	0	0	0	3	28	14
PMN	0	0	4	9	20	152
Classification rate (Test) = 75.64 %						

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Conclusion

- Mophological-based features
- Unbias the classifiers using *a priori* information of # samples
- About 75 % classification rate
- Rely on hand-segmented images
- Future works
  - incorporate automatic cell segmentation
  - apply other classifiers

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Fuzzy Clustering Patch-Based Automatic Nucleus Segmentation of Bone Marrow White Blood Cells

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Methodology

- GOAL : Segment nucleus of each cell
  - Tools:
    - Fuzzy Clustering
    - Mathematical Morphology

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Methodology

- Fuzzy C-Means Algorithm

$$\mathbf{v}_i = \frac{\sum_{k=1}^{n} [A_i(\mathbf{x}_k)]^m \mathbf{x}_k}{\sum_{k=1}^{n} [A_i(\mathbf{x}_k)]^m}, \quad i = 1, 2, \ldots, c, \text{ and } m > 1 \text{ (real)}$$

$$J_m(P) = \sum_{k=1}^{n} \sum_{i=1}^{c} [A_i(\mathbf{x}_k)]^m \|\mathbf{x}_k - \mathbf{v}_i\|^2$$

  – Goal: Partition data into c clusters with fuzzy pseudopartition $P = \{A_1, A_2, \ldots, A_c\}$ where A_i contains membership grades of all $\mathbf{x}_k$ to cluster i by minimizing $J_m(P)$

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Methodology

- Bayes Classifier

Assign an input vector $\mathbf{x}$ to class C_k if $y_k(\mathbf{x}) > y_j(\mathbf{x})$ for all $j \neq k$

$$y_k(\mathbf{x}) = P(C_k|\mathbf{x}) = \frac{p(\mathbf{x}|C_k)P(C_k)}{p(\mathbf{x})}$$

Assuming Normal distribution

$$p(\mathbf{x}|C_k) = \frac{1}{(2\pi)^{d/2}|\Sigma_k|^{1/2}} \exp\left(-\frac{1}{2}(\mathbf{x}-\boldsymbol{\mu}_k)^T \Sigma_k^{-1}(\mathbf{x}-\boldsymbol{\mu}_k)\right)$$

$$\ln(y_k(\mathbf{x})) = -\frac{d}{2}\ln(2\pi) - \frac{d}{2}\ln(|\Sigma_k|) - \frac{1}{2}(\mathbf{x}-\boldsymbol{\mu}_k)^T \Sigma_k^{-1}(\mathbf{x}-\boldsymbol{\mu}_k) + \ln(P(C_k))$$

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Experimental Results

- Proposed Segmentation Algorithm

1. Median Filtering
2. Oversegmentation (Patch Generation)
Use FCM to oversegment images ⇒ patches
3. Patch Combining
For each patch
Center of patch ≤ 60% of average ⇒ Nucleus
Otherwise ⇒ Non-nucleus
4. Final Touching
Morphological Operators: Opening and Closing

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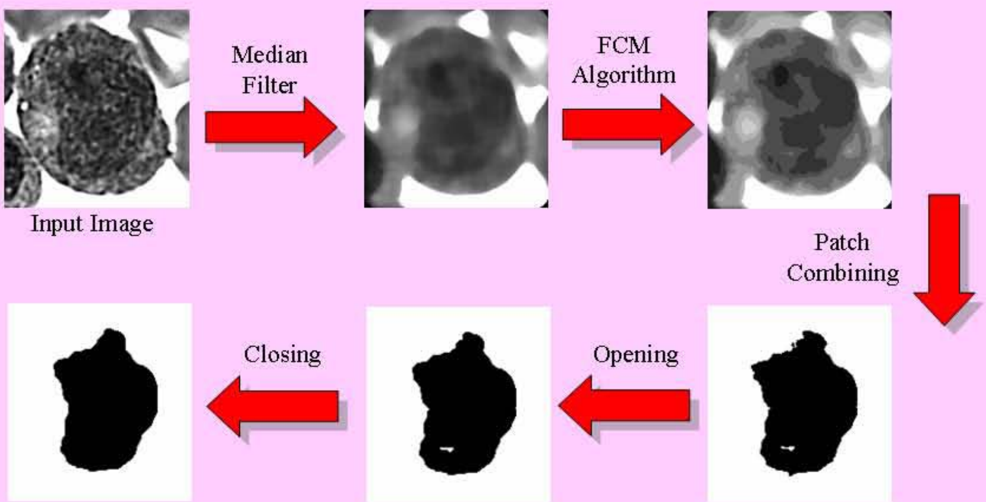
Experimental Results

- Proposed Segmentation Algorithm



Segmented Image

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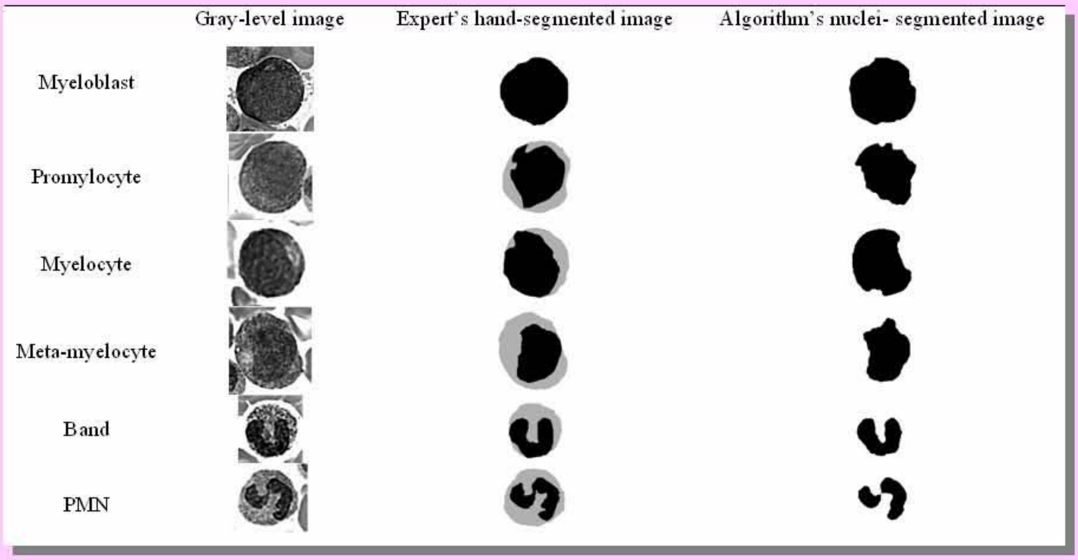
Experimental Results



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Experimental Results

- Evaluation Measure (Segmentation Error)

$$E_{Seg} = \frac{N_1 + N_2}{\text{Total number of pixels in the image}}$$

N_1 is the number of pixels in which the algorithm's decision is "Non-Nucleus" but the expert's decision is "Nucleus"

N_2 is the number of pixels in which the algorithm's decision is "Nucleus" but the expert's decision is "Non-Nucleus"

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Experimental Results

- Evaluation Measure (Segmentation Error)

	Myeloblast	Promyelocyte	Myelocyte	Metamyelocyte	Band	PMN
Segmentation Error (%)	9.23	16.07	14.73	10.21	8.60	7.01

Average Segmentation Error = 10.20 %

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Experimental Results

- Initial use of segmented nucleus in classification
  - Only 1 feature (area nucleus)
  - Bayes classifier with 10-fold cross validation
  - Using feature from automatic-segmented images
    - Classification rates: 59.55 % on training sets, 59.63 % on test sets
  - Using feature from hand-segmented images
    - Classification rates: 55.09 % on training sets, 55.22 % on test sets

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Conclusion

- A new nuclei-segmentation technique based on fuzzy clustering and mathematical morphology
- Use patch-based rather than pixel-based
- Promising classification performance
- Future works
  - Segment cytoplasm
  - Segment multi-cell images

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Acknowledgments

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- Dr. C. William Caldwell of Ellis-Fishel Cancer Center, University of Missouri for providing the data and ground truth,
- Dr. James Keller and Dr. Paul Gader for contribution through many technical discussions,
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Related Publications

- **N. Theera-Umpon**, "Fuzzy Clustering Patch-Based Automatic Nucleus Segmentation of Bone Marrow White Blood Cells," *ECTI Transactions on Electrical Eng., Electronics, and Communications* ,In Press.
- **N. Theera-Umpon**, "Fuzzy Clustering Patch-Based Automatic Nucleus Segmentation of Bone Marrow White Blood Cells," *27th Electrical Engineering Conference*, pp.125–128,Khon Kaen, Thailand, November 2004. [Best Paper Award]
- **N. Theera-Umpon**, "Automatic White Blood Cell Classification using Biased-Output Neural Networks with Morphological Features," *Thammasat International Journal of Science and Technology*, Vol. 8, No. 1, pp.64–71, January 2003.
- **N. Theera-Umpon** and P. D. Gader, "System Level Training of Neural Networks for Counting White Blood Cells", *IEEE Transactions on Systems, Man, and Cybernetics Part C: Applications and Reviews*, Vol. 32, No. 1, pp. 48–53, February 2002.
- **N. Theera-Umpon**, "Automatic White Blood Cell Classification in Bone Marrow Images using Morphological Features," *Proceedings of the 25th Electrical Engineering Conference*, pp. DS108–112, Prince of Songkla University, Thailand, November 2002.
- **N. Theera-Umpon**, E. R. Dougherty, and P. D. Gader, "Non-Homothetic Granulometric Mixing Theory with Application to Blood Cell Counting", *Pattern Recognition*, Vol. 34, No. 12, pp. 2547–2560, December 2001.
- **N. Theera-Umpon** and P. D. Gader, "Counting White Blood Cells Using Morphological Granulometries", *Journal of Electronic Imaging*, Vol.9, No.2, pp.170–177, April 2000.
- **N. Theera-Umpon** and P. D. Gader, "Training Neural Networks to Count White Blood Cells via a Minimum Counting Error Objective Function", *Proceedings of the 15th International Conference on Pattern Recognition*, pp. 299–302, Barcelona, Spain, September 2000.
- **N. Theera-Umpon** and P. D. Gader, "White Blood Cell Counting in Bone Marrow Images Via Classification-Free Granulometric Methods", *Proceedings of the SPIE Conference on Nonlinear Image Processing X*, Vol. 3646, pp. 260–269, San Jose, California, U.S.A., January 1999.

ภาคผนวก ฉ.

เอกสารประกอบการบรรยายพิเศษ

- จากการได้รับเชิญไปเป็นวิทยากรในการบรรยายพิเศษในหัวข้อ Computational Intelligence in Automatic White Blood Cell Counting ณ Kagawa University ประเทศญี่ปุ่น เมื่อเดือน ตุลาคม 2547 โดยมีคณาจารย์ และนักศึกษาระดับปริญญาตรี และบัณฑิตศึกษาของ Kagawa University เข้าร่วมรับฟังการบรรยาย (บรรยายเป็นภาษาอังกฤษ)

Computational Intelligence in Automatic White Blood Cell Counting

Nipon Theera-Umpon, Ph.D.
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Chiang Mai University
THAILAND

Special Lecture @ Kagawa University, JAPAN
October 2004

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Outline

- Introduction
- White Blood Cell Classification using NN and Morphological Features
  - Data Descriptions
  - Experimental Results
  - Conclusion
- Training NN to Count WBC via a Minimum Counting Error Objective Function
  - Data Descriptions
  - Experimental Results
  - Conclusion

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Introduction

- White blood cells grouped into discrete classes by age
- Numbers of cells in different classes aid doctors in diagnosis, e.g., AIDS, leukemia, cancers.
- Nuclei change shape and size with age

  ⇒ Mophological techniques
- Experts can produce counts that vary by as much as 15%
- No automated system for WBC differential counting in bone marrow

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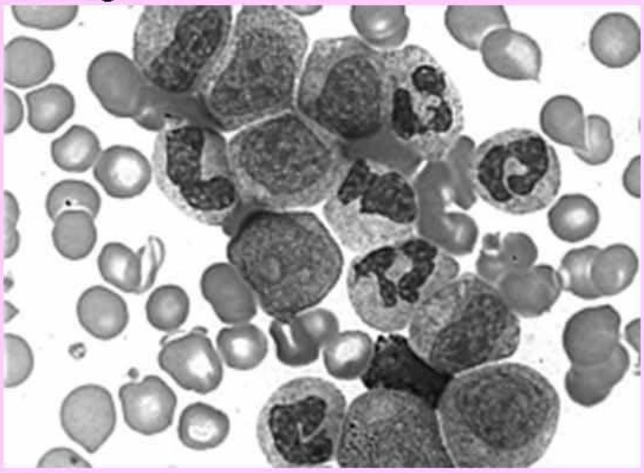
Introduction

- Sample image



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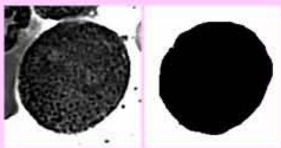
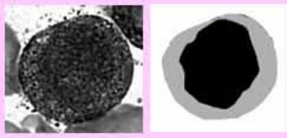
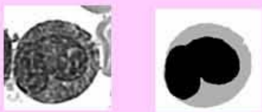


Myeloblast

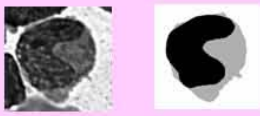


Promyelocyte

Myelocyte



Metamyelocyte



Band

PMN

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Methodology

- Morphological Granulometries
  - Morphological operations involving image S and structuring element E

$$\textit{Erosion}: (S \ominus E) = \cap \{S - e : e \in E\}$$

$$\textit{Dilation}: (S \oplus E) = \cup \{E + s : s \in S\}$$

$$\textit{Closing}: S \bullet E = (S \oplus (-E)) \ominus (-E)$$

$$\textit{Opening}: S \circ E = (S \ominus E) \oplus E$$

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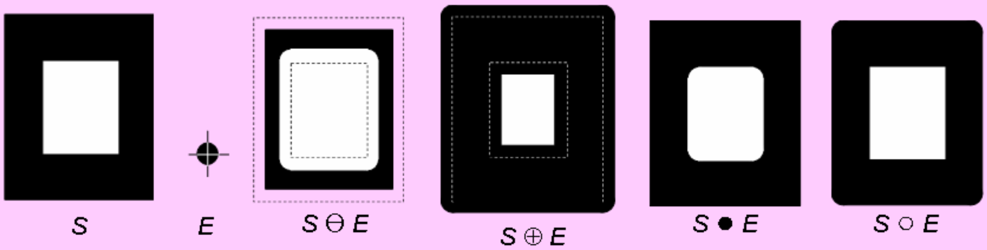

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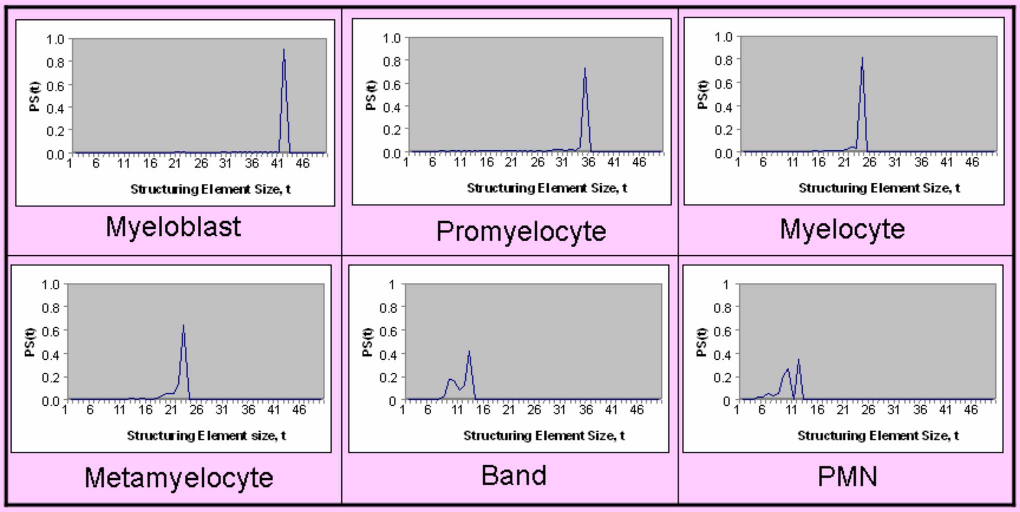

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  - second granulometric moments

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Experimental Results

- NN with 1 hidden layer consisting of 10 nodes
- Levenberg-Marquardt (LM) algorithm
- Max # epochs = 100, MSE = 10^{-6}
- 5-fold cross validation

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Experimental Results

- Desired output 0.9 and 0.1

Training

Alg → Actual ↓	Blast	Pro	Myelo	Meta	Band	PMN
Blast	80	0	0	0	0	0
Pro	2	26	7	1	0	0
Myelo	0	2	535	8	1	10
Meta	0	5	45	68	5	9
Band	0	0	1	0	140	39
PMN	0	0	12	6	8	714
Classification rate (Train) = 90.66 %						

Testing

Alg → Actual ↓	Blast	Pro	Myelo	Meta	Band	PMN
Blast	16	0	1	0	3	0
Pro	1	1	7	0	0	0
Myelo	0	6	116	8	0	9
Meta	0	0	17	9	3	4
Band	0	0	0	4	17	24
PMN	0	0	7	6	20	152
Classification rate (Test) = 72.16%						

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Experimental Results

- Desired output $d_j = 1 - \frac{n_j}{\sum_{j=1}^{6} n_j}$ and 0.1

Training

Alg → Actual ↓	Blast	Pro	Myelo	Meta	Band	PMN
Blast	80	0	0	0	0	0
Pro	0	27	9	0	0	0
Myelo	0	15	508	16	2	15
Meta	0	0	50	72	7	3
Band	0	0	0	4	139	37
PMN	0	0	22	19	63	636
Classification rate (Train) = 84.80 %						

Testing

Alg → Actual ↓	Blast	Pro	Myelo	Meta	Band	PMN
Blast	19	0	0	0	0	1
Pro	1	3	4	1	0	0
Myelo	2	4	114	14	1	4
Meta	0	0	17	10	4	2
Band	0	0	0	3	28	14
PMN	0	0	4	9	20	152
Classification rate (Test) = 75.64 %						

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Conclusion

- Mophological-based features
- Unbias the classifiers using *a priori* information of # samples
- About 75 % classification rate
- Rely on hand-segmented images
- Future works
  - incorporate automatic cell segmentation
  - apply other classifiers

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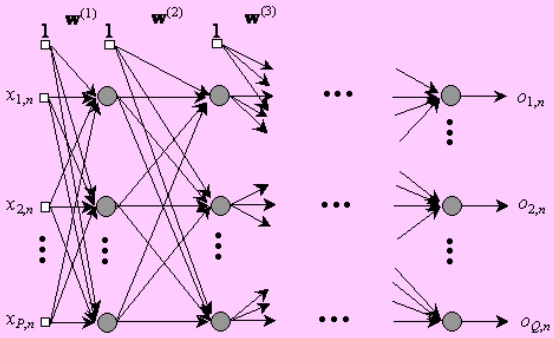
Training Neural Networks to Count WBC via a Minimum Counting Error Objective Function

- Use feed-forward classification network trained with back-propagation algorithm
- New training scheme running in the batch mode to achieve the minimum counting error



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Data Descriptions

- Data set contains 33 Myeloblasts, 61 Promyelocytes, 77 Myelocytes, 93 Metamyelocytes, 128 Bands, and 134 PMNs.
- 10 features are extracted from each single-cell image
- 6 features extracted from nucleus shape, i.e., circularity, elongation, thickness variance, and Fourier descriptors 3, 12, and 15
- 4 features are texture features, i.e., light number of patches in nucleus, energy of cytoplasm region, and correlation and variance in a cell

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Sigma Count

- $\mathbf{x}_n = [x_{1,n}\ x_{2,n}\ \ldots\ x_{P,n}]$: input vector
  - P : number of features
  - Q : number of classes
  - N : number of input vectors
  - $C_{exp,\,q}$: number of cells assigned to the q^{th} class by expert
- Define sigma count of the q^{th} class as

$$c_{sigma,q} = \sum_{n=1}^{N} o_{q,n} \quad , \quad q = 1,2,\ldots,Q$$

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Minimum Count Error Objective Function

- Minimum count error objective function is defined as

$$E = \frac{1}{2}\sum_{q=1}^{Q}\left[\left(\sum_{n=1}^{N} o_{q,n}\right) - c_{exp,q}\right]^2 = \frac{1}{2}\sum_{q=1}^{Q}\left[c_{sigma,q} - c_{exp,q}\right]^2$$

- Partial of E with respect to weight w_{ji} is

$$\frac{\partial E}{\partial w_{ji}} = \sum_{q=1}^{Q}\left\{\left[c_{sigma,q} - c_{exp,q}\right]\left[\sum_{n=1}^{N}\frac{\partial o_{q,n}}{\partial w_{ji}}\right]\right\}$$

- Factor $\partial o_{q,n}/\partial w_{ji}$ is found in the standard back-propagation algorithm
- There are no cell level desired outputs

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Evaluation Measures

$$\text{Evaluation : Counting Rate} = \left(1 - \frac{\sum_{q=1}^{6} \left|c_{exp,q} - c_{alg,q}\right|}{\sum_{q=1}^{6} \left|c_{exp,q}\right|}\right) \times 100\%$$

- $C_{alg,q}$ has 2 types : crisp and sigma count
- Crisp count assumes classifier assigns each input cell to one class (maximum output)
- There are 12 percentage values measured
  - percVal = { crClTr, crClTe, ccClTr, scClTe, scClTr, scClTe, crCoTr, crCoTe, ccCoTr, scCoTe, scCoTr, scCoTe }
  - where cr = classification rate, cc = crisp count rate, sc = sigma count rate, Cl = classification NN, Co = counting NN
  - Tr = training set, and Te = test set

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Algorithm

- Use 4-fold cross-validation

For (i = 1 to 4)   / fold 1 to 4 */*
    *Initial **initClassNet**;*
    *Train **initClassNet** using LM algorithm for 5 epochs;*
    ***InitEp** = 5;*
    ***While** (**initEp** ≤ 50)*
        *Train **initClassNet** using LM algorithm for 5 epochs;*
        *Initialize **classNet** and **countNet** with **initClassNet**;*
        *Train **classNet** using gradient descent for 50 epochs;*
        *Train **countNet** using gradient descent for 50 epochs;*
        *Test **classNet** & **countNet** on training & test sets;*
        *Calculate **percVal[i][initEp]**;*
        ***initEp** = **initEp**+5;*
    ***End** While (initEpoch ≤ 50);*
***End** For (i = 1 to 4);*
*Average the evaluation measures in **percVal**, over 4 folds;*

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Experimental Results

- Use network with 1 hidden layer containing 12 hidden neurons
- $\eta_{cnt} = 10^{-4}$, $\eta_{class} = 10^{-2}$
- Activation function = sigmoid
- Classification network is trained to output 1 at the output node corresponding to the actual class, and 0's at the other output nodes

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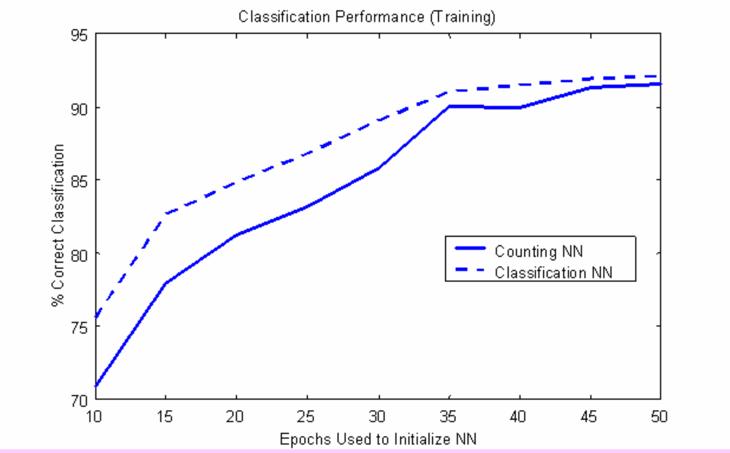
Experimental Results

- Classification rates on training set



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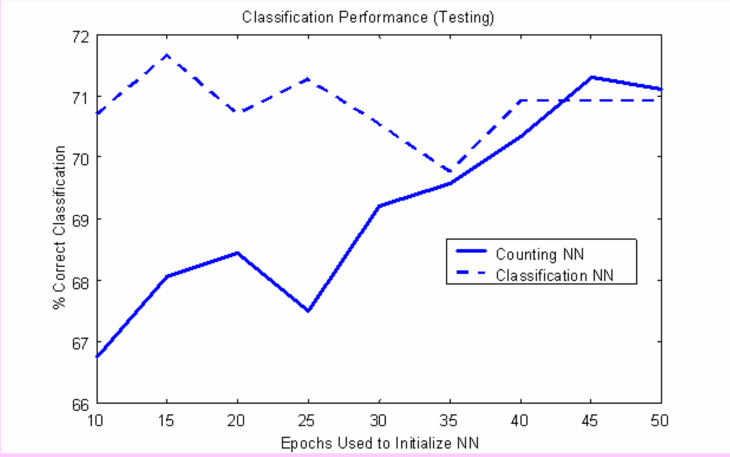
Experimental Results

- Classification rates on test set



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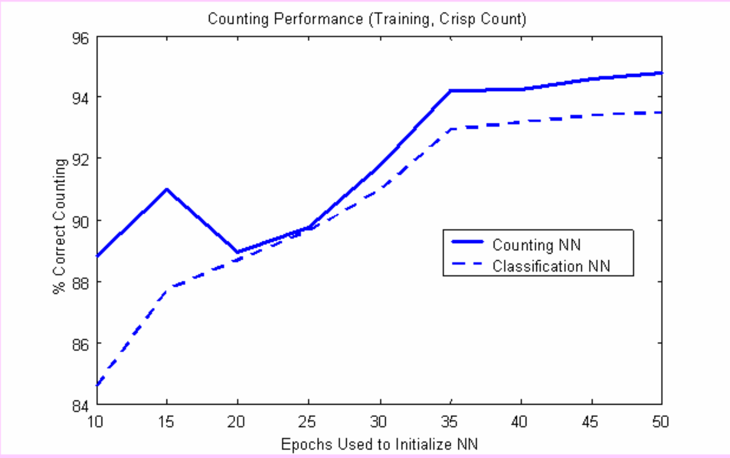
Experimental Results

- Crisp counting rates on training set



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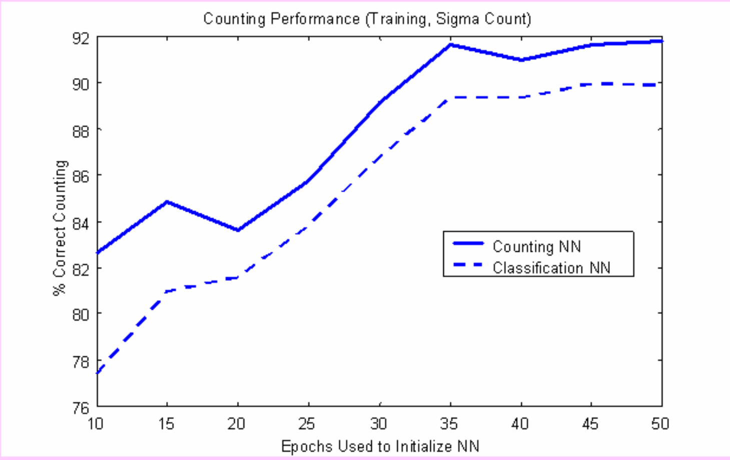
Experimental Results

- Sigma counting rates on training set



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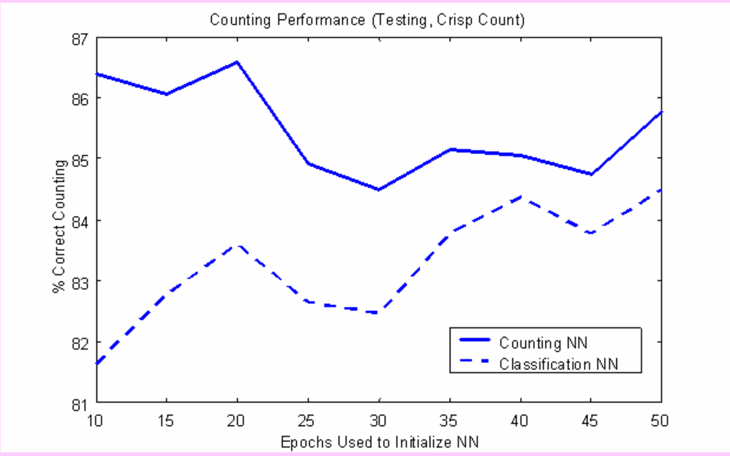
Experimental Results

- Crisp counting rates on test set



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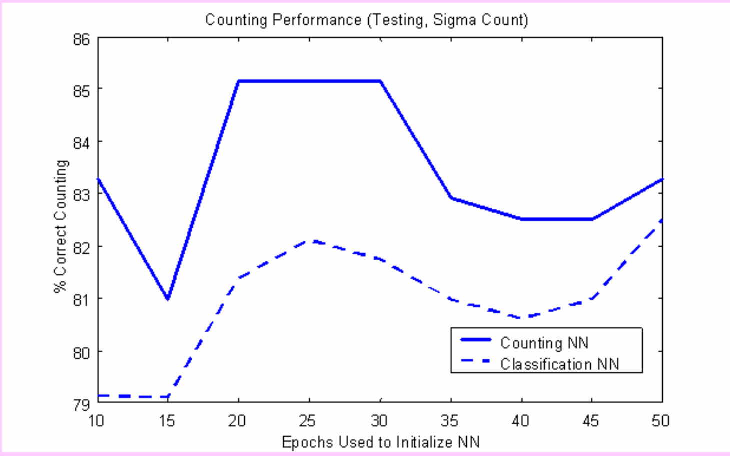
Experimental Results

- Sigma counting rates on test set



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Conclusion

- Counting network achieved more accurate counts than classification network
- Counting network has poorer classification performance
- In this particular problem, main goal = accurate counts
- Classification is only an indirect tool to achieve that goal
- Going directly to main goal is a good way to solve the problem

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Related Publications

- **N. Theera-Umpon**, "Fuzzy Clustering Patch-Based Automatic Nucleus Segmentation of Bone Marrow White Blood Cells," *27th Electrical Engineering Conference*, Khon Kaen, Thailand, November 2004.
- **N. Theera-Umpon**, "Automatic White Blood Cell Classification using Biased-Output Neural Networks with Morphological Features," *Thammasat International Journal of Science and Technology*, Vol. 8, No. 1, pp.64–71, January 2003.
- **N. Theera-Umpon** and P. D. Gader, "System Level Training of Neural Networks for Counting White Blood Cells", *IEEE Transactions on Systems, Man, and Cybernetics Part C: Applications and Reviews*, Vol. 32, No. 1, pp. 48–53, February 2002.
- **N. Theera-Umpon**, "Automatic White Blood Cell Classification in Bone Marrow Images using Morphological Features," *Proceedings of the 25th Electrical Engineering Conference*, pp. DS108–112, Prince of Songkla University, Thailand, November 2002.
- **N. Theera-Umpon**, E. R. Dougherty, and P. D. Gader, "Non-Homothetic Granulometric Mixing Theory with Application to Blood Cell Counting", *Pattern Recognition*, Vol. 34, No. 12, pp. 2547–2560, December 2001.
- **N. Theera-Umpon** and P. D. Gader, "Counting White Blood Cells Using Morphological Granulometries", *Journal of Electronic Imaging*, Vol.9, No.2, pp.170–177, April 2000.
- **N. Theera-Umpon** and P. D. Gader, "Training Neural Networks to Count White Blood Cells via a Minimum Counting Error Objective Function", *Proceedings of the 15th International Conference on Pattern Recognition*, pp. 299–302, Barcelona, Spain, September 2000.
- **N. Theera-Umpon** and P. D. Gader, "White Blood Cell Counting in Bone Marrow Images Via Classification-Free Granulometric Methods", *Proceedings of the SPIE Conference on Nonlinear Image Processing X*, Vol. 3646, pp. 260–269, San Jose, California, U.S.A., January 1999.