More Accurate Prediction of Replication Origins in Herpesvirus Genomes

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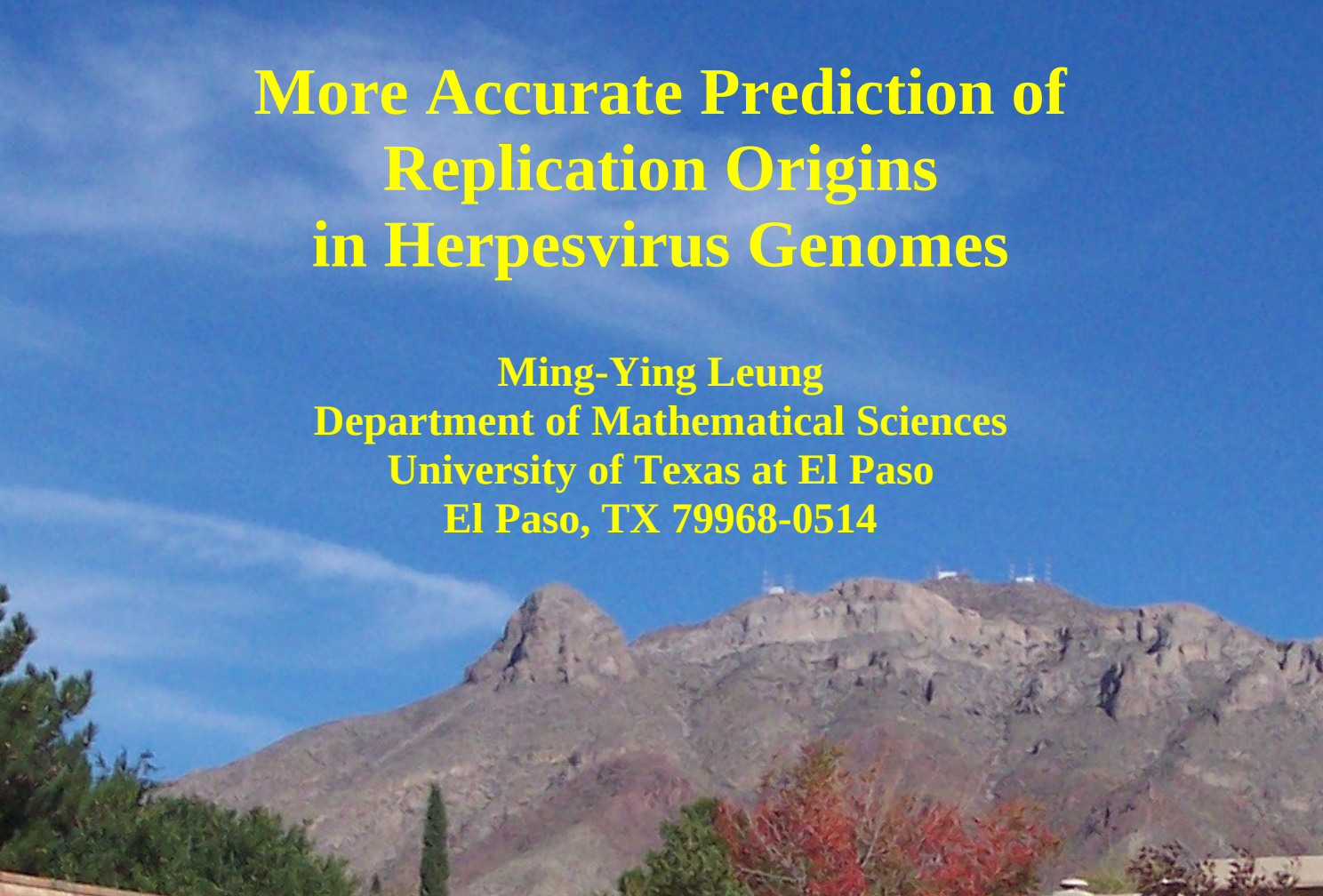
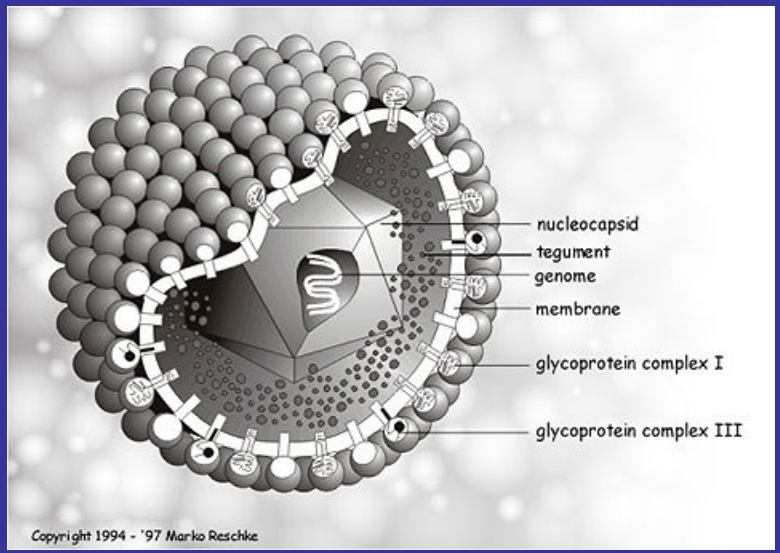
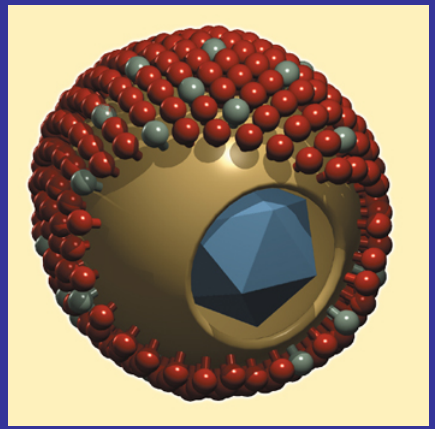


Outline:

- Herpesvirus genomes
- DNA palindromes
- Poisson process approximation of palindrome occurrences



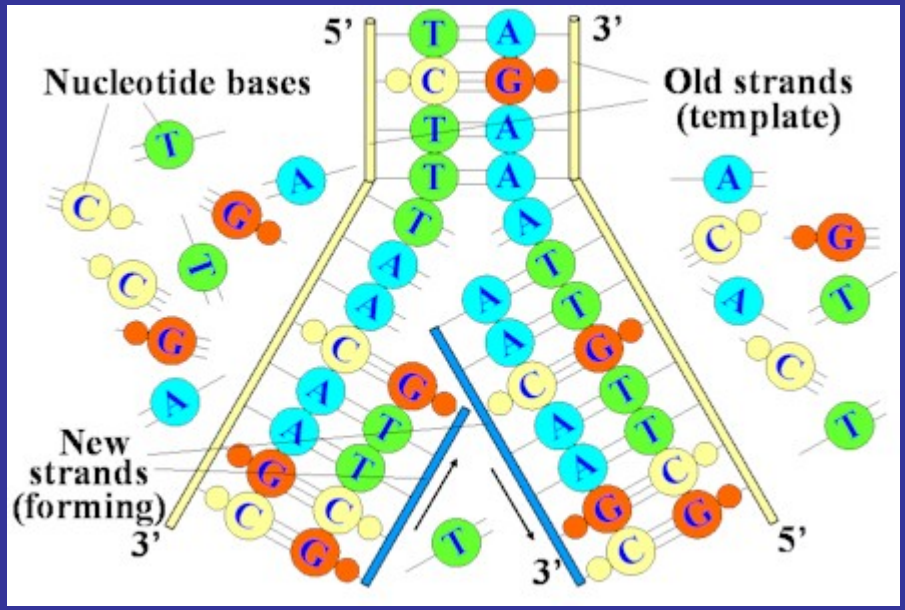
Cytomegalovirus (CMV) Particle



Genome sizes of ~100-250 kbp

Outline (cont'd):

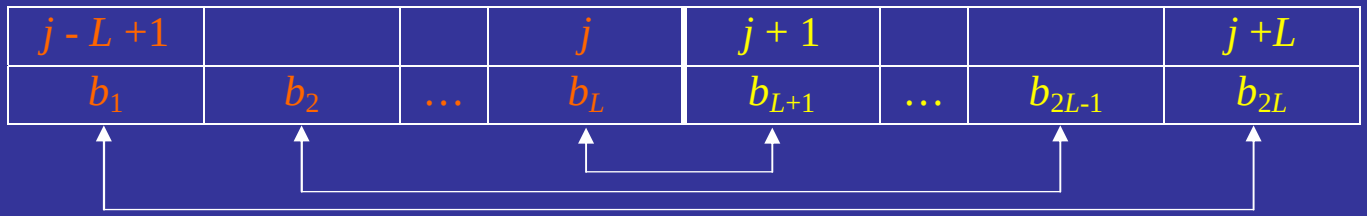
- Prediction of replication origins using scan statistics
- More accurate predictions using scoring schemes



DNA Replication at the Origin (Orilyt)

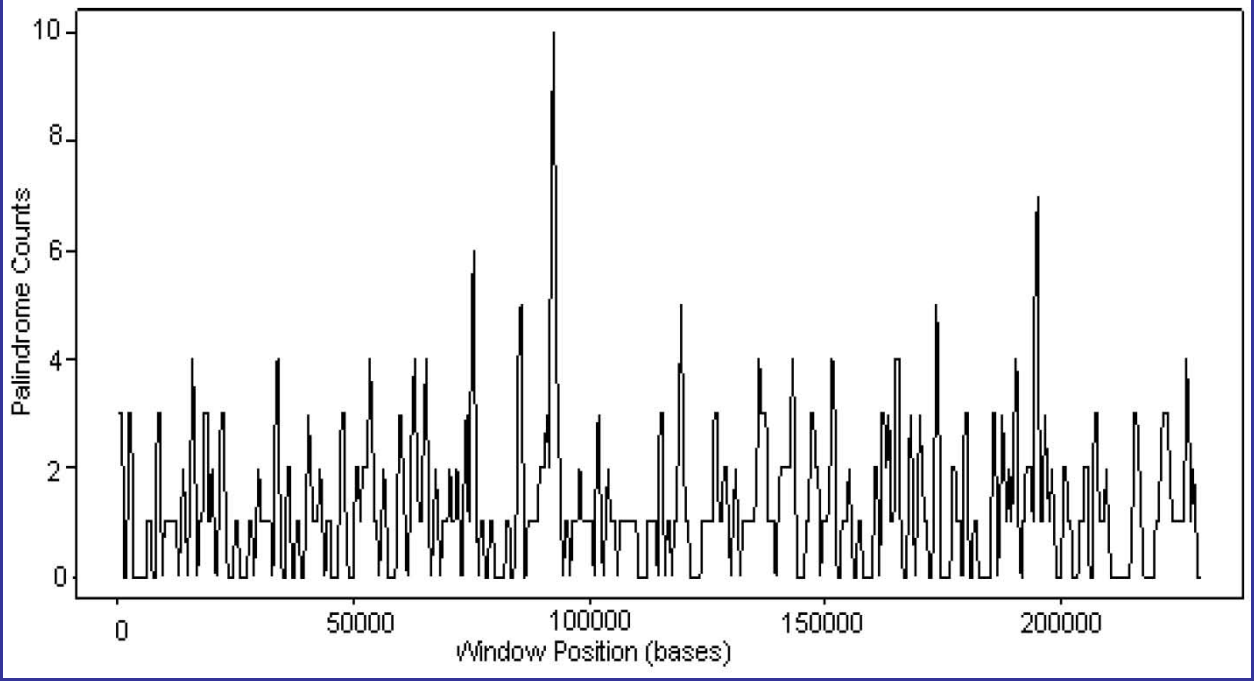
Palindrome: A string of nucleotide bases that reads the same as its reverse complement. A palindrome must be even in length, e.g. palindrome of length 10:

5’ ….. GCAATATTGC …..3’
3’ ….. CGTTATAACG …..5’



We say that a palindrome of length $2L$ occurs at position j when the $(j-i+1)$st and the $(j+i)$th bases are complementary to each other for $i=1,\ldots, L$. In an i.i.d. sequence model this occurs with probability $\left[2\left(p_A p_T + p_C p_G\right)\right]^L$.

Association of Palindromes Clusters with Replication Origins



Poisson process approximation

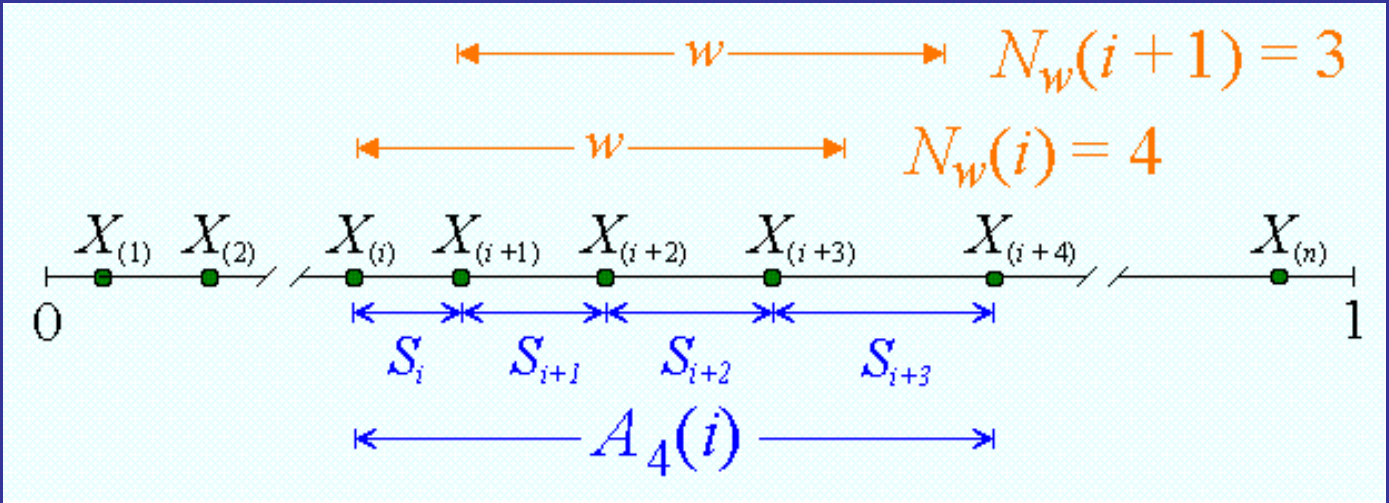
Let Ξ be the process representing the palindrome occurrences on a random nucleotide sequence generated by the i.i.d. model; and Z_λ be the Poisson process with rate λ.

Proposition (Leung *et al.* 2004 *J. Computat. Biol.*)
Assuming $p_A = p_T$, $p_C = p_G$ *and suppose that* $n, L \to \infty$ *in such a way that* $n\theta^L = \lambda$ where $\lambda \geq 1/32$ is a fixed positive constant, then

$$d_2(\mathcal{L}(\Xi), \mathcal{L}(Z_\lambda)) \leq cL\theta^{L/2} \to 0$$

Here d_2 *stands for the Wasserstein distance,* Ξ the palindrome process, and *c is an absolute constant no greater than* 131.

The Scan Statistic



$X_1, X_2, \ldots, X_n \sim$ i.i.d. Uniform (0,1)

$S_i = X_{(i+1)} - X_{(i)} = i^{\text{th}}$ spacing

$A_r(i) = S_i + \ldots + S_{i+r-1}$ = sum of r adjoining spacing

r-Scan Statistic $\quad A_r = \min_i A_r(i)$

Scan Statistics Prediction Results

Genome	Region	Palindrome	Feature
BHV1	77155 - 77168	3	
	102895 - 106948	22	
	113462 - 113636	5	1.75 mu[a] from Ori
	124582 - 124756	5	1.61 mu from Ori
	131268 - 135221	21	
EHV1	115125 - 119094	17	overlaps transcriptional regulator
	144064 - 148033	17	overlaps transcriptional regulator
EHV4	none		
HSV1	none		
HSV2	none		
VZV	none		
EBV	6772 - 11675	19	Contains OriP
	49460 - 54858	25	Contains OriLyt
HCMV	89585 - 94183	19	Contains OriLyt
	195029 - 195268	8	enhancer element

Scan Statistics Prediction Results (Cont'd)

Genome	Region	Palindrome	Feature
HCMV	89585 - 94183	19	Contains OriLyt
	195029 - 195268	8	enhancer element
HHV6	none		
HHV7	120758 -124422	16	
AHV1	113456 - 113759	5	
ATHV3	95350 - 100098	17	
MDV2	93143 - 93243	4	
	109331 - 110590	8	
MDV	none		
CCV1	none		
HVS2	none		

Scoring schemes

Palindrome count score (PCS): a palindrome is given a score 1 when its length is at or above $2L$.

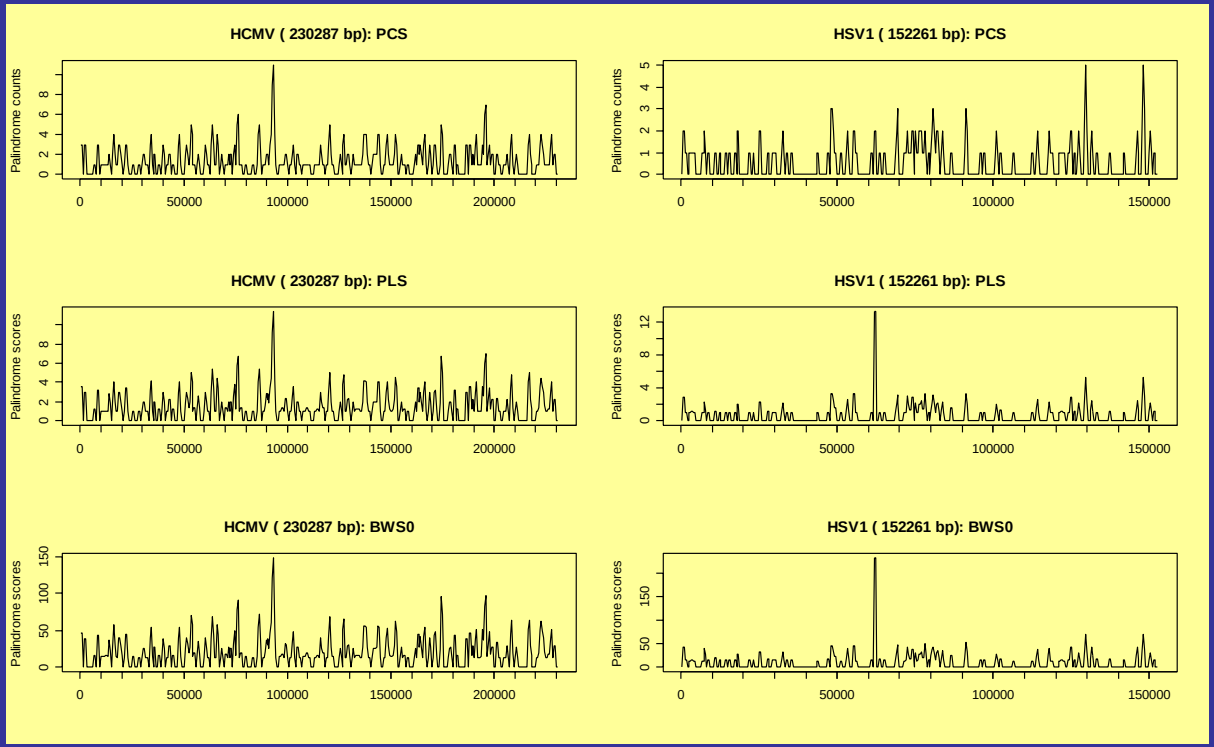
Palindrome length score (PLS): a palindrome of length at least $2L$ is given a score proportional to its length.
E.g., assign a score of s/L for a palindrome of length $2s$.

Base weighted score (BWS): a palindrome of length at least $2L$ is given a score equal to the negative log of the probability of its occurrence.
E.g., under the i.i.d. random sequence model, assign a score of

$$-(2\log p_A + 3\log p_C + 3\log p_G + 2\log p_T)$$

for the palindrome *CACGTACGTG*, where p_A, p_C, p_G, p_T are the percentages of the bases in the genome.

Sliding Window Plots for Various Scoring Schemes



Prediction results

Virus	Known ORIs/ Names			PCS	PLS	BWS
bohv1	111080-111300	(OriS)		1.75mu	1.6mu	1.6mu
	126918-127138	(OriS)		1.61mu	1.8mu	1.8mu
bohv4	97143-98850	(OriLyt)		-	-	-
cehv1	61592-61789	(OriL1)		-	0.1mu	0.1mu
	61795-61992	(OriL2)		-	0.2mu	0.2mu
	132795-132796	(OriS1)		-	0.1mu	0.1mu
	132998-132999	(OriS2)		-	0.002mu	0.002mu
	149425-149426	(OriS2)		-	0.02mu	0.02mu
	149628-149629	(OriS1)		-	0.1mu	0.1mu
cehv7	109627-109646			-	-	-
	118613-118632			-	-	-
ebv	7315-9312	(OriP)		contains ori	0.4mu	0.4mu
	52589-53581	(OriLyt)		contains ori	0.07mu	0.07mu
ehv1	126187-126338			-	-	-
ehv4	73900-73919	(OriL)		-	-	-
	119462-119481	(OriS)		-	-	-
	138568-138587	(OriS)		-	-	-

Prediction results (Cont'd)

Virus	Known ORIs/ Names			PCS	PLS	BWS
hcmv	93201-94646	(OriLyt)		contains ori	0.05mu	0.05mu
hhv6	67617-67993	(OriLyt)		-	-	-
hhv7	66685-67298			-	-	-
hsv1	62475	(OriL)		-	0.1mu	0.1mu
	131999	(OriS)		-	1.4mu	1.4mu
	146235	(OriS)		-	1.4mu	1.4mu
hsv2	62930	(OriL)		-	-	-
	132760	(OriS)		-	-	-
	148981	(OriS)		-	-	-
rcmv	75666-78970	(OriLyt)		overlaps ori	0.6mu	0.6mu
vzv	110087-110350			-	0.1mu	0.1mu
	119547-119810			-	0.2mu	0.2mu

Measures of Prediction Accuracy

$$\text{Sensitivity} = \frac{\text{no. of ORIs that are significant clusters}}{\text{no. of ORIs}}$$

$$\text{Specificity} = \frac{\text{no. of significant clusters that are ORIs}}{\text{no. of significant clusters}}$$

Improved prediction accuracy

	PCS	PLS					PWS				
		1	2	3	4	5	1	2	3	4	5
Sensitivity	0.17	0.28	0.48	0.59	0.66	0.69	0.28	0.48	0.59	0.62	0.66
Specificity	0.24	0.57	0.50	0.40	0.34	0.29	0.57	0.50	0.40	0.32	0.27

Ongoing work:

- Evaluation of statistical significance for the scoring schemes.
- Incorporate other sequence features such as close direct repeats and close inversions.

Acknowledgments

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